DIABETOLOG NYTT

År 2017 Årgång 30 Nr 6-7

SVENSK FÖRENING FÖR DIABETOLOGI
SWEDISH SOCIETY FOR DIABETOLOGY

DiabetologNytt

Medlemstidning för Svensk Förening för Diabetologi

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Övergången från sommar till höst brukar kännas lättare när de arbetsuppgifter som ligger framför oss är spännande och utvecklande. Så är verkligen fallet i år med EASD, höstmöte och världsdiabetesdag på agendan.

SFDs styrelse träffades i början av september i Stockholm för att lägga upp och planera det kommande årets aktiviteter. SFD kunde här introducera Niclas Abrahamsson (Akademiska Sjukhuset, Uppsala) och Erik Schwarcz (Universitetssjukhuset, Örebro) i styrelsearbetet. Niclas sitter även i styrelsen för Svenska endokrinologföreningen (SED) vilket är en stor tillgång i SFDs kommande samarbeten med SED. Magnus Löndahl från diabetesenheten Lund SUS är ny vetenskaplig sekreterare i SFD.

Styrelsen hade en öppen diskussion om SFDs strategiska mål och kom fram till att från och med 2019 endast ordna ett vetenskapligt möte per år. Detta för att kunna attrahera en större publik och föreläsare med stor dragningskraft. Vår plan är att dessa kommande möten blir något längre (tre dagar) där en dag viks åt kliniskt inriktade föreläsningar av typen ”meet the expert”, en dag innehåller vetenskap och en dag är mer fokuserad på samhällsfrågor som är kopplade till diabetes. Våren 2019 kommer det första mötet i detta format att hållas i Stockholm i samarbete mellan SFD och barnläkarföreningen.

För att bli ännu bättre på att kommunicera viktiga händelser i svensk diabetesvård och forskning, så vill SFD satsa mer på strategisk kunskapsstyrning. Styrelsen anser att detta är motiverat eftersom kunskapsspridning är ett av SFDs huvudmål och vi tror att detta kan bli en framgångsfaktor för att öka vårdgivares, patienters och allmänhetens medvetenhet om diabetesforskning och vårdprocesser i Sverige.

Ett betydelsefullt instrument för en kvalitetsgranskad kunskapsspridning är en gemensam lärobok. En utmärkt sådan finns sedan 20 år i form av boken ”Diabetes” (LIBER) med redaktörskap från Christian Berne och Carl-David Agardh. SFD har nu fört sta-

fettpinnen för denna mycket lästa bok vidare till Mona Landin Olsson som har tackat ja till att bli redaktör för en ny upplaga.

Under hösten kommer studien som går under namnet: Changing Diagnostic Criteria for Gestational diabetes in Sweden att startas upp (http://cdc4g.com/sv). Erik Schwarcz sitter i styrgruppen för denna studie som avser att studera effekterna av de nya riktlinjer för gestationell diabetes. Samtliga Sveriges regioner kommer i denna studie att stegvis lottas till de nya riktlinjerna som både gäller diagnos och mer aktiv behandlingsstrategi.

Ett annat arbete som pågår är samordningen mellan NDR, SFD och svenska medicinska retinaklubben att revidera inrapporteringen för retinopati i NDR. Den nya inrapporteringsmallen planeras att harmoniera med den gällande internationella klassifikationen och kommer att spikas under hösten.

Agendan för höstmötet 12-13/10 i Malmö www.jamlikvard.org samarrangeras med SKL och Svenska Psykiatriska föreningen och innehåller ett antal angelägna teman som psykisk ohälsa hos diabetespatienten, somatisk hälsa hos den psykiatriska patienten och en översikt av kommunala insatser.

Världsdiabetesdagen kommer att få stor uppmärksamhet i år på grund av den TV sända galan som arrangeras gemensamt av MTG och Diabetesförbundet. Denna gala kommer att sändas från Stockholm. Dagens medicin arrangerar även tillsammans med det nationella diabetesteamet (där SFD, barnläkarföreningen, SFSD och dietisternas riskförbund ingår) som ges på Operaterrassen i Stockholm. Vi har denna dag valt kommunikation och mångfald som teman, då vi tycker att dessa ämnen är angelägna att diskutera. Vi hoppas att inom kort kunna presentera innehållet till detta seminarium!

Vi går en spännande höst till mötes med andra ord!

David Nathanson
Ordf SFD

Redaktörspalten

Svensk Förening för Diabetologi (SFD) fyller i år 30 år. Salvador Dalis ”Minnets beständighet” med skulpturen ”Nobility of Time”, en smältande klocka, pryder framsidan av detta nummer.

Som redaktör är det en glädje att ha med rapporter från amerikanska diabetesmötet ADA i juni i San Diego, världens största diabeteskonferens, sid 229-248. Här finns både kliniska och vetenskapliga studier vid typ 1 och 2 diabetes. DEVOTE en studie av långverkande insulin som visar att degludec är kardiovaskulärt säkert. Studien CANVAS gör att SGLT2-hämmare stärker sin roll inom typ 2 diabetes med 33% mindre hjärtsvikt. Standardisering av CGM vid typ 1 diabetes diskuteras på sid 247. Förutom HbA1c är vid typ 1 diabetes minst lika viktigt att ha så lång tid som möjligt i normoglykemi - och minimera tiden med hyperglykemi respektive tiden med hypoglykemi.

LCHF risks for life diskuteras av Carmel Smart på sid 257 utifrån en studie med fallrapporter från Australien och Nya Zeeland.

TLV kan lära mycket av Frankrike då det gäller implementering av Libre vid typ 1 och 2 diabetes. Se sid 202. NT-rådets rekommendationer om Libre vid typ 2 diabetes finns på sid 210. Professor Jan Bolinder, Karolinska, ger på sid 214 sitt yttrande om TLV och deras pressrelease kring Libre. Anders Lönnberg, regerings utredare, vill på sid 228 att Sverige ska vara ett kraftfullt innovativt land, också med en öppenhet för medicinteknik.

I tidningen finns ISPADs Guidelines om diabetes in pre-school på sid 192, konsensus kring exercise management vid typ 1 diabetes sid 215 och referat av en artikel kring monogen diabetes på sid 192.

Önskan om en fin höst och vinter
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Redaktör

Hör av dig om du hört och läst något du vill sprida vidare.

NDR-nytt www.ndr.nu

Typ 1-diabetes och vikten av god riskfaktorkontroll

I en nyligen publicerad artikel i Circulation presenteras en studie där NDR undersöker sambandet mellan antalet riskfaktorer och risken för hjärt-kärlsjukdom och död hos individer med typ 1-diabetes jämfört med matchade kontroller. Fem traditionella och modifierbara kardiovaskulära riskfaktorer valdes ut; blodsockernivåer (HbA1c), blodtryck, blodfetter (LDL-kolesterol), albuminuri och rökning. Effekten av att uppnå målnivåer för de fem utvalda riskfaktorerna studerades för att ta reda på om en person med typ 1-diabetes kan eliminera sin förhöjda risk för hjärt-kärlsjukdom och död genom optimal riskfaktorkontroll. Alla patienter, 18 år eller äldre, med typ 1 diabetes och som registrerats i NDR från år 1998 till 2014 inkluderades i studien. För varje individ med diabetes inkluderades fem ålders-, kön-, och regionmatchade kontroller utan diabetes, slumpmässigt utvalda från befolkningen. Jämförelse gjordes av 33 333 patienter med typ 1-diabetes med 166 529 matchade kontroller. För varje riskfaktor som inte nådde målvärdet ökade risken för död och kardiovaskulär händelse gradvis. Slutsatsen är att individer med typ 1-diabetes som uppnår optimal riskfaktorkontroll av fem utvalda riskfaktorer markant reducerar den förhöjda risken för hjärt-kärlsjukdom och möjligtvis även eliminerar sin förhöjda risk för stroke och död.

Diabetesregistren för barn och vuxna går ihop och får gemensam hemsida

Från och med nästa år kommer NDR och Swediabkids att finnas på samma webbsida. Både Swediabkids och NDR har alltid haft drivkraften att vara verktyg i arbetet att förbättra vården och nästa steg är att harmonisera de två registren så att det går att följa personer med diabetes genom hela livet. Detta kommer att underlätta utvärderingen av diabetesvården och syftet är en ännu bättre vård för barn, ungdomar och vuxna med diabetes. Swediabkids ska ingå i den webbaserade lösning som finns för vuxenregistret NDR vilket innebär att även barn- och ungdomsdiabetesmottagningarna får möjlighet till direktöverföring från journal till registret. De sökfunktioner som redan finns i NDR ska anpassas för att också kunna användas för Swediabkids och de blir värdefulla verktyg i det lokala förbättringsarbetet även på barn- och ungdomsklinikerna. Dessutom kommer NDRs öppna utdataverktyg ”knappen” nästa år också innehålla resultat från barn- och ungdomsdiabetesvården.

NDRs diabetesenkät väcker frågor om hur det är att leva med diabetes

Hur det är att leva med diabetes har uppmärksammats i media med anledning av att NDR testar diabetesenkäten på flera medicinkliniker i landet. Till exempel har SVT Nyheter Halland gjort ett reportage från en av testklinikerna, se länk från NDRs hemsida. I reportaget tas upp att det ställs höga krav på den som har diabetes att ta hand om sin sjukdom på egen hand med till exempel blodsockerkontroller och dosering av insulin. Att hela tiden ha hängande över sig att man inte ska ha dåliga värden kan skapa stress och oro och det kan man behöva prata om med sin läkare eller diabetessjuksköterska. NDR är ett redskap för diabetesvården att följa upp den medicinska behandlingen och dess resultat, men fram till nu har det inte funnits med i registret hur personer med diabetes mår och hur deras vardag fungerar.

Enkäten innehåller förutom frågor om måendet även frågor som handlar om stödet från vården och om patienten är nöjd med sin behandling och sina hjälpmedel. Med enkäten får vården och patienterna nu ett redskap för att följa upp även dessa frågor. Läkarna och diabetessjuksköterskorna har naturligtvis pratat med patienterna om de här viktiga frågorna tidigare, men med hjälp av enkäten blir det på ett mer systematiskt sätt. Enkäten kan dels fungera som ett stöd i det enskilda vårdmötet men också då vården utvärderas på gruppnivå. Förutom de medicinkliniker som i nuläget testar enkäten så kommer den introduceras på ett antal primärvårdsenheter under hösten. Nästa år blir det möjligt för alla diabetesmottagningar som vill, att börja använda diabetesenkäten.

Vi vill passa på och än en gång tacka er för det fantastiska samarbetet och för all värdefull input. NDR utvecklas ständigt tack vare det. Vi hörs och ses.

Soffia Gudbjörnsdottir, registerhållare
Pär Samuelsson, utvecklingsledare
Ebba Linder, utvecklingsledare

”Spännande att gå från cell- till samhällsnivå”

Han blev doktorand som 20-åring och var bland de första att lyfta fram kaffets förtjänster vid diabetes. För DiabetologNytt berättar professor Claes-Göran Östenson om myndighetsuppdrag, japanska råttor och att aldrig bli färdig.

Ett nytt kapitel i livet. Det började förra året när Claes-Göran Östenson efter närmare fyra decennier som diabetesdoktor på Karolinska Sjukhuset sade hej då till sina patienter. Numera ägnar han sig åt dem indirekt – i egenskap av seniorprofessor inom diabetes typ 2 på Karolinska Institutet, KI, och genom ett flertal myndighetsengagemang. Officiellt jobbar han bara halvtid, vilket ger lite mer tid åt barnbarnen. Men börjar man rada upp alla uppdrag är det svårt att förstå när han egentligen är ledig. Vid sidan om forskningen på KI är han institutets diabetesrepresentant i 4D-programmet – ett samverkansprojekt mellan KI och Stockholms läns landsting med fokus på de vanligaste folksjukdomarna. Han jobbar också sedan 2006 för Socialstyrelsen i arbetet med att ta fram nationella riktlinjer för diabetes. I skrivande stund håller han på att avsluta årets revidering. Ovanpå detta är han ordförande för Nationella programrådet för diabetes vid Sveriges Kommuner och Landsting (SKL) och medlem i Läkemedelsverkets vetenskapliga råd. Det senare innebär heldagsmöten en gång i månaden.

– Jag inser att jag börjar bli en myndighetsperson, säger Claes-Göran och skrattar.

– Det känns intressant och roligt att jag kan använda min erfarenhet och expertis på det sättet – myndighetsuppdragen syftar ju också till att göra det bättre för patienterna. Men det var på ett sätt tråkigt att lämna personer som jag hade träffat ett par gånger om året i kanske 30 år. Samtidigt är ingen människa oumbärlig. Jag har duktiga kollegor som tar över.

Det är en solig sommarförmiddag när vi hörs på telefon. Claes-Göran sitter hemma i lägenheten i Solna, bara några minuters promenad från KI, där han alltså fortfarande är anställd som forskare. I laboratoriet är han i regel flera gånger i veckan – om han inte är i sommarhuset i skärgården eller på något utlandsjobb. Vid sidan om sina nationella uppdrag leder Claes-Göran sedan många år tillbaka forskningsprojekt i Vietnam, Malaysia, Uganda och Bolivia – länder där Sida har stöttat forskarutbildningar. Syftet är att förbättra diabetesvården och förebygga den ökade förekomsten av typ 2-diabetes.

– Diabetes ökar stort i länder i Asien och Afrika i och med att livsstilen håller på att förändras där, särskilt i städerna. Människor börjar få det bättre, de köper mat som inte är så bra och skaffar motorcyklar och bilar. Det är spännande att följa och att få vara med och försöka hitta lösningar, säger Claes-Göran.

I början på juni i år kom han hem från en tur i Uganda där en av utmaningarna är de begränsade möjligheterna att mäta plasmaglukos. En annan är förvaringen av insulin; då många saknar kylskåp kan insulinet som bäst förvaras ett par veckor nedgrävd i jorden. Universitetet i huvudstaden Kampala har ett direkt samarbete med KI, vilket bidrog till att Claes-Göran engagerade sig just där. Hans doktorands studier i Uganda har lärt honom vikten av att förstå människors olika villkor och tankar för att kunna försöka påverka deras livsstil.

– Många som är överviktiga vill absolut inte gå ner i vikt eftersom

Claes-Göran Östenson
Ålder: 68 år.
Bor: Lägenhet i Solna och sommarhus i Stockholms skärgård.
Familj: Fru (läkare och specialist i klinisk mikrobiologi), två döttrar och tre barnbarn.
Jobbar som: Seniorprofessor och forskargruppsledare för diabetes typ 2 vid Karolinska Institutet i Stockholm samt innehar flera myndighetsuppdrag, bland annat ordförande för Nationella programrådet för diabetes och medlem i Läkemedelsverkets vetenskapliga råd.
Favoritmat: Vågar jag säga annat än fisk och grönsaker? (men det är faktiskt sant)
Gör på fritiden: Går gärna länge på konstmuseer och har sedan många år abonnemang på Stockholms Konserthus. Spelar piano, reser, plockar svamp och bär i skogen på sommaren och åker långfärdsskridskor på vintern.
Det visste du inte om Claes-Göran: Har tillsammans med vänner vandrat i bland annat Alperna, Dolomiterna, Västbengalen strax under Himalayas toppar och i Yunnanprovinsen i sydvästra Kina.

att de är rädda för att folk då ska tro att de är sjuka och har Aids. Att uppmana människor att motionera genom att jogga väcker också motstånd, eftersom det i regel bara är barn som springer omkring i värmen.

Det var inte självskrivet att Claes-Göran skulle komma att bli en flitigt resande diabetesdoktor eller ens läkare. Han växte upp i Linköping med sina föräldrar och sin bror. Pappan arbetade inom spannmålshandeln och mamman var tandsköterska. Claes-Göran tyckte att det mesta i skolan var roligt men var särskilt intresserad av kemi. På gymnasiet hade han en klasskompis som hade snöat in sig på diabetes och en dag visade han Claes-Göran en artikel av KI-forskaren Rolf Luft – då en av de internationellt främsta inom sjukdomen. Artikeln väckte Claes-Görans nyfikenhet – kanske mer än han anade. Efter studenten sökte både Claes-Göran och hans kompis till läkarlinjen i Uppsala.

–Det var nog inte så överlagt. Jag hade inga läkare i släkten. Egentligen hade jag ett större intresse vid sidan av naturvetenskapen: konst och litteratur. Jag läste mycket, gick gärna på muséer och anordnade några gånger föreställningar med samtida poeter på skolan. Men jag hade väl en aning om att läkaryrket skulle kännas viktigt och väsentligt. Och mina föräldrar tyckte att det lät bra.

Redan andra terminen gick han till institutionen för histologi, där man forskade om diabetes, och sade att han ville börja forska. Han fick då i uppgift av professorn Claes Hellerström att skriva en uppsats om epifysen och tillbringade timmar på biblioteket där han slog i tjocka böcker och bläddrade i dammiga tidskrifter. Idag kommer Claes-Göran knappt ihåg vad han skrev, men professorn gillade det och erbjöd den då 20-årige Claes-Göran att bli doktorand hos honom. Tio år senare, 1979, disputerade han på en avhandling om det blodsockerhöjande hormonet glukagon (som med tiden visade sig ha stor betydelse för blodsockerkontrollen vid diabetes). Dessförinnan hade han hunnit göra sin AT i Västerås och jobbat deltid som lärare i histologi och cellbiologi för medicinstudenterna i Uppsala. Än idag tycker han att det är spännande med cellbiologi och hur man kan koppla mikroskopiska och molekylära funktioner till människor och samhälle.

–Jag har svårt att säga varför det blev just diabetes. Kanske berodde det på den där artikeln som min vän visade mig på gymnasiet. En annan orsak kan vara att Claes Hellerström var en väldigt trevlig, kunnig och stimulerande person med ett stort nätverk inom diabetesforskningen.

Efter avhandlingen rekryterades Claes-Göran direkt till Karolinska i Stockholm. De sökte någon till kliniken och laboratoriet som hade disputerat inom diabetes och på den tiden var det inte så många. Patientmässigt hade Claes-Göran inte mycket erfarenhet, men efter fem år på sjukhuset blev han specialist i klinisk endokrinologi. I slutet på 80-talet bör-

jade han och hans chef, professorn Suad Efendić, diskutera hur man skulle kunna göra en mer omfattande kartläggning över riskfaktorerna för och förekomsten av typ 2-diabetes. Detta var startskottet till det som sedermera blev den så kallade Stockholmsstudien, Stockholms diabetespreventiva program (SDPP), som Claes-Göran ledde. I studien ingick 8 000 personer i åldrarna 35–56 år, utspridda i fem kommuner i Storstockholm. När den drogs igång i början på 90-talet var det en av de största i sitt slag, även internationellt sett, och den första som visade att såväl kaffedrickande som minskad stress och ett stort socialt nätverk minskar riskerna för sjukdomen. Cirka tio år efter starten gjordes en uppföljning av drygt 70 procent av deltagarna. För Claes-Göran innebar arbetet med Stockholmsstudien en ny värld. Plötsligt hade han medarbetare som var allt från gymnastikdirektörer och dietister till tränare på Friskis & Svettis och chefer för restauranger och livsmedelsbutiker. Han var regelbundet ute på informationsmöten där han träffade projektledarna i respektive kommun. Där pratade han om diabetes och varför det var viktigt att alla hjälpte till – att matbutiker frontade grönsaker och restauranger erbjöd nyttig mat.

– Tyvärr såg vi inte någon effekt av arbetet som mer generellt upplyste invånarna om vikten av att motionera och äta rätt. De studier vi har gjort där en mindre grupp personer i riskzonen för att få diabetes erbjöds hjälp som personliga tränare och dietister, har däremot gett effekt. Slutsatsen är att om man ska rekommendera prevention så bör det vara på individnivå.

Hur kändes det att projektet inte gav de effekter som du kanske hade hoppats på?

–Även om det först blev en besvikelse var det ju viktigt att få erfarenheten. Syftet var att koppla ihop socialmedicin med endokrinologi och diabetesvård och jag är väldigt glad över det vi gjorde. Personligen har det gett mig större förståelse för hur livsstil och omgivningsfaktorer samverkar med genetiken vid utveckling av inte bara typ 2-diabetes utan även obesitas.

Under arbetet med studien blev Claes-Göran chef för Karolinska sjukhusets diabetespreventiva enhet och totalt har han och hans kollegor publicerat 80-90 vetenskapliga artiklar baserade på projektet. Ett 15-tal personer har även använt studien i sina doktorsavhandlingar och Claes-Göran har varit handledare till merparten. Nyligen avslutades även en 20-årsuppföljning av deltagarna i SDPP.

– Det har varit jättespännande att gå från cell- till samhällsnivå. Uppgiften som forskare, att föra ut sin kunskap i samhället, tycker jag är oerhört viktig.

Cellnivån har Claes-Göran fått uppleva i laboratoriet på KI. Sedan han började forska har han varit engagerad i att hitta nya läkemedel mot typ 2-diabetes – en resa som pågår än. På 90-talet i Vietnam började han titta på inhemska växter som har använts för att lindra diabetes i över 2 000 år. Claes-Göran har haft flera doktorander, bland annat i Bolivia och Malaysia, som har forskat på att hitta den effektiva substansen i lokala naturläkemedel och försöka framställa den syntetiskt. Kliniska studier har genomförts i Vietnam och flera experiment har gjorts på den koloni av råttor med spontan typ 2-diabetes som Claes-Göran tog hem till KI från Japan för snart 30 år sedan.

– Utländska växtextrakt får man inte testa hur som helst i Sverige, och att ta fram nya läkemedel är komplicerat, tidskrävande och dyrt – det kan kosta miljarder. Naturligtvis vill alla forskare hitta nya mediciner och jag hoppas att vi kommer lyckas. Jag har en doktorand i Bolivia som presenterar en avhandling på en ny substans nästa år. Men att gå från det till ett godkänt läkemedel är en lång resa.

Vad tänker du om att du kom att viga ditt liv åt just diabetes?

– Jag är jättenöjd. Arbetet har gett mig så mycket, bland annat många internationella kontakter. 2010 var jag till exempel en av arrangörerna till en stor europeisk diabeteskongress på Stockholmsmässan med 18 000 deltagare från hela världen. Jag har aldrig haft någon tanke på att jag skulle vilja jobba med något annat, säger Claes-Göran och tillägger:

– Det är ju så när man håller på med forskning: man blir aldrig färdig. Man har alltid sökarljuset på och känner ett driv.

Hur har det funkat att kombinera karriär med familjeliv?

– Jag har ju jobbat mycket genom åren men om du frågar mina två döttrar så tror jag inte att de har tyckt att det har varit så pestigt med en pappa som har varit läkare – de är själva doktorer och forskare idag. Det ser jag som ett gott tecken, som att det jag har hållit på med måste ha verkat ganska kul – även om det förstås ibland har tagit tid från familjen.

Claes-Görans plan är att fortsätta inom diabetesfältet på en regulatorisk nivå och med forskningen. Drömmen är att få hålla på så länge han får och orkar. Men han ser också fram emot att tillbringa ännu mer tid med sina tre barnbarn – dem träffar han och hämtar på dagis så ofta han kan.

– Barnbarnen är en jätterolig del av mitt nya liv. När jag är med dem minns jag roliga detaljer från mina egna barns uppväxt, men slipper känna något ansvar för uppfostran.

Louise Fauvette
Frilansjournalist
På uppdrag för DiabetologNytt

Forskare cyklar 250 mil, för bättre fothälsa vid diabetes

En reseberättelse

Med avhandlingen i cykelväskan gav jag mig, Ulla Hellstrand Tang, ut på Hoj17 för att fullgöra högskolans tredje uppgift, att föra ut forskningsresultat för diskussion i samhället. Hoj17 är en klimatsmart aktion för bättre fothälsa organiserat av Göteborgs Diabetesförening. Under den 250 mil långa cykelturen arrangerade diabetesföreningarna runt om i landet, från Jonsered i väst till Jokkmokk i norr, fotmöten för att diskutera varför det är så stora regionala skillnader i prevention och behandling av fotkomplikation vid diabetes. Politiker och vårdprofession uppmanades att tillsammans med patientorganisationerna samlas kring en gemensam strategi för minskade fotskador.

Vid finalen av Hoj17 på Jonsereds Herrgård medverkade, från vänster, Stefan Hellstrand, Tekn. Dr.; Fredrik Löndahl, ordf. i Diabetesförbundet; Kent Olaisson, ordf. i Diabetesföreningen i VGR; Leif Sundberg, patientrepresentant, Cafégruppen; Conny Jalkegård, Erimed; Mirjana Vidicek, medicinsk fotterapeut i VGR; Christel Dahlström, medicinsk fotterapeut, medicinmottagningen, Mölndals sjukhus, Sahlgrenska Universitetssjukhuset; Margareta Jonsson, medicinsk fotterapeut i VGR; Ninni Jonsson, Cinnamon samt Ulla Hellstrand Tang, Med. Dr. och leg. ortopedingenjör, Ortopedteknik, Sahlgrenska Universitetssjukhuset.

Initiativet till Hoj17 togs den 16 april 2016 av mig, Monica Ullbrandt, och Birgitta Kihlberg, båda aktiva i diabetesrörelsen. Från patientorganisationerna formulerades uppropet för Hoj17, nämligen ”Kolla min fot”. Kravet är i enlighet med Socialstyrelsens rekommendationer att alla personer med diabetets bör fotundersökas, riskgraderas och erbjudas adekvat prevention och vård för att främja god fothälsa som förhindrar fotsår och amputation[1]. Flera källor pekar mot att vården är ojämlik. Jämförelser från Socialstyrelsen visar att det är stora regionala skillnader i andelen amputationer vid diabetes[2]. Från Nationella Diabetesregistret presenteras att det beror på var i landet man bor ifall man som diabetiker får sina fötter fotundersökta eller inte[3]. I Västra Götalandsregionen (VGR) finns skillnader i vilken utsträckning personer med typ 2 diabetes remitteras till fotvård[4].

Faktaruta

Ulla Hellstrand Tang, disputerade den 30 mars med avhandlingen ”The Diabetic Foot – assessment and assistive devices” vid Institutionen för Kliniska vetenskaper, Avdelning för Ortopedi [4]. I avhandlingen föreslås ett strukturerat sätt att undersöka fötterna vid diabetes med hjälp av checklistan i webprogrammet D-Foot. Vidare framkommer att enklare prefabricerade inlägg kan användas för prevention av fotsår. Forskningsresultaten testas nu i klinisk vardag på Ullas arbetesplats, Ortopedteknik, Område 3, Sahlgrenska Universitetssjukhuset.

Hoj17 (www.hoj17.se) fick stöd av Diabetesförbundet, VGR och privata aktörer inom ortopedteknik och sårvård.

Förberedelser

Förberedelserna satte igång under sommaren 2016. Rutten planerades på cykelvänliga vägar med hjälp av cykelkartor. Cykel, cykelvagn, packväskor, tält, sovsäck,

Vid paneldebatten i Jonsered deltog sjukhusdirektör Agnetha Folestad, Lundby Capio Närsjukhus; Christel Dahlström, medicinsk fotterapeut, medicinmottagningen, Mölndals sjukhus, Sahlgrenska Universitetssjukhuset; Susanne Asteberg, sårsköterska, ortopedmottagningen, Mölndals sjukhus, Sahlgrenska Universitetssjukhuset; Fredrik Löndahl, ordf. i Diabetesförbundet; Kent Olaisson, ordf. i Diabetesföreningen VGR; Pär Samuelsson, Nationella Diabetesregistret; Ulla Hellstrand Tang, Med. Dr. och leg. ortopedingenjör, Ortopedteknik, Sahlgrenska Universitetssjukhuset; Stefan Hellstrand, Tekn. Dr. samt Leif Sundberg, Cafégruppen.

gasolkök införskaffades och verktygslådan gjordes iordning. Forskningsenkäter sammanställdes. I enkäterna fanns frågor om huruvida fotundersökning, fotvård, ortopedtekniska hjälpmedel och vård i multidisciplinära fotteam erbjuds vid diabetes. Aktiviteter pågick runt om i landet. Lokalföreningarna bokade plats för möten, bjöd in politiker och press, ordnade cykelkortege och fotkontroller samt spred information om fotmötena.

Debatt och möten

Den 30 juli 2017, efter 90 dagar och 250 underbara mil på cykel når jag målet, Jonsereds Herrgård. Vid finalen la Göteborgs Diabetesförening upp fotfrågan på bordet. Kalla fakta om den ojämlika fotsjukvården för personer med diabetes i Västra Götalandsregionen presenterades. I paneldebatten gavs handfasta förslag till hur VGR kan halvera antalet fotsår och amputationer. Patientrepresentant Leif Sundberg berättade hur värdefullt det är att ha en fot fri från fotsår. Positivt utfall, i ekologiska, ekonomiska och sociala termer, vid en halvering av amputationer presenterades av Tekn. Dr. Stefan Hellstrand. Arrangörerna avslutade mötet med önskan att till hösten 2017 sitta ner vid samma bord som politiker för att lägga en plan för minskade amputationer i VGR. Avsikten är att i gemensam aktion verka för en fotsjukvård i toppklass, med och för patienten.

Men låt oss nu börja från början. Den 29 april gick startskottet för Hoj17 från Jonsereds Herrgård under hejarop och salut. Sjukhusdirektör Agnetha Folestad, Capio Lundby Närsjukhus, lyckönskade mig på färden mot Norrköpin.

Strålande resultat

Det första mötet, i Norrköping den 12 maj var framgångsrikt. Diabetesförbundets direktör Cecilia Gomez, Östergötlands Diabetesförening och fotterapeuter bokade in mötestid med politiker. Syftet var att till hösten diskutera strategier för bättre prevention och vård av fotkomplikation vid diabetes i Östergötland.

Tre veckor efter starten cyklade jag in till mötet i Stockholm. Politiker, patientföreträdare och vårdprofessionen bestämde att till hösten 2017 samlas för att diskutera vilka regionala fotproblem som Stockholm har att lösa. Färre fotsår, färre amputationer och bättre livskvalitet för personer med diabetes sattes upp som långsiktigt mål.

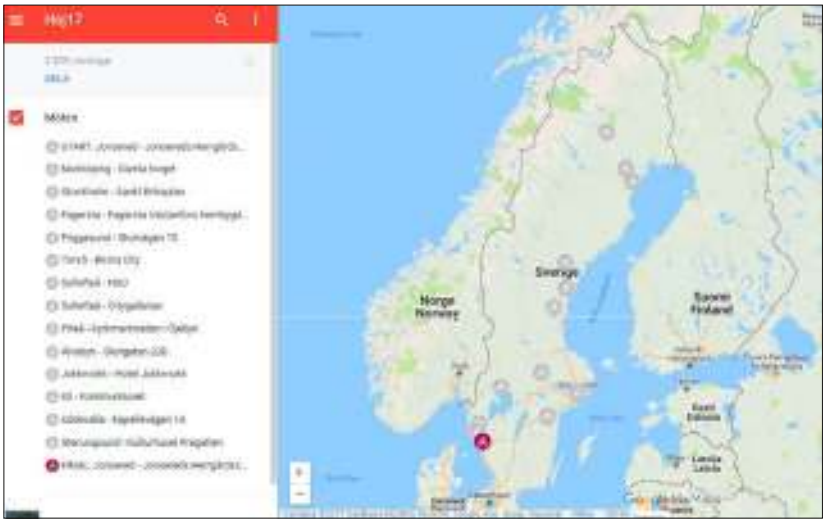
På väg norrut sker möten i Västmanland, Hälsningland och Västernorrland. Efter nio veckors cykling kommer jag till mötet i Piteå. Där krokar diabetesförbundets representant arm med fotterapeuter och lokalföreningen för att tillsammans verka för att alla personer med diabetes ska fotundersökas årligen, enhetligt en förbestämd god struktur. Fötter i riskzonen bör remitteras vidare för åtgärder (ortopedteknik och specialistvård).

På väg till mötet i Jokkmokk passerar jag det imponerande vattenfallet i Storforsen och Polcirkeln. Lappland imponerar.

I Jokkmokk samlades fotterapeuter, representanter från Diabetesföreningen Jokkmokksbygden med omnejd, Diabetesförbundet och Hoj17 för att tillsammans med politiker jobba

Ulla eskorterades till torgmötet i Norrköping.

Polcirkeln passeras.



Cykelturen gick från Jonsered i väster till Jokkmokk i norr. I åtta regioner ordnade lokala diabetesföreningar 13 debattmöten.

för en bättre prevention och vård av fotkomplikation vid diabetes i Norrbotten.

Naturliv

Trettionio nätter somnade och vaknade jag till naturens ljud i mitt tält. Tranor, orrar, enkelbeckasiner och brölande råbockar gav krydda åt naturlivet. Det blev soliga frukoststunder vid blänkande vatten och annorlunda middagsplatser. Åsynen av björnspåret i granskogen fick min puls att öka. Den röda älgkalven i björksnåret var förtjusande.

Lyckat fotmöte på Hotell Jokkmok

Resan söderut

Cykel, cykelvagn och tio packväskor färdades exotiskt på Inlandsbanan söderut från Jokkmokk till Värmland. Vid mötet i Kil presenterades Värmlandsmodellen av diabetesfotkoordinator Marie Bejmo. Hon fängslade publiken när hon berättade om ett 17 års arbete för att halvera antalet amputationer i länet. Tekn. Dr. Stefan Hellstrand visade värdet av en hållbar hälso- och sjukvårdssatsning, att minska antalet fotsår och amputationer.

Efter 13 veckor på cykel når jag VGR och deltar i tvärprofessionella möten i Uddevalla, Stenungsund och Jonsered. Patienter gav värdefulla berättelser, bl. a. om förekomst av fotsår som ej behandlats multidisciplinärt.

Mission completed

Under Hoj17, ett unikt klimatsmart projekt, har fothälsan diskuterats i nio regioner. Tretton möten har arrangerats. Kravet på fotundersökningar för alla med diabetes och insatser för de med riskfot fick stor uppmärksamhet i media. Hoj17 renderade inslag i TV nyheter, fyra sändningar i lokalradio, 15 tidningsartiklar och fick tusentals läsare i de sociala medierna. Tvärprofessionella nätverk för samverkan har skapats. Patientorganisationerna, fotterapeuter, ortopedingenjörer, fysioterapeuter, läkare, sjuksköterskor har blivit inspirerade att tillsammans med politiker gå till handling för bättre prevention och vård av fotkomplikation vid diabetes. Landsting som redan gjort en framgångsresa, att halvera antalet amputationer, står med öppna armar för att ta emot delegationer från andra delar av landet. Här kan nämnas Södermanland och Värmland som kan visa föredömliga till följd av decennier av strukturerat förbättringsarbete.

Ulla Hellstrand Tang
För DiabetologNytt

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Sett & Hört

Gemensamt ansvar att svensk diabetesvård är av yttersta världsklass, då det gäller diabeteshjälpmedel. Debattinlägg.

Alltsedan möjligheten att behandla personer med diabetes med insulin tillkom har vården och redskapen för behandling utvecklats avsevärt. Utvecklingen har skett i samarbete mellan vårdprofessioner, forskare, personer med diabetes, anhöriga, vårdorganisatörer och industri. Därför uppfattar vi att Sarkadi med flera i Dagens Medicin försöker slå in öppna dörrar när de skriver att vården behöver samskapas med personer med diabetes.

Som läkare i diabetesvården vet vi att företrädare för personer med diabetes, oftast representerade av Diabetesförbundet, är en viktig del i utformandet av diabetesvården. Diabetesförbundet är en självklar del av paraplyorganisationen Nationella diabetesteamet. Vården genomförs i samråd med personen med diabetes och, hos barn med diabetes, i samråd också med barnets familj. Vad som passar en familj är inte alltid bra för en annan.

Det går inte att säga att vissa familjers lösningar är mer spetsbetonade än andras då varje person är expert på sitt eget liv, och värd att respektera utifrån sitt enskilda val. Därför ser vi att den av Ekholm med flera lanserade titeln ”spetspatienter” avviker från vårdens humanistiska ideal och modern vårdideologi som baseras på individualiserad vård, se Dagens Medicin.

Teknikutvecklingen har förbättrat diabetesvården och ger hopp om ytterligare förbättringar inom en snar framtid. Förbättringar av tekniska hjälpmedel kan göras av många olika aktörer, vanligast är den kommersiella industrin men utvecklingen kan också drivas av andra såsom akademi eller användare. Kraven på produkten måste dock vara desamma oavsett vem som utvecklar den. Därför finns krav på CE-märkning och godkännande av tillsynsmyndigheter. Beslutsfattarna, i form av regering, riksdag och myndigheter, har givit vårdprofessionerna ansvaret att se till att vården bedrivs i enlighet med vetenskap och beprövad erfarenhet.

Som förskrivare av hjälpmedel är vi ansvariga för att användaren får säkra och välfungerande hjälpmedel samt att användaren har fått utbildning i och kunskap om hur dessa ska användas på ett säkert och ändamålsenligt sätt. Därför vände vi barndiabetesläkare oss till Läkemedelsverket och Inspektionen för vård och omsorg och bad om råd för hur vi skulle förhålla oss till att anhöriga modifierar insulinpumpar, i synnerhet då pumpanvändaren är ett barn som inte på egen hand kan förväntas göra en riskanalys.

En jämförelse kan göras med bilar. Även en extremt duktig bilförare är beroende av att kunna förlita sig på att gas, broms, ratt och säkerhetsbälte fungerar som de ska.

På samma sätt behöver även den mest erfarna person med diabetes ha tillgång till säkra hjälpmedel för att genomföra insulinbehandlingen. Här behöver regelverk och myndighetsfunktioner utvecklas för att passa in i dagens snabba teknikutveckling. När dagens regelverk skrevs hade nog ingen trott att insulinpumpar skulle kunna programmeras om. Vem bär ansvaret för att förhindra en olycka innan den sker? Den relevanta frågan är inte om något barn ännu kommit till skada genom obehöriga ingrepp i medicinteknisk utrustning, utan hur vi ska förhindra att det sker.

Vi har ett gemensamt ansvar att se till att svensk diabetesvård är av yttersta världsklass och att personer med diabetes i Sverige har tillgång till moderna, säkra och välfungerande hjälpmedel på jämlik basis. Tillsammans behöver vi fortsätta arbetet med att skapa största möjliga nytta med tillgängliga godkända hjälpmedel.

Skriven av: Frida Sundberg, Anna Olivecrona och David Nathanson. Från www.dagensmedicin.se

Nyhetsinfo 3 augusti 2017
www red DiabetologNytt

NDRs expert Staffan Björck går emot Socialstyrelsen. T2D patienter ska ha bättre målblodtryck. Nu!

Enligt Staffan Björck visar data från diabetesregistret även att patienter med typ 2-diabetes som går på specialistkliniker har bättre tryck än de som går i primärvården - och då går det bättre.

Socialstyrelsen är ute på tunn is när den inte tar hänsyn till aktuell forskning kring blodtrycksgränser i de nationella riktlinjerna, anser kritiker, skriver Jens Key www.dagensmedicin.se

– Det är rätt häftigt att säga att man inte rekommenderar patienter med diabetes att ha normalt blodtryck längre. Det ett stort experiment med en halv miljon människor som har diabetes, säger läkaren Staffan Björck, docent i njurmedicin vid Sahlgrenska akademien, Göteborgs universitet, till Dagens Medicin.

Fram till för några år sedan fanns normalt blodtryck som tydligt målvärde i Socialstyrelsens riktlinjer för diabetsvården. Men kring 2010-2011 började myndigheten ändra uppfattning och 2015 försvann det ur riktlinjerna, berättar han. Samtidigt avstannade den förbättring av blodtrycket för patienter med diabetes som kunnat följas i det nationella diabetesregistret sedan starten. Något Staffan Björck anser har ett tydligt samband.

– Ja rimligen. Det kom signaler om att blodtrycksrekommendation skulle höjas runt 2010-2011 och det är där vi ser ett trendbrott.

I fjol publicerade Brittish Medical Journal Staffan Björcks stora studie över alla personer i diabetesregistret. Den visade på ett linjärt samband mellan ökat blodtryck och ökad risk för hjärt- kärlsjukdomar. Staffan Björck hoppades att resultat skulle göra att Socialstyrelsen ändrade uppfattning när myndigheten i år publicerade nya riktlinjer. Men förhoppningen kom på skam.

– Därför blir jag mycket besviken när uppdaterade riktlinjer inte har tagit hänsyn till litteratur efter 2008. Socialstyrelsen borde ha samlat expertis och värderat ny forskning, säger han.

Enligt Socialstyrelsen finns det dock inget i riktlinjerna som hindrar den behandlande läkaren att sätta upp individuella blodtrycksmål för sina patienter.

Antyder inte din kritik att den behandlande läkaren inte är tillräckligt insatt? Det är ju ändå den personen som har behandlingsansvaret.

– Jo, men vi har 1 200 vårdcentraler som alla behandlar typ 2 diabetes - och som dessutom har en oändlig massa andra krämpor att ta hand om. Så de vill ha robusta riktlinjer. De håller sig vid de rättesnören som finns, det är inte lätt, säger Staffan Björck.

Han förklarar att den tjocka lunta som utgör de nationella riktlinjerna inte är något som lätt stoppas i fickan för att sedan användas i den kliniska vardagen. Det som läkarna kommer ihåg är de indikatorer som finns. Och i riktlinjerna finns blodtrycksmålet 140/85 mm Hg angivet som eventuellt behandlingsmål.

– Så riktlinjerna blir styrande ändå. Det är inte det finstilta som läses.

Han har fört fram sin kritik till Socialstyrelsen men svaret är att riktlinjerna ligger fast.

– Så det är skrivet i stjärnorna när man tittar på detta igen.

http://www.bmj.com/content/354/bmj.i4070

FRÅN SOCIALSTYRELSEN

Hej Staffan,
Jag har fått din fråga vidarebefordrad och ska försöka klargöra hur vi skriver och resonerat i relation till blodtryckssänkning i de nationella riktlinjerna för diabetesvård. Hör såklart av dig om du har ytterligare frågor eller synpunkter.

1. Vi har i de nationella riktlinjerna för diabetesvård inga rekommendationer som säger vilket blodtrycksmål som ska uppnås. Våra riktlinjer har i stor del ett styr- och ledningsperspektiv och är inte utformade att ge rekommendationer om exempelvis blodtrycksmål utifrån olika förutsättningar.

a. Det vi säger i våra rekommendationer är att blodtryckssänkande behandling av personer med diabetes och högt blodtryck har hög prioritet/angelägenhetsgrad (se utdrag ur tillstånd- och åtgärdslistan nedan).

2. I det vetenskapliga underlaget skriver vi dock om behandlingsmål generellt inom diabetesvården (se länk nedan). Huvudbudskapet där är individanpassning utifrån olika förutsättningar. Vårat resonemang där skrevs inför publiceringen 2015 och bygger på referenser från 2015. Jag har även stämt av de referenserna med senare utgivna internationella konsensusdokument. Bedömning är att de är överensstämmande med hur vi uttrycker oss. Ett utdrag (se länk till fullständigt dokument längre ner):

”Ett riktvärde för behandlingsmål när det gäller blodtryck kan vara under 140/85 mm Hg. Målet bör utformas utifrån en individuell bedömning av nytta och risk. Lägre blodtrycksmål kan övervägas för unga patienter och för patienter med förhöjd albuminutsöndring ▶

i urinen (makroalbuminuri), eller förhöjd kardiovaskulär risk - förutsatt att behandlingen kan ges utan besvär för patienten."

Vilket får anses vara överensstämmande med vad man ifrån ex ADA skriver 2017:

…Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of 140 mmHg and a diastolic blood pressure goal of 90 mmHg. A Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden...

Vi är medvetna om att nya ESH/ESC guidelines kommer 2018 och att det finns de som argumenterar för sänkta målvärden på basen av SPRINT. Där fanns ju dock inte diabetiker med varför betydelsen för utformning av diabetes-guidelines är osäker. Vi följer såklart utvecklingen kontinuerligt i vår förvaltning av riktlinjerna och gör vid behov uppdateringar. I nuläget finns dock ingen plan att ändra våra skrivningar angående behandlingsmål.

Kommentar

I avvaktan på Framtiden förefaller det rimligt

... att Sverige följer ADA 2017, som utgör uppdatering av senaste och bästa vetenskapliga dokumentationen.

... att patienter med typ 2 diabetes kan ha målblodtryck 130/80 för individer med hög kardiovaskulär risk, yngre patienter och patienter med begynnande njurpåverkan i form av mikroalbuminuri - och patienter som klarar detta målblodtryck utan biverkningar.

... att patienter med typ 1 diabetes har som tidigare målblodtryck 130/80.

Nyhetsinfo 1 augusti 2017
www red DiabetologNytt

Se också sid 249.

New ADA/AADE Standards Combine Diabetes Education. Diab Care

The American Diabetes Association and the American Association of Diabetes Educators have combined the concepts of diabetes self-management education and support for the first time in their updated guidelines published in Diabetes Care and the Diabetes Educator.

Diabetes self-management education (DSME)

The document outlines 10 specific standards for DSMES programs, including individualization, quality improvement, evaluation of population served, participant progress and ongoing support

New recommendations from the American Diabetes Association (ADA) and American Association of Diabetes Educators (AADE) combine the concepts of diabetes self-management education and support for the first time.

The document, published online July 28 in both Diabetes Care and the Diabetes Educator, is an update from 2014, when guidelines for diabetes self-management support and diabetes self-management education had been outlined separately.

Today, the view is that "diabetes self-management education and support (DSMES) is a critical element of care for all people with diabetes and those at risk for developing the condition," write task force cochairs and certified diabetes educators Joni Beck, PharmD, and Deborah A Greenwood, PhD, RN, and colleagues.

DSMES is the ongoing process of facilitating the knowledge, skills, and ability necessary for prediabetes and diabetes self-care, as well as activities that assist a person in implementing and sustaining the behaviors needed to manage his or her condition on an ongoing basis, beyond or outside of formal self-management training," they explain.

While the standards define evidence-based DSMES services that meet or exceed Medicare's diabetes self-management training (DSMT) regulations, they don't actually guarantee reimbursement. "The hope is that payers will view these standards as a tool for reviewing DSMES reimbursement requirements and consider change to align with the way their beneficiaries' engagement preferences have evolved," the authors say.

Currently, less than 5% of Medicare beneficiaries use the DSMES benefits that are covered.

The standards apply to diabetes educators in a variety of settings and within new and emerging models of care, such as virtual visits, accountable care organizations, patient-centered medical homes, and value-based payment models.

These same DSMES standards are used both for ADA recognition and AADE accreditation and also

can serve as a guide for nonaccredited and nonrecognized diabetes education providers.

Although there is overlap between DSMES services and those of the National Diabetes Prevention Program (National DPP) lifestyle-change program, the two are tailored to different audiences (diabetes vs prediabetes) and have different goals (diabetes management vs prevention). Recognition of DPP programs is handled by the US Centers for Disease Control and Prevention. Centers providing both types of services have been shown successful, but they need to meet both sets of standards.

The new document details 10 specific standards for DSMES programs: internal structure, stakeholder input, evaluation of population served, quality coordinator overseeing DSMES services, the DSMES team, curriculum, individualization, ongoing support, participant progress, and quality improvement.

While previous standards have used the term "program," the current terminology is "services," which "more clearly delineates the need to individualize and identify the elements of DSMES appropriate for an individual.

This revision encourages providers of DSMES to embrace a contemporary view of the new complexities of the evolving healthcare landscape," the authors write.

Expect the next revision sooner than 3 years from now, they say. "Given the rapidly changing healthcare environment and the ever-growing field of technology, the 2017 Standards Revision Task Force recognizes the potential need to review the literature for evidence-driven updates more frequently in the future as advances in healthcare delivery are evolving."

Diabetes Care. Published online July 28, 2017.
From www.medscape.com

Article

http://care.diabetesjournals.org/content/35/11/2393

By the most recent estimates, 18.8 million people in the U.S. have been diagnosed with diabetes and an additional 7 million are believed to be living with undiagnosed diabetes. At the same time, 79 million people are estimated to have blood glucose levels in the range of prediabetes or categories of increased risk for diabetes. Thus, more than 100 million Americans are at risk for developing the devastating complications of diabetes (1).

Diabetes self-management education (DSME) is a critical element of care for all people with diabetes and those at risk for developing the disease. It is necessary in order to prevent or delay the complications of diabetes (2–6) and has elements related to lifestyle changes that are also essential for individuals with prediabetes as part of efforts to prevent the disease (7,8). The National Standards for Diabetes Self-Management Education are designed to define quality DSME and support and to assist diabetes educators in providing evidence-based education and self-management support. The Standards are applicable to educators in solo practice as well as those in large multicenter programs—and everyone in between. There are many good models for the provision of diabetes education and support. The Standards do not endorse any one approach, but rather seek to delineate the commonalities among effective and excellent self-management education strategies. These are the standards used in the field for recognition and accreditation. They also serve as a guide for nonaccredited and nonrecognized providers and programs.

Because of the dynamic nature of health care and diabetes-related research, the Standards are reviewed and revised approximately every 5 years by key stakeholders and experts within the diabetes education community. In the fall of 2011, a Task Force was jointly convened by the American Association of Diabetes Educators (AADE) and the American Diabetes Association (ADA). Members of the Task Force included experts from the areas of public health, underserved populations including rural primary care and other rural health services, individual practices, large urban specialty practices, and urban hospitals. They also included individuals with diabetes, diabetes researchers, certified diabetes educators, registered nurses, registered dietitians, physicians, pharmacists, and a psychologist. The Task Force was charged with reviewing the current National Standards for Diabetes Self-Management Education for their appropriateness, relevance, and scientific basis and updating them based on the available evidence and expert consensus.

The Task Force made the decision to change the name of the Standards from the National Standards for Diabetes Self-Management Education to the National Standards for Diabetes Self-Management Education and Support. This name change is intended to codify the significance of ongoing support for people with diabetes and those at risk for developing the disease, particularly to encourage behavior change, the maintenance of healthy diabetes-related behaviors, and to address psychosocial concerns. Given that self-management does not stop when a patient leaves the educator's office, self-management support must be an ongoing process.

Although the term "diabetes" is used predominantly, the Standards should also be understood to apply to the education and support of people with prediabetes. Currently, there are significant barriers to the provision of edu- ▶

cation and support to those with prediabetes. And yet, the strategies for supporting successful behavior change and the healthy behaviors recommended for people with prediabetes are largely identical to those for individuals with diabetes. As barriers to care are overcome, providers of DSME and diabetes self-management support (DSMS), given their training and experience, are particularly well equipped to assist individuals with prediabetes in developing and maintaining behaviors that can prevent or delay the onset of diabetes.

Many people with diabetes have or are at risk for developing comorbidities, including both diabetes-related complications and conditions (e.g., heart disease, lipid abnormalities, nerve damage, hypertension, and depression) and other medical problems that may interfere with self-care (e.g., emphysema, arthritis, and alcoholism). In addition, the diagnosis, progression, and daily work of managing the disease can take a major emotional toll on people with diabetes that makes self-care even more difficult (9). The Standards encourage providers of DSME and DSMS to address the entire panorama of each participant's clinical profile. Regular communication among the members of participant's health care teams is essential to ensure high-quality, effective education and support for people with diabetes and prediabetes.

In the course of its work on the Standards, the Task Force identified areas in which there is currently an insufficient amount of research. In particular, there are three areas in which the Task Force recommends additional research:

1. What is the influence of organizational structure on the effectiveness of the provision of DSME and DSMS?
2. What is the impact of using a structured curriculum in DSME?
3. What training should be required for those community, lay, or peer workers without training in health or diabetes who are to participate in the provision of DSME and to provide DSMS?

Finally, the Standards emphasize that the person with diabetes is at the center of the entire diabetes education and support process. It is the individuals with diabetes who do the hard work of managing their condition, day in and day out. The educator's role, first and foremost, is to make that work easier (10).

DEFINITIONS

DSME.

The ongoing process of facilitating the knowledge, skill, and ability necessary for prediabetes and diabetes self-care. This process incorporates the needs, goals, and life experiences of the person with diabetes or prediabetes and is guided by evidence-based standards. The overall objectives of DSME are to support informed decision making, self-care behaviors, problem solving, and active collaboration with the health care team and to improve clinical outcomes, health status, and quality of life.

DSMS.

Activities that assist the person with prediabetes or diabetes in implementing and sustaining the behaviors needed to manage his or her condition on an ongoing basis beyond or outside of formal self-management training. The type of support provided can be behavioral, educational, psychosocial, or clinical (11–15).

STANDARD 1

Internal structure

The provider(s) of DSME will document an organizational structure, mission statement, and goals. For those providers working within a larger organization, that organization will recognize and support quality DSME as an integral component of diabetes care. Documentation of an organizational structure, mission statement, and goals can lead to efficient and effective provision of DSME and DSMS. In the business literature, case studies and case report investigations of successful management strategies emphasize the importance of clear goals and objectives, defined relationships and roles, and managerial support. Business and health policy experts and organizations emphasize written commitments, policies, support, and the importance of

outcomes reporting to maintain ongoing support or commitment (16,17).

Documentation of an organizational structure that delineates channels of communication and represents institutional commitment to the educational entity is critical for success. According to The Joint Commission, this type of documentation is equally important for both small and large health care organizations (18). Health care and business experts overwhelmingly agree that documentation of the process of providing services is a critical factor in clear communication and provides a solid basis from which to deliver quality diabetes education. In 2010, The Joint Commission published the Disease-Specific Care Certification Manual, which outlines standards and performance measurements for chronic care programs and disease management services, including "Supporting Self-Management" (18).

STANDARD 2
External input

The provider(s) of DSME will seek ongoing input from external stakeholders and experts in order to promote program quality.

For both individual and group providers of DSME and DSMS, external input is vital to maintaining an up-to-date, effective program. Broad participation of community stakeholders, including individuals with diabetes, health professionals, and community interest groups, will increase the program's knowledge of the local population and allow the provider to better serve the community. Often, but not always, this external input is best achieved by the establishment of a formal advisory board. The DSME and DSMS provider(s) must have a documented plan for seeking outside input and acting on it.

The goal of external input and discussion in the program planning process is to foster ideas that will enhance the quality of the DSME and/or DSMS being provided, while building bridges to key stakeholders (19). The result is effective, dynamic DSME that is patient centered, more responsive to consumer-identified needs and the needs of the community, more culturally relevant, and more appealing to consumers (17,19,20).

STANDARD 3
Access

The provider(s) of DSME will determine who to serve, how best to deliver diabetes education to that population, and what resources can provide ongoing support for that population.

Currently, the majority of people with diabetes and prediabetes do not receive any structured diabetes education (19,20). While there are many barriers to DSME, one crucial issue is access (21). Providers of DSME can help address this issue by:

- Clarifying the specific population to be served. Understanding the community, service area, or regional demographics is crucial to ensuring that as many people as possible are being reached, including those who do not frequently attend clinical appointments (9,17,22–24).
- Determining that population's self-management education and support needs. Different individuals, their families, and communities need different types of education and support (25). The provider(s) of DSME and DSMS needs to work to ensure that the necessary education alternatives are available (25–27). This means understanding the population's demographic characteristics, such as ethnic/cultural background, sex, and age, as well as levels of formal education, literacy, and numeracy (28–31). It may also entail identifying resources outside of the provider's practice that can assist in the ongoing support of the participant.
- Identifying access issues and working to overcome them. It is essential to determine factors that prevent individuals with diabetes from receiving self-management education and support. The assessment process includes the identification of these barriers to access (32–34). These barriers may include the socioeconomic or cultural factors mentioned above, as well as, for example, health insurance shortfalls and the lack of encouragement from other health providers to seek diabetes education (35,36).

STANDARD 4
Program coordination

A coordinator will be designated to oversee the DSME program. The coordinator will have oversight responsibility for the planning, implementation, and evaluation of education services.

Coordination is essential to ensure that quality diabetes self-management education and support is delivered through an organized, systematic process (37,38). As the field of DSME continues to evolve, the coordinator plays a pivotal role in ensuring accountability and continuity in the education program (39–41). The coordinator's role may be viewed as that of coordinating the program (or education process) and/or as supporting the coordination of the many aspects of self-management in the continuum of diabetes and related conditions when feasible (42–49). This oversight includes designing an education program or service that helps the participant access needed resources and assists him or her in navigating the ▶

health care system (37,50–55).

The individual serving as the coordinator will have knowledge of the lifelong process of managing a chronic disease and facilitating behavior change, in addition to experience with program and/or clinical management (56–59). In some cases, particularly in solo or other small practices, the coordinator may also provide DSME and/or DSMS.

STANDARD 5
Instructional staff

One or more instructors will provide DSME and, when applicable, DSMS. At least one of the instructors responsible for designing and planning DSME and DSMS will be a registered nurse, registered dietitian, or pharmacist with training and experience pertinent to DSME, or another professional with certification in diabetes care and education, such as a CDE or BC-ADM. Other health workers can contribute to DSME and provide DSMS with appropriate training in diabetes and with supervision and support.

Historically, nurses and dietitians were the main providers of diabetes education (3,4,60–64). In recent years, the role of the diabetes educator has expanded to other disciplines, particularly pharmacists (65–67). Reviews comparing the effectiveness of different disciplines for education have not identified clear differences in the quality of services delivered by different professionals (3–5). However, the literature favors the registered nurse, registered dietitian, and pharmacist serving both as the key primary instructors for diabetes education and as members of the multidisciplinary team responsible for designing the curriculum and assisting in the delivery of DSME (1–7,68).

Expert consensus supports the need for specialized diabetes and educational training beyond academic preparation for the primary instructors on the diabetes team (69–72). Professionals serving as instructors must document appropriate continuing education or comparable activities to ensure their continuing competence to serve in their instructional, training, and oversight roles (73).

Reflecting the evolving health care environment, a number of studies have endorsed a multidisciplinary team approach to diabetes care, education, and support. The disciplines that may be involved include, but are not limited to, physicians, psychologists and other mental health specialists, physical activity specialists (including physical therapists, occupational therapists, and exercise physiologists), optometrists, and podiatrists (68,74,75).

More recently, health educators (e.g., Certified Health Education Specialists and Certified Medical Assistants), case managers, lay health and community workers (76–83), and peer counselors or educators (84,85) have been shown to contribute effectively as part of the DSME team and in providing DSMS. While DSME and DSMS are often provided within the framework of a collaborative and integrated team approach, it is crucial that the individual with diabetes is viewed as central to the team and that he or she takes an active role.

Certification as a diabetes educator (CDE) by the National Certification Board for Diabetes Educators (NCBDE) is one way a health professional can demonstrate mastery of a specific body of knowledge, and this certification has become an accepted credential in the diabetes community (86). An additional credential that indicates specialized training beyond basic preparation is board certification in Advanced Diabetes Management (BC-ADM) offered by the AADE, which is available for nurses, dietitians, pharmacists, physicians, and physician assistants (68,74,87).

Individuals who serve as lay health and community workers and peer counselors or educators may contribute to the provision of DSME instruction and provide DSMS if they have received training in diabetes management, the teaching of self-management skills, group facilitation, and emotional support. For these individuals, a system must be in place that ensures supervision of the services they provide by a diabetes educator or other health care professional and professional back-up to address clinical problems or questions beyond their training (88–90).

For services outside the expertise of any provider(s) of DSME and DSMS, a mechanism must be in place to ensure that the individual with diabetes is connected with appropriately trained and credentialed providers.

STANDARD 6
Curriculum

A written curriculum reflecting current evidence and practice guidelines, with criteria for evaluating outcomes, will serve as the framework for the provision of DSME. The needs of the individual participant will determine which parts of the curriculum will be provided to that individual.

Individuals with prediabetes and diabetes and their families and caregivers have much to learn to become effective self-managers of their condition. DSME can provide this education via an up-to-date, evidence-based, and flexible curriculum (8,91).

The curriculum is a coordinated set of courses and educational experiences. It also specifies learning outcomes and effective teaching strategies (92,93). The curriculum must be dynamic and reflect current evidence and

practice guidelines (93–97). Recent education research endorses the inclusion of practical problem-solving approaches, collaborative care, psychosocial issues, behavior change, and strategies to sustain self-management efforts (12,13,19,74,86,98–101).
The following core topics are commonly part of the curriculum taught in comprehensive programs that have demonstrated successful outcomes (2,3,5,91,102–104):

1. Describing the diabetes disease process and treatment options-Incorporating nutritional management into lifestyleIncorporating physical activity into lifestyle
2. Using medication(s) safely and for maximum therapeutic effectivenessMonitoring blood glucose and other parameters and interpreting and using the results for self-management decision making
3. Preventing, detecting, and treating acute complicationsPreventing, detecting, and treating chronic complications
4. Developing personal strategies to address psychosocial issues and concernsDeveloping personal strategies to promote health and behavior change

While the content areas listed above provide a solid outline for a diabetes education and support curriculum, it is crucial that the content be tailored to match each individual's needs and be adapted as necessary for age, type of diabetes (including prediabetes and diabetes in pregnancy), cultural factors, health literacy and numeracy, and comorbidities (14,105–108). The content areas will be able to be adapted for all practice settings.
Approaches to education that are interactive and patient centered have been shown to be effective (12,13,109–112). Also crucial is

the development of action-oriented behavioral goals and objectives (12–14,113). Creative, patient-centered, experience-based delivery methods—beyond the mere acquisition of knowledge—are effective for supporting informed decision making and meaningful behavior change and addressing psychosocial concerns (114,115).

STANDARD 7
Individualization

The diabetes self-management, education, and support needs of each participant will be assessed by one or more instructors. The participant and instructor(s) will then together develop an individualized education and support plan focused on behavior change.

Research has demonstrated the importance of individualizing diabetes education to each participant's needs (116). The assessment process is used to identify what those needs are and to facilitate the selection of appropriate educational and behavioral interventions and self-management support strategies, guided by evidence (2,63,116–118). The assessment must garner information about the individual's medical history, age, cultural influences, health beliefs and attitudes, diabetes knowledge, diabetes self-management skills and behaviors, emotional response to diabetes, readiness to learn, literacy level (including health literacy and numeracy), physical limitations, family support, and financial status (11,106,108,117,119–128).
The education and support plan that the participant and instructor(s) develop will be rooted in evidence-based approaches to effective health communication and education while taking into consideration participant barriers, abilities, and expectations. The instructor will use clear health communication principles, avoiding jargon, making information culturally relevant, using language- and literacy-appropriate education materials, and using interpreter services when indicated (107,129–131). Evidence-based communication strategies such as collaborative goal setting, motivational interviewing, cognitive behavior change strategies, problem solving, self-efficacy enhancement, and relapse prevention strategies are also effective (101,132–134). Periodic reassessment can determine whether there is need for additional or different interventions and future reassessment (6,72,134–137). A variety of assessment modalities, including telephone follow-up and other information technologies (e.g., Web based, text messaging, or automated phone calls),

may augment face-to-face assessments (72,87,138–141).

The assessment and education plan, intervention, and outcomes will be documented in the education/health record. Documentation of participant encounters will guide the education process, provide evidence of communication among instructional staff and other members of the participant's health care team, prevent duplication of services, and demonstrate adherence to guidelines (117,135,142,143). Providing information to other members of the participant's health care team through documentation of educational objectives and personal behavioral goals increases the likelihood that all the members will work in collaboration (86,143). Evidence suggests that the development of standardized procedures for documentation, training health professionals to document appropriately, and the use of structured standardized forms based on current practice guidelines can improve documentation and may ultimately improve quality of care (135,143–145).

STANDARD 8
Ongoing support

The participant and instructor(s) will together develop a personalized follow-up plan for ongoing self-management support. The participant's outcomes and goals and the plan for ongoing self-management support will be communicated to other members of the health care team.

While DSME is necessary and effective, it does not in itself guarantee a lifetime of effective diabetes self-care (113). Initial improvements in participants' metabolic and other outcomes have been found to diminish after approximately 6 months (3). To sustain the level of self-management needed to effectively manage prediabetes and diabetes over the long term, most participants need ongoing DSMS (15).

The type of support provided can be behavioral, educational, psychosocial, or clinical (11–14). A variety of strategies are available for providing DSMS both within and outside the DSME organization. Some patients benefit from working with a nurse case manager (6,86,146). Case management for DSMS can include reminders about needed follow-up care and tests, medication management, education, behavioral goal setting, psychosocial support, and connection to community resources.

The effectiveness of providing DSMS through disease management programs, trained peers and community health workers, community-based programs, information technology, ongoing education, support groups, and medical nutrition therapy has also been established (7–11,86,88–90,142,147–150).
While the primary responsibility for diabetes education belongs to the provider(s) of DSME, participants benefit by receiving reinforcement of content and behavioral goals from their entire health care team (135). Additionally, many patients receive DSMS through their primary care provider. Thus, communication among the team regarding the patient's educational outcomes, goals, and DSMS plan is essential to ensure that people with diabetes receive support that meets their needs and is reinforced and consistent among the health care team members.

Because self-management takes place in participants' daily lives and not in clinical or educational settings, patients will be assisted to formulate a plan to find community-based resources that may support their ongoing diabetes self-management. Ideally, DSME and DSMS providers will work with participants to identify such services and, when possible, track those that have been effective with patients, while communicating with providers of community-ba-

sed resources in order to better integrate them into patients' overall care and ongoing support.

STANDARD 9
Patient progress

The provider(s) of DSME and DSMS will monitor whether participants are achieving their personal diabetes self-management goals and other outcome(s) as a way to evaluate the effectiveness of the educational intervention(s), using appropriate measurement techniques.

Effective diabetes self-management can be a significant contributor to long-term, positive health outcomes. The provider(s) of DSME and DSMS will assess each participant's personal self-management goals and his or her progress toward those goals (151,152).

The AADE Outcome Standards for Diabetes Education specify behavior change as the key outcome and provide a useful framework for assessment and documentation. The AADE7 lists seven essential factors: physical activity, healthy eating, taking medication, monitoring blood glucose, diabetes self-care–related problem solving, reducing risks of acute and chronic complications, and psychosocial aspects of living with diabetes (93,153,154). Differences in behaviors, health beliefs, and culture as well as their emotional response to diabetes can have a significant impact on how participants understand their illness and engage in self-management. DSME providers who account for these differences when collaborating with participants on the design of personalized DSME or DSMS programs can improve participant outcomes (147,148).

Assessments of participant outcomes must occur at appropriate intervals. The interval depends on the nature of the outcome itself and the time frame specified based on the participant's personal goals. For some areas, the indicators, measures, and time frames will be based on guidelines from professional organizations or government agencies.

STANDARD 10
Quality improvement

The provider(s) of DSME will measure the effectiveness of the education and support and look for ways to improve any identified gaps in services or service quality using a systematic review of process and outcome data.

Diabetes education must be responsive to advances in knowledge, treatment strategies, education strategies, and psychosocial interventions, as well as consumer trends and the changing health care environment. By measuring and monitoring both process and outcome data on an ongoing basis, providers of DSME can identify areas of improvement and make adjustments in participant engagement strategies and program offerings accordingly.

The Institute for Healthcare Improvement suggests three fundamental questions that should be answered by an improvement process (149):

- What are we trying to accomplish?
- How will we know a change is an improvement?
- What changes can we make that will result in an improvement?

Once areas for improvement are identified, the DSME provider must designate timelines and important milestones including data collection, analysis, and presentation of results (150). Measuring both processes and outcomes helps to ensure that change is successful without causing additional problems in the system. Outcome measures indicate the result of a process (i.e., whether changes are actually leading to improvement), while process measures provide information about what caused those results (144,150). Process measures are often targeted to those processes that typically impact the most important outcomes.

References
See 154 references on
http://care.diabetesjournals.org/content/35/11/2393

Nyhetsinfo 31 juli 2017
www red DiabetologNytt

EU-kommissionen godkänner utökad indikation för Victoza (liraglutide). ”motverkar kardiovaskulära händelser vid T2DM”

EU-kommissionen har godkänt utökad indikation för Novo Nordisk Victoza (liraglutide) så att den reflekterar att behandling med läkemedlet förbättrar blodsockernivåer och motverkar kardiovaskulära händelser som en del i behandlingen mot diabetes typ 2.

Victoza är sedan tidigare godkänt för behandling av vuxna med otillräckligt kontrollerad typ 2-diabetes, som monoterapi med motion och diet, när metformin anses otillräcklig

Nyhetsinfo 28 juli 2017
www red DiabetologNytt

Managing diabetes in preschool children ISPAD Guidelines. Pediatric Diabetes. 2017;1–19.

1 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

The target hemoglobin A1c (HbA1c) for all children with type 1 diabetes, including preschool children, is recommended to be <7.5% (<58 mmol/mol) (B).

This target is chosen with the aim of minimizing hyperglycemia, severe hypoglycemia, hypoglycemic unawareness, and reducing the likelihood of development of long-term complications (B).

Intensive insulin therapy, i.e. as close to physiological insulin replacement as possible with preprandial insulin doses and basal insulin, should be used, with frequent glucose monitoring and meal-adjusted insulin regimens. (C).

• Insulin pump therapy is the preferred method of insulin administration for young children (aged <7 years) with type 1 diabetes (E). If pump therapy is not available, multiple daily injections (MDIs), with consideration of use of an injection port, should be used from the onset of diabetes (E).

• For preschool children using intensive insulin therapy, preprandial administration of bolus insulin given for correction if blood glucose is high and for at least part of the meal is preferable to giving the whole dose during or after the meal (C). Greg Dooley is parent of a child with type 1 diabetes diagnosed at age 2, cofounder of the type 1 diabetes blog Inspired by Isabella (www. inspiredbyisabella. com); Jeff Hitchcock is parent of a child with diabetes diagnosed at age 2, founder and president of Children with Diabetes (www. childrenwithdiabetes.com)

This article is a new chapter in the ISPAD Clinical Practice Consensus Guidelines Compendium. The complete set of guidelines can be found for free download at www. ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association.

Carbohydrate counting is best introduced at onset of diabetes (E).

• The small insulin doses of preschool children may necessitate diluting insulin for precise dosing (E).

• Syringes with ó unit marking and pens with at least ó unit dosing increments should be used to facilitate more accurate insulin dosing if a pump is not used (or as a back-up to pump use) (E).

• Continuous glucose monitoring (CGM) can be helpful as an approach to adjusting insulin doses (E). Some CGM devices are approved for this use. If CGM is not available, 7 to 10 plasma glucose checks per day are usually needed for satisfactory glucose control (E).

• Injection, infusion, and CGM sites should be properly prepared and regularly rotated in order to reduce the likelihood of lipohypertrophy, scarring, infection, rashes, skin reaction, and dry skin (E).

• Injection, infusion, and CGM sites should be inspected by diabetes team members at every clinic visit to detect and treat any skin problems, such as skin reactions, lipohypertrophy, or lipohypotrophy (E).

• The use of pumps and CGM are often limited by skin reactions to the adhesive. A skin moistener that preserves water can be used to prepare the site a few days prior to insertion. Topical corticosteroid (group I or II) can be used to treat skin reactions and to manage itching after removal (E).

Life style interventions designed to reduce the risk of subsequent cardiovascular disease in children with type 1 diabetes are needed, and should be directed toward the entire family and not just the individual child with type 1 diabetes (C).

Family-centered meal routines with restrictions on continuous eating habits (grazing) are important

to ensure dietary quality and optimize glycemic control in preschool children (C).
Diabetes education should be provided to staff at preschools and schools where children with type 1 diabetes are enrolled, in order to ensure that equal participation in all preschool/school activities occurs and is safely managed (E).

Optimal glycemic control, involving the minimizing of both hypoglycemia and hyperglycemia will give the child the best opportunity to concentrate, participate, and learn while at preschool and school (C). Weight, height (or length if <18 months), and Body Mass Index Standard Deviation Score (or percentiles) should be monitored on growth charts in all children with type 1 diabetes (E).

2 | INTRODUCTION

This chapter focuses on components of care unique to toddlers and preschool-aged children with type 1 diabetes. These guidelines are written in particular for children with type 1 diabetes aged 6 months to 6 years. Children <6 months of age at diagnosis should be suspected of having diabetes other than type 1 including monogenic diabetes, and their management is discussed in the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines on "The diagnosis and management of monogenic diabetes in children and adolescents".1 Preschool children are dependent on others for all aspects of their care. For the families (primarily parents) of preschool children with type 1 diabetes, their diabetes teams, and other caregivers, including school and day care staff members and babysitters, treatment is a constant challenge. Yet, despite this hurdle, it is important to strive for normoglycemia, as current knowledge about the implications of dysglycemia makes reducing the likelihood of acute and chronic complications imperative from the time of diabetes onset. Optimizing glycemic control for children in this age group often requires treatment using strategies that differ from those employed for older children and adolescents with type 1 diabetes. These strategies need to take into consideration the cognitive, motor, and social immaturity of preschool children as well as their small body size and growth pattern. In addition to their dependence on others for insulin administration and glucose monitoring, preschool children are also dependent on others for aspects of their lifestyle related to healthy eating and engagement in physical activity. Lifestyle choices and preferences established during early childhood provide a window of opportunity for ingraining healthy habits that will be perpetuated throughout the child's life. The early establishment of positive behaviors is necessary to ameliorate the high risk of cardiovascular disease that is associated with diabetes. Providing adequate education and support of lifestyle changes requires that the multi-disciplinary diabetes team uses a family-based approach to ensure that the whole family is appropriately supported. Supporting the family is necessary for promoting health in the preschool child with type 1 diabetes. Early childhood is important for establishing the "salutogenic" (health promoting) capacity needed for a long life with type 1 diabetes.2 The core aspect of a person's salutogenic capacity is a good "sense of coherence", consisting of an everyday perception of comprehensibility, manageability, and meaningfulness of health promoting actions taken in everyday life. The main sources of the child's salutogenic capabilities are the parents. Supporting the parents to endure the burden of intensified insulin treatment, including their need for counseling and sleep, is essential to promote and maintain the health and well-being of the child. It is also important to support the parents to involve the child in diabetes-related tasks such as helping to select a finger for monitoring, site for injection/infusion, and to encourage age-appropriate positive problem solving strategies when diabetes-related problems occur. Screening and promotion of optimal health-related quality of life should be regularly undertaken in preschool children with type 1 diabetes as in any child with type 1 diabetes. It is important to use validated parent and parent-proxy screening questionnaires to capture factors important to the quality of life of children and their parents as both are important and impactful on diabetes management. Children younger than 7 years with type 1 diabetes constitute a minority of the population of all pediatric patients with type 1 diabetes. In small centers, this will make the number of very young patients small and the time needed to gain experience in care of this patient group will be longer. Close collaboration between centers is necessary in order to optimize quality of care for preschool children with type 1 diabetes.

3 | GROWTH AND DEVELOPMENT IN THE FIRST YEARS OF LIFE

Growth and development in the first years of life are characterized by an intricate interplay between genetic, metabolic, hormonal, and environmental factors. "Growth" is an increase in size of the body and its constituent organs. "Development" is the differentiation of the form and function of the organs, and refers to not only somatic development but also neurocognitive, and psychosocial development. Rapid changes in growth and development occur in the first ▶

years of life. In the first year of life children grow 25 to 30 cm, in the second year approximately 12 cm, (comparable to the growth spurt in puberty) and in years 3 to 6 around 6 to 8 cm/y. Weight triples in the first year of life, increases by approximately 2.5 kg in the second year, followed by an increase of around 2 kg/y in the next 3 to 4 years. A peak in subcutaneous tissue mass is observed around 9 months of age, which subsequently decreases until 6 years of age. In order for preschool children to experience normal growth and development, it is essential that they maintain near normoglycemia, aiming to increase glucose time in range, and are provided with sufficient nutrients.3–6 Restrictive diets or lack of food make it difficult to provide essential nutrients for growth and development, and should be avoided. It is essential to monitor weight, height (or length if <18 months), and BMI-SDS (or percentiles) on growth charts in all children with type 1 diabetes at every clinic visit. This requirement of sufficient nutrition is in part due to the brain's high metabolic expenditure in infancy and childhood (3 times higher than in adults). Body proportion at birth is characterized by a large head and prominent abdomen. After birth, the brain and the cranium continue to grow and reach 4/5 of the adult size by the end of the second year, growing much faster than many other body parts including the extremities.7

4 | THE BRAIN AND COGNITIVE DEVELOPMENT IN CHILDREN WITH EARLY ONSET TYPE 1 DIABETES

The brain is metabolically highly demanding, accounting for 20% of the total energy requirement in adults.8 In the adult, the brain depends on a continuous supply of glucose as fuel. In the neonate, glucose is essential for different intracerebral pathways.9 Brain development requires different nutrients to support the 5 key processes: (1) neuron proliferation, (2) axon and dendritic growth, (3) synapse formation, pruning, and function, (4) myelination, and (5) neuron apoptosis. Regional and temporal variation in glucose utilization suggests that glucose is essential not only for energy production in the brain, but potentially for cellular proliferation and synaptogenesis as well.10 In the neonatal and infant brain, alternative energy sources may be identified such as ketone bodies, which are transported over the blood-brain barrier in times of glucose shortage. The ketone bodies are a substrate for lipid synthesis, although not essential.11

In addition to somatic growth, preschool children experience rapid cognitive development. Children start by investigating objects in their immediate environment, eventually expanding to exploring anything within reach. Mobility and thus physical activity increases with age.

Multiple risk factors have been associated with potential suboptimal cognitive and fine motor development in children and adolescents with type 1 diabetes. These factors include early onset of disease (typically defined as <5 years of age),12 disease duration, history of moderate to severe ketoacidosis (including those at diagnosis),13,14 severe hypoglycemia (including seizures or unconsciousness),15 cumulative exposure to hyperglycemia, and possibly, the sex of the child.16 A meta-analysis showed that the risk of cognitive disruption is largest for children with early-onset diabetes and that the effect is detectable after a mean diabetes duration of 6 years.17 The mean effect size is moderate but might not be large enough to affect school performance. Clinicians should be concerned about diabetic ketoacidosis (DKA), severe hypoglycemia and hyperglycemia, all being detrimental for the health of the preschool child.

When reviewing these findings, it is important to distinguish between statistically significant group differences vs clinically significant findings. Statistically significant group differences may or may not translate into a functional impact on the daily life of a child, which has not been fully explored in children with type 1 diabetes. However, we know that early brain and cognitive development are important for later success in school and beyond. Glucose uptake by the brain is insulin-independent and mainly driven by the concentration of glucose. This directly exposes the neuronal cells of the brain to oxidative stress and glucotoxicity in hyperglycemia, and to lack of fuel in hypoglycemia.

The maturation of gray matter in the brain is intense throughout the toddler and preschool years. Gray matter development slowly curtails over time beginning around puberty. In contrast, white matter maturation (that is necessary for processing speed and coordinated, fluid movements) continues until early adulthood.18,19

During toddler and preschool years, the brain is highly sensitive to metabolic disturbances, and potential abnormalities have repeatedly been identified in magnetic resonance imaging (MRI) studies of young brains exposed to glycemic extremes, as in type 1 diabetes.20–23 The mechanisms by which early brain development is affected by type 1 diabetes are not clearly understood. Long-term exposure to hyperglycemia as well as hypoglycemia (especially with seizures) and oxidative stress caused by glycemic variability have been suggested as contributing factors. The main effects seem to occur in the early phase of the disease. It

has been suggested that metabolic conditions such as hyperglycemia and ketoacidosis at diagnosis can be predisposing events that makes the brain more vulnerable to subsequent metabolic insults.13,16 Some, but not all, studies investigating cognition in childhood onset type 1 diabetes, report decrements in the domains of intelligence quotient (IQ) (verbal IQ in particular), executive functions (attention, working memory, and response inhibition), delayed memory (episodic recall), and processing speed (paper-pencil); however, these differences are generally not reported until the children are studied later in childhood.24,25 One possibility is that chronic exposure to different aspects of dysglycemia is additive, and that brain and cognitive changes only become apparent over time.

Studies that specifically target the youngest children with type 1 diabetes have found only modest differences in cognitive function compared with peers. Among a large group (n = 144) of children aged 4 to 7 years, small differences in the following areas were reported: IQ, especially verbal, executive functions, and internalizing mood disorders.26 The cognitive differences remained when controlled for parental IQ and level of internalizing mood disorders. Longitudinal follow-up of these children is ongoing and may reveal how these differences change with time, further exposure to diabetes (including hypoglycemia and hyperglycemia), and brain development.27

A young child who has executive functioning difficulties, language/literacy deficits, slowed processing speed, or fine motor coordination difficulties will likely require professional attention at some point in their youth. Typically, these children are referred to a neuropsychologist or other learning specialist during the early elementary years. These children can require specialized tutoring, small group instruction, support in the classroom, or other assistance. For all children with cognitive development issues, early identification and remediation are crucial to avoid poor outcomes. Optimal glycemic control will give young children with type 1 diabetes the best opportunity to concentrate, participate, and learn while at preschool and school. By achieving good glycemic control, including mitigating prolonged exposure to hyperglycemia, and by providing early identification and intervention of academic, cognitive, or motor issues, health care professionals are best able to help children avoid any negative impact of type 1 diabetes on everyday function. For further reading, the ISPAD guidelines on psychological care of children and adolescents with type 1 diabetes comprehensively addresses this subject.28 See also the ISPAD Guidelines on hypoglycemia.29

5 | GLYCEMIC TARGETS AND CONTROL IN PRESCHOOL CHILDREN WITH TYPE 1 DIABETES

Optimizing glycemic control for preschool children with type 1 diabetes is crucial for their future, both with respect to acute and longtime diabetes complications as well as their neurocognition, brain structure, and health-related quality of life (HRQoL). ISPAD published glycemic targets for hemoglobin A1c (HbA1c; <7.5%, (<58 mmol/mol) and for self measured blood glucoses (SMBGs) (from optimal to high risk) in the latest guidelines 2014 (Table 1).30 The targets are applicable to all pediatric age groups, including preschool children, and the aim should be to achieve optimal glycemic control. The American Diabetes Association31 in 2014 redefined blood glucose targets for all pediatric age groups to be at the same level as ISPAD.32 In United Kingdom, glycemic targets for all pediatric age groups are recommended in the National Institute for Clinical Excellence (NICE) guidelines, recently updated to an even lower HbA1c level of ≤6.5% (≤48 mmol/mol; the numbers are based on the published studies).33 It is important that the diabetes team and family share the same target HbA1c and glucose ranges. Otherwise, there is a high risk of discrepancy that can go both ways. Sometimes parents strive for lower glucose levels than the diabetes team, who at times may articulate that the family is too strict and take too many glucose checks, especially at night. At other times, the parents have their own set of higher glucose targets that they feel fit better with their daily life, finding the targets set by the health care team unachievable. When evaluating glycemic targets together with the family, it might be useful to express them as time spent within target and time below or above target. It is important that both the diabetes team and the families consequently use a language that tells the child that a glucose value can be high, low or normal, and that the glucose level is never "bad". The knowledge of a ▶

glucose value often calls for action, but never for blaming or punishing the child.

Parents express that diabetes management style can make a difference.

A positive, non-judgmental, attitude will likely have a positive influence on the way a young child views and manages his/her type 1 diabetes as he/she gets older. Parents should be encouraged to adopt a "matter-of-fact" approach to the routines (injections/pump site changes, finger pricks, and meal times), treating numbers as just numbers/data points, and not apologizing for aspects of care such as finger pricks, site changes, and injections that cannot be avoided. Maximizing the amount of time glucose values are in range needs to be the target for multi-disciplinary diabetes teams, as well as the family/caregivers. Diabetes education34,35 and a clearly set glycemic target36 are very important.37,38 Age-specific challenges need to be considered and age-appropriate actions taken to achieve these.

As discussed above, there are detrimental effects of hyperglycemia; yet it is an existing practice to allow glucose levels to reach the hyperglycemic range in the youngest age group in order to avoid hypoglycemia at all costs. This is unsafe, and treatment should instead aim to minimize both hyperglycemia and hypoglycemia in the effort to achieve (near) normoglycemia. If the diabetes team is inexperienced in treating preschool children with type 1 diabetes, support and advice should be sought from more experienced colleagues.

TABLE 1 Glycemic targets in preschool children with type 1 diabetes according to ISPAD, ADA and NICE guidelines ISPAD30 American Diabetes Association31 NICE33 Preprandial glucose target 4.0-8.0 mmol/L (70-145 mg/dL) 5.0-7.2 mmol/L (90-130 mg/dL) 4.0-7.0 mmol/L (72-126 mg/dL) Postprandial glucose target (2 h post meal) 5.0-10.0 mmol/L (90-180 mg/dL) 5.0-9.0 mmol/L (90-162 mg/dL) Bedtime 6.7-10 mmol/L (120-180 mg/dL) 5.0-8.3 mmol/L (90-150 mg/dL) Overnight 4.5-9.0 mmol/L (80-162 mg/dL) HbA1c target <58 mmol/mol (<7.5%) <58 mmol/mol (<7.5%), a lower target of <53 mmol/mol (<7%) can be set if it can be achieved without hypoglycemia ≤48 mmol/mol (≤6.5%)
Abbreviations: HbA1c, hemoglobin A1c; ISPAD, International Society for Pediatric and Adolescent Diabetes, NICE, National Institute for Clinical Excellence.

It might not just be the HbA1c level that is important. Glycemic variability may play a role in the development of diabetic complications,39,40 but the long-term impact of glycemic variability remains controversial.41,42 In adults using continuous glucose monitoring (CGM), glycemic variability was significantly lower in those without complications compared with those with complications (Standard Deviation SD 3.4 vs 4.1 mmol/L), despite comparable HbA1c values.43 Age-specific, family-centered diabetes education plays a key role in achieving metabolic targets, together with flexible insulin regimens, glucose monitoring, and carbohydrate (CHO) counting.30,34,44 Hyperglycemia is a major risk factor for (recurrent) ketoacidosis45 and microvascular complications later in life.46,47 Long-term tracking of glycemic control from childhood until adulthood has been reported.48–52 There is a correlation between the HbA1c achieved within the first few months after diabetes diagnosis, the glycemic control later in life, and the risk for cardiovascular complications.

A lower HbA1c achieved at an early phase of life with diabetes is associated with a lower HbA1c later on.48–52 Long-term studies, for example, the Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC), describe a prolonged effect of prior glycemic levels on diabetic complications, called glycemic memory. This effect is independent of more recent glycemic control. The DCCT showed a significant difference of around 2% in HbA1c between the intensive and conventional groups, but 1 year after the closeout of the study, HbA1c levels were approximately the same (around 8%).46,47 Nevertheless, the intensive group

showed fewer microvascular complications, with a risk reduction in retinopathy even 18 years after the end of the study.53 The DCCT-EDIC results have led to the recommendation of early tight glycemic control to reduce the risk for diabetic microvascular and macrovascular complications.47,54,55 The ISPAD guidelines on microvascular and macrovascular complications provides a more detailed discussion.56 Early onset of diabetes at a very young age will lead to a longer duration, which in itself is associated with a higher lifelong risk of complications, compared with persons with later onset type 1 diabetes. 57 So far, conflicting data exist to whether the prepubertal years contribute to the same degree as the pubertal years for the development of microvascular complications.58 Suboptimal metabolic control in children with early prepubertal diabetes onset may further contribute to the risk of complications.59–61 Persons with poor glycemic control during childhood have a high risk of long-term complications, even if substantial improvement is achieved as young adults,62 and NICE emphasizes the need to reduce the risk of long-term complications of type 1 diabetes in a population that will have a long duration of diabetes because the condition starts before adulthood.

6 | INSULIN THERAPY IN PRESCHOOL CHILDREN

Insulin treatment guidelines for preschool children are essentially similar to older children and adolescents, but age-dependent aspects have to be taken into consideration. See the ISPAD guidelines for further reading on insulin and insulin analogs in pediatric use.63 Worldwide, most preschool children with diabetes use insulin injections to manage their diabetes. Although insulin pump use should be considered for many of these children," injection, injection therapy is used in many centers in the following instances: early in the course of the disease in their remission period; children who were using an insulin pump but have experienced pump failures "or skin reactions", "inexperience of the diabetes team in using pumps in this young age group," and if living in limited resource settings where insulin pumps are unavailable. Approval of insulin analogs in different age groups is regulated by authorities. Two examples are the European Medicines Agency (EMA) (www.ema.europe.eu) approvals and the US Food and Drug Administration (FDA) (www.fda.gov) as of June 2017 (Table 2). When using injections for insulin delivery, pain can be reduced by usage of subcutaneous catheters changed every third day (Insuflon; Unomedical, Lejre, Denmark or I-port: Medtronic MiniMed, Northbridge CA, USA).64

6.1 | Insulin dosing

Preschool children with optimal glycemic control usually need somewhat less insulin than older children. The total insulin dose has been reported to be 0.4 to 0.8 U/kg/d (median 0.6 U/kg/d) in preschool children with well controlled type 1 diabetes after the remission phase.65 Insulin pumps offer both greater flexibility in insulin dosing and a better means to deliver very small, precise doses of insulin than when using injections,66 and are thus considered the preferred method for insulin delivery in infants, toddlers, and preschoolers with diabetes, although earlier randomized studies have failed to show an effect on glycemic control.63 If pump therapy is not available due to lack of economic resources, multiple daily injections (MDIs), with consideration of use of an injection port, can be used. If the diabetes team is not experienced enough in pump treatment of preschool children, advice should be sought from a more experienced center to optimize quality of care.

6.2 | Basal insulin

When using injections for insulin treatment, the special diurnal pattern of insulin requirements in preschool children should be taken into consideration in designing an individualized basal dosing scheme. The low requirement of insulin and tendency toward low glucose

TABLE 2 Approved insulin analogs in different age groups according to EMA and FDA Approved by EMA from age Approved by FDA for (studied from age)
Insulin lispro "Adults and children" (2 y)
"Adults and children" (3 y)
Insulin aspart ≥2 y "Adults and children" (2 y)
Insulin glulisine ≥6 y "Adults and children"
(4 y) Insulin detemir ≥1 y "Adults and children" (2 y)
Insulin glargine ≥2 y Adults and pediatric patients" (6 y)
Insulin degludec ≥1 y ≥1 y
Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.

levels are often most obvious during the night and especially between 3 and 6 AM. Preschool children often need much more insulin late in the evening between 9 PM and 12 midnight.67–69 This creates typical patterns when programming the basal rates of an insulin pump used by a preschool child. With MDIs, a basal insulin analog can reduce hypoglycemia, including nighttime hypoglycemia, compared with NPH insulin.70–72

The combination of the low body weight, and thus low total insulin dose, demands special conside- ▶

ration when using commercially available insulin pumps. A pump with a very high precision in delivering very small basal rates should be chosen for a preschool child. Sometimes further reduction in the dose is needed, necessitating dilution of the current U-100 insulin,65,73,74 or an intermittent basal rate of 0 U/h for limited periods, i.e. every second hour during the night. Use of these approaches may help to meet the needs of the young child and the planning of the child's insulin treatment has to be carefully discussed (with advantages and disadvantages) with the parents so that they are well aware of the benefits and risks of the chosen strategy. The given insulin should always be prescribed and documented in normal units to avoid hazardous misunderstandings regarding insulin dosing, especially if the child is admitted to hospital. A pump containing diluted insulin should be labeled with information regarding the currently contained concentration of insulin (Table 3).

A glucose and meal-adjusted basal-bolus insulin regimen (delivered by injections or pump) requires that the basal rate can be fine-tuned by the parents in accordance with the child's current insulin sensitivity.

Insulin sensitivity can be increased after very active days, such as a day at the beach or out in the snow (decreased insulin resistance). The overnight basal might then be reduced by 10% to 30% when using a pump or a similar decrease in bedtime long-acting insulin. Insulin sensitivity can be markedly reduced (increased insulin resistance) for example during fever when the basal rate might need to be increased by 20% to 100% according to glucose levels when using a pump, or a similar increase in dose of long-acting insulin. Under these circumstances, glucose levels have to be extremely carefully monitored and parents need constant access to support from the diabetes team.

6.3 | Bolus dosing

Although still often used, twice daily insulin dosing in this age group does not give the flexibility needed in adapting doses to varying situations in daily life. It is difficult to fine-tune, and difficult for the family to understand and adjust on their own, which is a necessity for a successful insulin treatment. A glucose and meal-adjusted basalbolus insulin regimen (delivered by injections or pump) can be adapted to the preschool child's daily activities, and is the preferred type of insulin treatment.

Preschool children often need proportionally larger bolus doses than older children, often constituting 60% to 80% of the total daily insulin dose (TDD). The often used rule of 500 (500/TDD = how many grams of CHO is covered by 1 U of insulin) for bolus calculations, as detailed in the ISPAD guidelines on insulin therapy63 rarely fits the youngest children as it often underestimates the insulin dose.70,75,76 Different strategies can be used; either use a 330 or 250 rule (gives 50%-100% more insulin) instead of 500, or, which is preferable, to observe and calculate the correct proportion between insulin and CHO from real life meals. To calculate the insulin to CHO ratio from a given meal, divide the CHO content in the meal (in grams) by the insulin dose in units that gives an appropriate glucose profile after the meal. The need for insulin at breakfast is often very high, and one might consider using 150/TDD in the calculation, or calculate from real life meals as above.

The timing of the prandial bolus is important. As outlined in the review by Bell et al,77 several studies show that preprandial bolus insulin is preferable to insulin administered during or after the meal and should thus be routinely advised for all toddlers and preschoolers, even the most unpredictable eaters. However, the dose can be split into 1 preprandial and 1 during the meal when eating is erratic or new foods are offered.

The dose given during the meal can be based on what the parent estimates the child will eat of the remaining meal, taking into consideration the food that has just been eaten and the child's remaining appetite. Small inaccuracies in calculation of up to 5 to 7 g CHO will usually not be problematic.78 Larger inaccuracies may result in possible hypoglycemia or hyperglycemia 2 to 3 hours after eating, but not immediately.79 These can be anticipated and treated with additional CHO or a small correction dose of insulin. With a pump, a combination bolus (also called combo or dual wave bolus) can be helpful, i.e. part of the bolus is given before the meal and the remainder over 20 to 40 minutes. If the child stops eating before the meal is finished, the remainder of the bolus can be suspended. When giving these relatively large bolus doses, one must remember that they interact with the need for basal insulin in the following hours. Thus, the total basal rate can be relatively low, around 20% to 40% of TDD. In preschool children, it is often estimated that the effect of a subcutaneous bolus of rapid-acting insulin analogs (eg, as lispro, aspart, or glulisine) lasts for only 2 to 3 hours (active insulin time in pumps).75

At breakfast there is often some degree of insulin resistance, and it is common to experience a marked glucose peak after breakfast in spite of an adequate insulin dose taken before the meal. The nutri-

tional content of the breakfast has to be discussed and planned by the dietitian together with the parents. Increasing the insulin dose (lower insulin-to-CHO ratio) too much can risk hypoglycemia before lunch. In this situation, it may be helpful to give the prandial insulin 10 to 20 minutes before breakfast. The need for a large bolus dose of insulin to cover breakfast might necessitate a very low or suspended basal rate during the following 3 hours. For some children, a small amount of fruit (5-10 g of CHO) may be given 2 hours after breakfast (without insulin) to avoid hypoglycemia, but it is preferable not to establish a practice that necessitates skipping a bolus as this may continue as the child gets older.

When using MDIs with frequent glucose checking and mealadjusted insulin dosing, one possible strategy is to give a rapid-acting insulin analog for all meals, with the exception of the last meal of the day when short-acting regular insulin can be used to meet the increase in glucose before midnight. Part of the dose can be given as rapid-acting analog insulin to avoid needing to give the dose 30 minutes before the meal; the insulins can be mixed in a syringe or given as separate injections (if an injection aid is used).

TABLE 3 Different strategies for delivering minute basal rates. No pumps that are available today can be adjusted to the insulin concentration. Thus, if using diluted insulin, recommended doses from the bolus calculator must be recalculated to the diluted concentration Advantages Disadvantages Diluted insulin (i.e. 10 or 50 U/mL) Fine tuning of basal rates is possible. All technical features of the pump can be used, such as temporary basal rate changes and bolus calculations. Possible to set extremely low basal rates and make changes in small increments. Risk of mistakes due to the delivered insulin dose not being the same as that displayed on the screen. Pain can occur when large volumes are given as bolus doses. Impractical to prescribe doses with diluted insulin More expensive insulin.
"Empty" hours without basal rate
• The pump gives exactly the doses displayed on the screen, decreased risk of mistakes in dosing for instance when insulin is given temporarily with pen. Use of more stable commercially available insulins is possible. Increased risk of occlusion in tubing due to low flow rate. Increased risk of ketosis due to planned hours without insulin. Some of the pumps' technical features (as temporary basal dose changes) cannot be used.

7 | NUTRITIONAL NEEDS OF THE PRESCHOOL CHILD WITH TYPE 1 DIABETES

Breastfeeding should be encouraged for all infants, including infants with diabetes (World Health Organization [WHO] recommendation, www.who.int). Complementary foods, preferably iron-rich, should be commenced from 4 to around 6 months of age.80 If breastfeeding is not possible, an iron-fortified infant formula should be given as the main milk drink until 12 months of age. A routine regarding breast- or formula-feeding is important for infants with diabetes as this enables appropriate interpretation of glucose levels and basal and bolus insulin adjustments. This may involve 3 to 4 hourly feeds (of approximately 150-240 mL) during the day with complementary solids. Continuous or hourly breastfeeding is discouraged as this makes insulin dosing difficult. Breast milk has approximately 7.4 g CHO per 100 mL; so for infants 6 months and older it is possible to bolus before the feed for at least 5 to 7 g CHO and 15 g CHO in older babies (>9 months).

Optimal nutrition is required to provide sufficient energy and nutrients to meet the rapidly changing needs of children at this stage of life. Dietary recommendations are based on healthy eating principles suitable for all preschool children, with the aim of establishing family based meal-time routines that promote glycemic control and reduce cardiovascular risk factors. CHO counting is important to permit the matching of insulin dose to CHO intake on intensive insulin regimens,44 and should be taught to the family at the onset of diabetes.

Nutritional advice must be individualized and adapted to cultural and family traditions. A pediatric diabetes dietitian should provide education, monitoring,

and support at regular intervals throughout the preschool years, as parents of preschool children with diabetes report meal-times as one of the most difficult components of their child's care.81 Preschoolers require more frequent review than older children,44 with a suggestion for reassessment twice annually until the age of 6. There is international agreement that CHO should not be restricted in children with type 1 diabetes as it may result in deleterious effects on growth. Care should be taken when giving dietary education, so that methods of quantifying CHO do not increase total fat and/or saturated fat intake.44 Although caregivers may prefer highfat snacks to avoid affecting glucose levels, this should be discouraged as they will provide unnecessary calories, an unhealthy fat intake, and negatively impact dietary quality.

Preschool children with type 1 diabetes should consume a diet that emphasizes fruit, vegetables, whole grain bread and cereals, dairy foods and appropriate types and amounts of fats. Low fat diets are not suitable for children under 2 years of age. Lower glycemic index (GI) choices, such as wholegrain bread and cereals can be introduced as substitutes for higher GI food choices from 2 years of age. Iron deficiency can be a concern in this age group; adequate consumption of lean meat or alternatives is important and should not be overlooked because of the increased focus on CHO.

A guide to the macronutrient distribution of the total daily energy intake in preschool children is as below. However, this should be based on an individualized assessment. Carbohydrates: 45 to 55 Energy (E) %.44,82 Average intakes 150 g/d in children aged 1ó to 3 years; 200 g/d in children 4 to 10 years.83 Protein: 15 to 20 E % (decreasing with age from approximately 1.5 g/kg body weight/day in 6-month-old infants to 1 g/kg body weight/day in preschoolers)84 Fat: 30 to 35 E % (less than 10 E% saturated fat, less than 10 E% polyunsaturated fat, and more than 10 E% mono-unsaturated fat). Infants less than 12 months may consume up to 40% energy from fat.

It is important to encourage all children, including children with type 1 diabetes, to eat plenty of fruit and vegetables. Examples of recommendations from Australia,85 United States,86 and the Nordic countries87 are expressed in different ways but consistent in content, and state 180 g vegetables (2ó servings) and 150 g fruit (1 serving) daily from 2 years of age85; or 1ó serving of fruit and vegetables daily between 1 and 3 years.86 400 g of fruits/vegetables are recommended each day from 4 years of age.87

Research has shown the dietary quality of preschool children with diabetes is poorer than their healthy peers.88Studies have shown that preschool children with type 1 diabetes consume less fruit and vegetables and have higher saturated fat intakes than peers89 and than recommendations would advise.90,91 Poor food intake may increase the risk of cardiovascular disease. Eating habits in young children can influence food choices later in life,92 so early intervention with increased attention to an increase in fruit and vegetable intake and decrease in saturated fat is needed. Just like healthy children, children with diabetes may require up to 10 exposures to a new food before it is accepted.93 Several studies show that children with type 1 diabetes are more overweight compared with children in the general population,91,94 with the youngest children (<6 years) being the most overweight.95,96 It is important to plot the growth chart including assessments of weight for length or height regularly to identify excessive weight gain, in order to commence interventions that involve the whole family. Encouraging participation in family meals has been recommended to promote dietary quality97 and social interaction. Age-appropriate finger foods should be encouraged for self-feeding, and the reintroduction of a bottle as an easy method of CHO intake discouraged. Bottles can lead to overconsumption of fluids, increasing CHO intake and placing other nutrients at risk.

8 | ESTABLISHING POSITIVE FOOD BEHAVIORS AND MEAL-TIME ROUTINES

Establishing positive food behaviors and meal-time routines are im-

portant for preschool children with type 1 diabetes, as these behaviors impact glycemic control81,98 and encourage life-long nutrition practices.92 Normal early childhood development, including seeking independence, transient food preferences, variable appetite, food refusal, and behavioral resistance often make meal times challenging for parents and carers. Parents of children with type 1 diabetes report more disruptive meal behaviors, including longer meal duration and more frequent food refusal compared with controls99,100; even for children using insulin pump therapy.101 Research has demonstrated positive correlations between suboptimal dietary adherence and higher glucose levels.81,89,101,102 Caregivers' fear of hypoglycemia associated with food refusal or unpredictable dietary patterns can result in force feeding, grazing continually over the day, and postprandial insulin administration, causing prolonged periods of hyperglycemia.

Family-centered meals are important to model eating practices and to encourage new foods. For small children, meal times should be limited to approximately 20 minutes per meal.103 Conventional insulin regimens require adherence to a structured plan of CHO intake, and parents frequently report problems with this approach.81

Intensive insulin management offers greater flexibility in meal timing and CHO quantities. To assist the reliable intake of CHO at meal-times and to minimize food refusal, the following strategies should be adviced:

structured meal-times avoidance of continuous eating habits small snacks including limits on low CHO foods as these fill the child up limits on the time spent at the table avoidance of force feeding reassurance by all team members regarding the usual nonseverity of hypoglycemic episodes related to inadequate CHO consumption.

Parents should be adviced that postprandial bolus insulin is problematic as it can become an established habit and also reinforces anxiety about the child under-eating. Fear of hypoglycemia can lead to under-bolusing for meals, resulting in inadequate bolus doses given over the day and subsequent hyperglycemia. Continuous eating (grazing) makes interpretation of glucose levels and insulin dose adjustments difficult. A regular meal pattern with 1 small snacking episode between meals (7-15g CHO preceded by an appropriate insulin dose) will assist with preventing food refusal as the child will be hungrier at main meals. A dietitian should advise regarding age appropriate CHO amounts as it is necessary to ensure the anticipated CHO intake is reasonable based on age, growth, and the child's previous intake. Unreasonable expectations of a child's intake may result in food refusal and subsequent hypoglycemia. Food refusal should generally be dealt with effectively and similarly to toddlers without diabetes. Preschool children becoming increasingly independent can recognize parental stress and quickly learn to use their diabetes as a way of getting their favorite foods. It is important to emphasize parental patience and to encourage parents not to use food bribes.

All diabetes team members should provide the family with clear and consistent messages regarding food and meal-time behaviors. Distractions such as the television and toys should be removed at mealtimes. Research has demonstrated that disruptive child behaviors can be reduced by establishing specific rules and consequences for mealtimes and teaching parents behavioral strategies for meals.104 There is consensus that continuation of support by a pediatric dietitian throughout childhood and adolescence is essential for optimal care.

In parental experience, it can be difficult at times to give preprandial bolus doses of insulin due to the fear of food refusal and resultant hypoglycemia. Strategies to handle this need to be discussed with the parents (as above) and all aspects of the risk of dysglycemia following postprandial bolus doses need to be explored. Should a child have a high plasma glucose because of eating something unplanned, a calm explanation of the need to cover food with insulin is necessary.

9 | LIFESTYLE FACTORS IN PRESCHOOL CHILDREN

The American Heart Association (AHA) has identified certain childhood conditions (including type 1 diabetes) associated with extremely high risk of cardiovascular disease, calling for treatments to minimize this risk.105 Lifestyle habits, such as nutritional preferences,92 physical activity,106 and time spent sedentary,107 that are established in childhood have a great propensity to follow into adulthood. Thus, lifestyle factors in early childhood have a dual impact on later cardiovascular risk, observable both as early markers of atherosclerosis during adolescence108 and also as a set of behaviors that influences the child's risk of cardiovascular disease as an adult and even into senescence. Children tend to follow the lifestyle habits of their parents and entire family regarding physical activity,109 TV watching110 and food choices,97,111,112 and this has been found to influence children´s food habits throughout their lives.92 Lifestyle supporting interventions should thus be directed toward the parents and entire family and not the individual child with type 1 diabetes mellitus (T1DM).

There is no contradiction between population-based interventions to promote increased physical activity or healthier food choices in all children and interventions that are routinely part of the diabetes care delivered by the diabetes team. Preschool children with type 1 diabetes can benefit from both efforts, but targeted interventions are necessary to meet the specific needs of children with type 1 diabetes.

10 | PHYSICAL ACTIVITY

Physical activity confers many health benefits for all children. A strong graded inverse cross-sectional association has been observed between physical activity, insulin resistance,113,114 and body fat.115 Spending more time in moderate and vigorous physical activity is associated with decreased cardiometabolic risk factors in children. 116 When designing physical activity interventions to reduce the risk of cardiovascular disease in children, including children with type 1 diabetes, it is important to focus on high-intensity physical activity to be most effective.116 Engaging in regular physical activity is also necessary in order to acquire and improve gross motor skills.117 Many countries recommend at least 60 min/d of moderate and vigorous physical activity for all children,118 and WHO recommends this at least from 5 years of age.119 Some countries have changed their recommendations for physical activity in preschool children from 60 minutes of moderate and vigorous physical activity to 180 minutes of any intensity of physical activity per day.120,121 This change of recommendation has been questioned because the reduction in the risk of cardiovascular and metabolic problems might be too low with lower intensity of physical activity.115,116 It has been shown that outdoor playing and especially spacious outdoor playing environments are associated with increased physical activity in preschool children.122 Asking families about the amount of time spent playing outdoors can be a useful way to quantify the physical activity of a preschool child with type 1 diabetes.

Physical activity should be promoted in all children with type 1 diabetes.

Both having diabetes and being a girl has been reported to be associated with lower levels of physical activity in preschool children with type 1 diabetes, indicating that particularly young girls with type 1 diabetes are at high risk of being too physically inactive.123

11 | PRACTICAL MONITORING OF GLYCEMIC CONTROL

In this section, "blood glucose" values refer to glucose values measured by capillary blood check ("finger prick" and "blood glucose monitoring") although meters generally display plasma glucose. Since plasma glucose is 11% higher than whole blood glucose, this term is used when exact numbers are mentioned.

11.1 | Blood glucose checking

Glycemic control is often evaluated with blood glucose monitoring (SMBG). All families with a child with diabetes should be taught how to measure and interpret plasma glucose values. A high precision glucometer (error less than 10%) should be used in preschool children, both when relying on SMBG for glycemic monitoring and when using the glucometer for calibration of CGM. Accuracy in everyday monitoring situations should be ensured by follow-up with the diabetes team. This shall include education on the importance of ensuring that the fingertips are clean and dry before monitoring blood glucose, as sugar on the fingertips is a common reason for erroneously high blood glucose levels. The child should be introduced to checks glucose monitoring and interpretation according to age appropriate and individual capabilities, as the development of the mathematical understanding of numbers and time is gradual.

Most children with type 1 diabetes can by the age of 7 be capable of taking blood glucose checks and performing some basic interpretation of glucose levels under supervision. However, this should always be overseen by a parent or other caregiver, as independent self-care is not expected from any preschool child with type 1 diabetes.

General advice on SMBG monitoring is available in the ISPAD guidelines on Assessment and monitoring of glycemic control.29 In children younger than 7 years of age, the recommended checking frequency of 4 to 6 times per day is rarely sufficient when striving for target glucose and HbA1c levels. Even with a higher monitoring frequency of 7 or 10 checks per day, the number of undetected hypoglycemia and hyperglycemic events in insulin treated preschool children are high.124,125 Observational studies from different countries show that a common frequency of SMBG in preschool children with type 1 diabetes is 7 to 10 checks per day.125,126 Nighttime SMBG is recommended by many diabetes teams, and performed by most families with preschool children.127 Preschool children with diabetes can spend a long time in the hypoglycemic range without detection, despite nighttime monitoring of SMBG.125 Many parents are sleep-deprived due to nighttime checking of plasma glucose.127,128 The normal activities of the child have to be interrupted in order to measure a blood glucose value during daytime. Thus, SMBG has several limitations as a method of monitoring glycemic control.

11.2 | Continuous glucose monitoring

CGM can provide an effective mode of monitoring for low and high glucose levels, allowing for efficacious insulin adjustment. When available, CGM with alarms is generally the preferred method for monitoring of glucose levels in children younger than 7 years of age with type 1 diabetes. CGM should be available and utilized as a tool for adjusting insulin doses. Parent experience from Children with diabetes (CWD) conferences: "I have seen many young children in the age group of 5 to 6 who understand both the numbers and trend arrows on their CGM". We also know from personal experience that children who are diagnosed young sometimes grasp 'the numbers' of diabetes very quickly. Data on CGM use in preschool children are limited, but suggest low overall rates of use,126,129 often due to financial constraints. Parental satisfaction with CGM use is high, in large part because the technology can decrease the likelihood of severe hypolycemia.130 When parents/caregivers share their thoughts and interpretations, real-time CGM information, including a color-coded screen with arrows, and alarms can often be understood by preschool children from around age 5 to 6 years. Talking with the child in an age-appropriate way about actual CGM information gradually increases the child´s understanding and participation in their insulin treatment.

Even if children can have some understanding of this, interpretation and necessary steps of action are always the responsibility of the parent/caregiver. Use of CGM devices in preschool children can be hampered by issues of adhesion and skin irritation.131,132

The ability of some CGM devices to remotely transmit glucose values to a phone can be of benefit for parents/caregivers who rely on others for part-time care of their child with diabetes, for example, while at day care or preschool.

CGM enables deepened analysis and understanding of glycemic patterns (such as postprandial glycemic excursions), and downloading data from the device is a pedagogic tool for the team when discussing solutions to various problems with the parents of a child with diabetes. Downloading at home by parents should be encouraged, and can form a basis for self-adjustment of insulin doses for experienced families.

12 | USE OF INSULIN PUMPS WITH AND WITHOUT CGM IN PRESCHOOL CHILDREN

Preschool children are unique consumers of novel insulin delivery and device technologies, as they are dependent on caregivers for all aspects of device use. Recent technologies, such as pumps and CGM, can be particularly helpful to parents and caregivers of preschool children who are extremely dependent on fine-tuning of small insulin doses, both with regard to size and timing of insulin doses.

An insulin pump system is available that can suspend insulin delivery when glucose levels, as measured by CGM, are predicted to become low, and thus reduce the risk and duration of hypoglycemia. 133 On the other hand, insulin pumps and CGM are associated with increased cost and may increase the provider burden; insulin pumps may also carry additional risks associated with pump and infusion set malfunctions.

Insulin doses in preschool children need to be modified frequently as children of this age are growing rapidly and have changing patterns of eating and sleeping. The decrease in size of insulin pumps and CGM devices (including the infusion sets/sensors) over the past few years make these therapies more acceptable for preschool children. The safety of insulin pump and CGM use in this population appears to be similar to that seen in other age groups.130,134 It is essential for the family to have access to blood ketone checking to detect problems with the supply of insulin from the pump. See the section on ketone monitoring below and the ISPAD guidelines on sick days.135 Regular downloading of data from the pump (and CGM if used), both at home and in clinic, allows patterns of dosing136 and glucose levels to be recognizable. Always give extra insulin with a pen or syringe in case of suspicion of problems with insulin delivery from the pump. If the child is prone to ketosis, replacing part of the overnight basal (30%-40%) with a small dose of long-acting insulin (detemir, glargine or degludec) may help, but might also reduce the flexibility in basal insulin administration by temporary basal rates.

Parents of preschool children who switch from MDI to insulin pumps report more flexibility and freedom, as well as less stress and anxiety related to their child's care.137 Data suggest a decrease in HbA1c129,134 and reductions in rates of severe hypoglycemia95,134 after implementation of insulin pumps in preschool children. Insulin pump features that enable automatic bolus calculations based on insulin sensitivity factors and insulin to CHO ratios can aid caregivers in insulin administration.

Insulin pump therapy may be effective in helping to manage toddlers' eating behaviors by facilitating split bolus dosing. The pump calculates "insulin on board", i.e. how many units from a previous dose of insulin that still exerts a glucose-lowering effect. A phone app that can calculate "in- ▶

sulin on board" can be used for calculation of bolus doses of insulin when on injection therapy.

Although CGM provides an overwhelming amount of data, it is important to look for daily patterns (eg, the "modal day" when downloading data), and adjust insulin-to-CHO ratios and correction factors only after a repeated pattern has been identified. The frequency of insulin pump and CGM use varies between centers. Barriers to the use of these treatment options in preschool children need to be explored.

13 | SKIN CARE

There are very few data on special considerations regarding skin care in preschool children with type 1 diabetes but CGM-related skin problems seem to be most common in very young users.132 CGM-related skin problems are not associated with atopy.138 In general, recommendations for site use (including site selection, site preparation, and site rotation) are similar as for older children. Many preschool children receive insulin injections and insert infusion sets and CGM sensors in their buttocks, an area often covered by a diaper. The abdomen, upper arm, and upper thigh regions are also commonly used. For children under the age of 6 using insulin pumps, data suggest that rates of scarring and lipohypertrophy are high (50% and 45%, respectively) but not different than in older children.139

Injection, infusion, and CGM sites should be properly prepared and regularly rotated in order to reduce the likelihood of lipohypertrophy, superficial scarring, infection, rashes, skin reactions, and dry skin.

Injection, infusion, and CGM sites should be inspected by diabetes team members at every visit to the clinic to detect any skin problem or lipo-hyper/hypotrophy early, in order to treat promptly. The use of pumps and CGM are often limited by skin reactions to the adhesive. Prepare the site a few days prior to insertion by the use of a skin moistener that preserves water. Topical corticosteroid (group I or II) can be used to treat skin reactions and break the vicious circle of itching after removal.

14 | KETONE MONITORING

Measuring ketone bodies in blood (betahydroxybutyrate, BOHB) should be recommended as the primary method of detecting and monitoring ketosis in preschool children with type 1 diabetes; see the ISPAD Guidelines on Sick days.135 Measurement of acetoacetate in urine can be used as an alternative, but gives less precise information. As preschool children do not urinate on command, especially when sick, results from blood ketone monitoring will be more easily available both for the child and parent. Blood ketone checking also gives the health care professional much better information to provide advice over the phone or in the emergency room.

Ketones should be monitored when there is a suspicion of lack of insulin raised either by high blood glucose (2 values above 14 mmol/L within 2 hours that do not decline on a correction insulin dose) or when the child shows symptoms suggestive of ketosis (vomiting, nausea, stomach pain, fever, or unclear illness). Elevated glucose levels and ketone levels suggest lack of insulin and should promptly be treated with injection of insulin 0.1 U/kg (or 10% of TDD) every second hour until BOHB is below 0.5 mmol/L. If levels are above 3.0 mmol/L, the family should seek guidance by phone or in person immediately, possibly in an emergency room, due to the high risk of ketoacidosis. Slightly elevated BOHB (usually <1.0 mmol/ mol) in combination with normal or low glucose levels indicates combined lack of CHO and insulin, commonly associated with gastroenteritis in preschool children. This can most often be treated at home with ingestion of sugary fluids and administration of extra insulin subcutaneously.

See the ISPAD Guidelines on Sick days for further advice.135 Ketoacidosis is a life-threatening acute complication of diabetes that demands care at a skilled hospital unit. Six percent of children younger than 6 years in the United States and 4% of children in Germany/Austria (from data from the Type 1 Diabetes Exchange clinic registry and the Prospective Diabetes Follow-up Registry: DPV) have suffered from ketoacidosis during the past year.45 Education of families on prevention of ketoacidosis is an essential part of diabetes care.140 See the ISPAD Guidelines on Diabetic Ketoacidosis for further advice.140

15 | HYPOGLYCEMIA

Hypoglycemia, including fear of hypoglycemia, is a limitation to striving for normoglycemia. The risk of hypoglycemia presents a major physiological and psychological barrier to achieving optimal glycemic control, and may result in significant emotional morbidity for patients and caregivers.29,141,142 Young age is traditionally regarded as a marker of high risk of severe hypoglycemia during insulin treatment. 29The frequency of severe hypoglycemia has decreased over time in all children.29,35,143,144 In Germany and Austria, fewer than 2% of children younger than 6 years with type 1 diabetes have experienced a severe hypoglycemic event with seizures/unconsciousness during the previous year; in the United States this figure is less than 3%.126

The erratic daily life of a preschool child (food intake, activity, sleep, and sick days) has been

regarded as the explanation for the historically high risk of severe hypoglycemia in preschool children with type 1 diabetes. Preschool children are not yet able to identify and articulate their symptoms and it can be very difficult for caregivers to detect these symptoms. Prolonged nocturnal hypoglycemia is not uncommon in children younger than 7 years with type 1 diabetes as detected in CGM studies,125,145–147which is associated with a higher risk of severe hypoglycemia.146

The fear of an hypoglycemic event, rather than the frequency of hypoglycemic events, is associated with higher HbA1c and poorer HRQoL.141 The role of fear of hypoglycemia cannot be underestimated for parents of children with type 1 diabetes.142 Asking about frequency and severity of hypoglycemia is typical in a clinic visit, and it may also be helpful to ask about thoughts and feelings during and after the hypoglycemic event. Fear of nocturnal hypoglycemia is a particular challenge.142 Fear is not correlated with the numbers of hypoglycemic episodes, but is related to their severity, especially in mothers of children who have experienced a hypoglycemic seizure. The use of insulin pumps and CGM has been reported to decrease the risk of hypoglycemia.148,149 Insulin pumps with low glucose suspend features appear to further reduce the time spent in hypoglycemia.150,151

The comparison of data between the United States T1D Exchange and German/Austrian DPV registries showed that an HbA1c of <7.5% (<58 mmol/mol) can frequently be achieved in children younger than 6 years with type 1 diabetes without an increased risk of severe hypoglycemia. 126 In many countries, children younger than 7 years most frequently have the lowest HbA1c. In Sweden, 74% of insulin-treated children younger than 7 years have HbA1c < 7.4% (<57 mmol/mol), and the overall frequency of severe hypoglycemia (seizures/unconsciousness) in the pediatric age (0-18 years) is 2.5%.152

For definitions and further information see the ISPAD Guidelines on Hypoglycemia.29

15.1 | Treatment of mild hypoglycemia in infants

and preschool children Oral glucose as tablets, gel, or a drink (0.3 g glucose/kg bodyweight) is the preferred method of hypoglycemia treatment.29,153 This dose will raise plasma glucose approximately 2.5 to 3.6 mmol/L (45- 64 mg/dL).29 It is important not to give too much CHO when treating hypoglycemia, in order to avoid subsequent hyperglycemia. Giving something that contains fat (ie, milk and chocolate) will slow down the gastric emptying, and cause a slower rise in plasma glucose.154 Sucrose sweetened confectionary should not be routinely used to treat hypoglycemia, as it can lead to increased risk of dental caries and food refusal if the child learns that sweets are substituted for unconsumed food. It is important that hypoglycemia is not over-treated, as 5 to 7 g CHO is usually adequate in raising the plasma glucose to normal levels for small children using intensive therapy.

To treat hypoglycemia in breast- or formula-fed infants, CHO gel, diluted juice, or a glucose polymer from a spoon or bottle can be offered. Honey should not be given to infants younger than 1 year due to risk of botulism.

16 | SCREENING FOR ASSOCIATED DISEASES

Early onset of type 1 diabetes is associated with a higher frequency of celiac disease compared ▶

with older children, which affects the treatment situation of the child,155–157 and may influence the risk of complications and quality of life. Repeated screening for celiac disease, thyroid disease, and other autoimmune disorders is essential.158

17 | LIVING WITH DIABETES IN THE FAMILY

For people living with type 1 diabetes and their families, the management of the condition is complex and individual. Daily challenges imposed by type 1 diabetes include cognitive and emotional burdens that can take the form of increased vigilance to dietary intake, symptom monitoring, and frustrations with glucose excursions. For caregivers of preschool children with type 1 diabetes, additional complexities are encountered, including the necessity to adapt to developmental changes to ensure adequate psychological adjustments for the child and themselves, and to facilitate care in the context of other care providers such as preschool staff.159 Clinicians need to be aware of the overwhelming sense of responsibility and worry which parents of preschool children with type 1 diabetes can feel. Parents who have access to a supportive network (relatives and/or friends) have lower risk of diabetes-related stress and burnout. 128 It is important to educate secondary caregivers about type 1 diabetes and insulin treatment. Attention should be given to the needs of the siblings of a child with type 1 diabetes.

As children grow, they understand more about health and illness. When appropriate, it needs to be explained that diabetes is not caused by eating too much sugar, and that you cannot catch diabetes from another person. This needs to be actively taught to friends and relatives as well to avoid common misconceptions about diabetes. Parents are an integral part of the diabetes team and have the most important supportive role to play over the years as their children eventually learn to self-manage their diabetes. Providing this support can be difficult when parents have their own stressors to deal with, and struggle with the constant vigilance needed to ensure the safety of their child. Dashiff et al160 report that parents of older children with type 1 diabetes experience an ongoing struggle, worry, and frustration about their parenting role. During young childhood, parents take responsibility for all diabetes-related tasks such as insulin administration, dosing calculations, blood glucose checking, and so It is important that they do this in a way that is neither threatening nor frightening for their child. Involving the child in aspects of diabetes management as soon as possible (eg, finger pricks and CHO counting) is recommended, so the child can begin to develop a sense of ownership/management of their own health. A supportive and emotionally warm parenting style is important for promoting improved quality of life for children with type 1 diabetes.161

Establishing good habits in the early years will form the basis for optimal diabetes self-management during adolescence and into adulthood. 2,92,106,107 In order to create an environment in which parents feel confident and comfortable, it is crucial that they are appropriately supported by all members of their multi-disciplinary team and that they have adequate access to appropriate support when they need it. The way that parents model diabetes-related tasks will have a direct impact on the way their children learn. Supporting parents toward a positive adjustment to living with diabetes will help them to effectively model those tasks and assignments involved in daily life with diabetes. It is important to engage both fathers and mothers in diabetes care from the onset, and to keep them both involved in everyday diabetes care throughout the childhood years.

Parents express that it is important to explain to their child in very simple and clear terms what type 1 diabetes involves. There are certain aspects of diabetes management that are not negotiable (glucose checking, insulin injections/pump site changes, CGM use, etc), and the child needs to begin to understand that as early as possible. It is important to involve the child in diabetes management as soon as possible so they can begin to develop a sense of ownership/management of their own disease. Reinforcing such an attitude early on will help to shape the child's attitude and approach to diabetes in the future.

Parents report that diabetes will often initially disrupt the normal parent-child relationship, as diabetes frequently comes first in the mind of the parent in response to a child's requests. It is important for parents to ask themselves, "If my child didn't have type 1 diabetes, would I say no to this request?", and thus strive to reestablish the normal parent-child relationship.

18 | SCREENING CHILDREN FOR PSYCHOSOCIAL DISTRESS

Regular screening of children for psychosocial distress is important to ensure that difficulties are identified early, and appropriate support and treatment plans established as soon as possible. Most children are not able to complete questionnaires or report on their own level of emotional distress in a reliable manner until they are approximately 7 to 8 years of age. Therefore, either talking with them directly about how they feel, or asking their parents to report

on their children's psychosocial well-being is recommended. For children who are older, there are several pediatric measures of depressive symptoms that are validated and reliable for use with children as young as 7 years of age, varying in length and depth of detail. These include the Children's Depression Inventory (CDI)162 and the Center for Epidemiologic Studies – Depression (CES-D) scale.163 Both measures are self-reported questionnaires containing items on types of symptoms (eg, sadness and low self-esteem) and functional areas (eg, not having friends, schoolwork is not as good as it was before, and arguing with others). Pediatric quality of life can be addressed by specific questionnaires such as the Pediatric Quality of Life Inventory (PedsQL) generic and Type 1 Diabetes modules.164 These measures offer a child self-report for youth ages 5 to 7 and also for youth ages 8 to There are also PedsQL parent proxy reports for children ages 2 to 18.164 Diabetes-specific emotional distress can be assessed in children ages 8 to 11 Problem Areas in Diabetes Survey-Children (PAIDC) and teens Problem Areas in Diabetes Survey-Teens (PAID-T) and parent's diabetes-specific emotional distress can also be assessed (PPAID- C and P-PAID-T) in measures developed by Weissberg-Benchell and colleagues. Similarly, diabetes-specific emotional distress from age 8 can be assessed by the PAID-Parent (PAID-PR) scale and from age 8 in youth with the PAID-Peds scale, both developed by Markowitz et al.165,166 Parental anxiety can have a direct and negative effect on diabetes management and health outcomes. There can often be a comorbidity of depression; however, they are 2 separate conditions and should be treated separately. They may act in opposite directions with regard to diabetes management and control, so we recommend assessing anxiety separately from depression. The Center for Epidemiological Studies-Depression Scale (CESD) is often used as a measure of depressive symptoms in adults, and the Beck Depression as well as the Beck Anxiety scales are also often used. Worries about diabetes impact on glycemic control in children, should be acknowledged and addressed.

19 | PRESCHOOL CARE

Many preschools provide excellent care for children with type 1 diabetes. Parents and health care professionals should work together to overcome any difficulties and ensure the safety and well-being of the child with type 1 diabetes when cared for outside the home setting. It is crucial that every child is supported effectively to achieve their full potential. Legislation protects children with type 1 diabetes in many countries. One example is the Equality Act 2010 (England, Scotland, and Wales) which dictates that schools must make reasonable adjustments to ensure that children with disabilities are not put at a substantial disadvantage compared with their peers. For diabetes, this means schools ensuring they have enough staff trained so that the child with diabetes can take part in all aspects of preschool and school life. Contingency plans must be in place to train replacement staff quickly. The Kids and Diabetes in Schools (KiDS) program of the International Diabetes Federation (IDF) offers education and guidance for families and school staff on ways to help children with type 1 diabetes manage in school. KiDS information is available in 10 languages (as of June 2017) and can be accessed online at http://www. idf.org/education/kids. In addition to ensuring the rights of the child with diabetes, it is important to create trust and cooperation between the preschool, the family, and the diabetes team. An individually written diabetes management plan is helpful in this cooperation to help the child with type 1 diabetes,167 and should include information about and practical training for the use of diabetes-related technologies.168 Both the parents and the diabetes team need to share the responsibility for educating the preschool institution, especially when the child is newly diagnosed with diabetes or when additional diagnosis such as celiac disease occurs. Preschool staff often find CHO counting helpful as it gives them a tool to assess the dose of insulin to be given in relation to the food intake and current glucose level. In countries where there are no regulations to support the child with diabetes, the diabetes team together with the parent organizations should advocate for improved regulations. Parents express that while regulations certainly help to ensure documentation and agreements on daily care, maintaining a close relationship with the school (staff, teachers, etc) is equally if not more important to ensure effective daily management of their child's diabetes. Parents can be in very close contact with the school, including offering training sessions, educational materials for other parents etc, which will lead to better and more effective diabetes management. This helps them to feel more comfortable/ less stressed when sending their child to preschool.

20 | ALTERNATIVE AND COMPLEMENTARY THERAPIES

At times families try alternative indigenous remedies and even discontinue insulin. This can be avoided if parents are counseled regarding the absolute necessity of insulin for the child's survival. Alternative therapies may be tolerated if important for the family as ▶

long as they do not interfere with the regular diabetes care, including insulin doses, glucose monitoring and healthy food choices, or impact the child's growth or development or deplete economic resources needed for insulin treatment.

21 | CARE FOR THE PRESCHOOL CHILD WITH TYPE 1 DIABETES IN LIMITED RESOURCES SETTINGS

Whenever possible, the guidelines described above in the preceding sections should be followed. It is important to remember that building a good rapport with the family and providing comprehensive diabetes education are inexpensive, and remain the most effective strategies to improve diabetes management by the family.37 Knowledge about the effects of insulin, food, and physical activity on glucose levels are essential to protect the child from acute and chronic complications of diabetes under all circumstances. The first few visits of the family are the most crucial in this regard. Initial approach to diagnosis and treatment is based upon staffing and facilities at specialized centers for the care of young children with diabetes, with many centers recommending hospitalization.

Parents should be counseled and educated in detail. The challenges in managing type 1 diabetes in the preschool child are several-fold higher in resource limited settings. Awareness, health infrastructure, and number of medical professionals trained in the management of childhood diabetes are inadequate for a significant proportion of the population in many countries in South East Asia and sub-Saharan Africa. The diagnosis is often delayed, and may even be missed in some cases, resulting in death before diagnosis. Common misdiagnoses are gastroenteritis, pneumonia, asthma, urinary tract infection, genital tract infection (candidiasis), enuresis, and malaria. Parents may take longer to come to terms with the diagnosis and the need for life-long insulin therapy. The financial implications of the condition add to the psychological distress brought about by the diagnosis. Risk of acute and chronic complications, as well as mortality, is higher in these children due to suboptimal management. 169 In the United States, young people of African descent have increased risk of short-term complications (ketoacidosis and severe hypoglycemia) when adjusted for socioeconomic status,170 and higher HbA1c even when adjusted for mean glucose levels.171 HbA1c was higher even when fasting glucose is <7 mmol/L in black individuals both with and without diabetes compared with white, but the prognostic value of HbA1c for predicting cardiovascular disease, nephropathy and retinopathy were similar.172

The financial issues need to be addressed upfront by the treating team. The challenge of finding ways to support the families lies chiefly with the care providers. The team should be familiar with the governmental and non-governmental agencies in the area that may provide financial assistance for procuring insulin and glucose strips, and ensure that parents have access to these before the child is discharged home. Most preschool children in resource-limited settings remain on regular and NPH insulin administered by insulin syringes. With only regular and NPH available (as in the DCCT study), a multiple injection therapy with regular insulin for meals and NPH insulin at bedtime can be effective in teaching the family the relationship between insulin dose and CHO content of the meal. CHO counting can be used in this situation. The challenge to overcome will be the lunchtime injection at school. It is very important to motivate and explain this to the school staff as the alternative of giving a twice daily mixture of regular and NPH does not result in a physiological insulin profile. In a situation where food availability is unpredictable, a child on twice daily injections will experience hypoglycemia, while the child on multiple injections can adjust mealtime doses accordingly. Few patients are able to afford analog insulin and pen devices.

The use of insulin pumps is only affordable by a low percentage of the population. Administration of small doses is therefore a practical challenge. In young infants, parents may be taught to dilute insulin with normal saline (available in 10 mL vials). The use of 0.3 mL insulin syringes (100U/ml, 30 U in total) allows an accurate administration of half units, appropriate for most preschool children. Similarly, use of CGM remains unavailable for most children with type 1 diabetes in the resource-limited scenario, and frequent self-monitoring of blood glucose is the only method for monitoring glycemia. However, even this may not be feasible for some families due to the high cost of blood glucose strips. If possible, the child can be recommended a meal plan with a relatively consistent CHO intake at meal and snack times during the day to match the insulin regimen. The family can be taught to have a high index of suspicion for hypoglycemia and treating it on suspicion, relying mostly on urinary glucose monitoring for insulin dosing, and to use SMBG at least on sick days if available.173 With limited number of strips, the family can, for example, measure before and 2 hours after lunch 1 week, and before and after dinner the next to get a more stringent picture of the day compared with random checks. Urine strips should be available for ketone mo-

nitoring during sick days.

Another issue that may compound the challenge in resourcelimited settings is that some parents may have low levels of literacy and health literacy, meaning thereby that they cannot read the numbers on the insulin syringe and on the glucometer. For example, in India, literacy rate is 74.04% according to the 15th official census in 2011 (http://www.census2011.co.in/literacy.php). In such cases, it is helpful to identify a suitably literate relative, friend or neighbour who can undergo diabetes education along with the parents and assist them in the domiciliary management. The parents should also be encouraged to learn the basics of reading and writing. In the case of low literacy, a simpler insulin regime such as twice daily dosing with premixed insulin can be given. Hearing the number of clicks from an insulin pen can obviate the need to read the number of units. Teaching the parents to recognize "Hi" and "Lo" on glucometer, to treat hypoglycemia based on symptoms alone, and to recognize hyperglycemia and ketonuria by urinary strips is also useful to prevent lifethreatening episodes.

Vomiting in a child with diabetes should always be regarded as imminent ketoacidosis, and appropriate treatment should be sought immediately in the absence of knowledge and diagnostic measurements.

If the child is not feeling well with other symptoms, the first line of treatment should be something containing sugar to treat impending hypoglycemia. This should be well known by all the older children and adults who are close to the child with diabetes, and they should know where to readily find a source of sugar. To conclude, the goals of management of type 1 diabetes in resource-limited settings must be situated in the context of the resource-limited environment and based on the family's educational and financial status. Avoidance of acute life-threatening complications and continuation of regular treatment and follow-up are the immediate goals.

22 | FUTURE NEEDS OF PRESCHOOL CHILDREN WITH TYPE 1 DIABETES

"Diabetes during early childhood creates a psychosocial challenge to the families of these children. Successful management of infants and toddlers with diabetes depends on a well functioning and educated family, the availability of a diabetes health care team experienced in the treatment of these youngsters, and the involvement of the extended family, child care personnel and others who play a role in their daily care" (Daneman).174

The addition of new tools should enable families living with type 1 diabetes to provide increasingly effective therapy and support for preschool children with diabetes. The cognitive, motor and social immaturity, as well as the small body size of preschool children must be considered when designing new equipment, including sensors, insulin pumps, and (hybrid) closed-loop solutions for insulin delivery.

It is important to include children younger than 7 years in both epidemiological and clinical studies regarding treatment strategies and tools (both technical equipment and pharmacological) and outcomes; moreover, when the youngest children with type 1 diabetes are included in these studies, data regarding children with early-onset diabetes must be presented separately to enable subgroup analysis. Children younger than 7 years with type 1 diabetes constitute only approximately 10% of the population of all children and adolescents with type 1 diabetes,126,152 but in many countries the incidence in this subgroup is increasing most quickly. Collaboration between centers is thus necessary in order to conduct studies that are sufficiently powered.

REFERENCES 1-174 and better tables from www.ispad.org

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HTA-rapport och DN-Debatt: Använd Avastin i stället för Lucentis

Frågan om användning av läkemedel utanför godkänd indikation har blossat upp igen. I dag skriver Dagens Nyheter om en utvärdering av läkemedlen bland andra Lucentis (ranibizumab) och Avastin (bevacizumab), som gjorts av HTA-centrum vid Sahlgrenska universitetssjukhuset i Göteborg.

HTA-centrumet anser att båda läkemedlen kan användas för behandling av åldersförändringar av gula fläcken, trots att endast Lucentis är godkänd för den indikationen. Det finns inga mätbara och kliniskt relevanta skillnader mellan de båda läkemedlen, anser professor Henrik Sjövall, vid Sahlgrenska universitetssjukhuset, och stödjer sig på utvärderingen som publicerats i en rapport.

”Det finns inget stöd för att rutinmässigt använda det dyrare Lucentis i stället för Avastin, säger Henrik Sjövall till tidningen.

I DN av Kerstin Wickström, klinisk expert på Läkemedelsverket.

”Det är inte så att vi avråder läkare från att använda Avastin, vi värnar den fria förskrivningsrätten som läkare har. Men vi kan bara förorda användningen av ett godkänt läkemedel”, säger Kerstin Wickström.

Enligt HTA-utvärderingen skulle Västra Götalandregionen kunna spara upp till 85 miljoner kronor per år om det billigare Avastin skulle användas i stället för Lucentis. Ungefär hälften av alla landsting och regioner använder Avastin utanför godkänd indikation i dag.

Lucentis marknadsförs av Novartis. Avastin marknadsförs av Roche. Avastin är ett läkemedel som anävänds vid cancer och patentet är utgånget.

Från lakemedelsvarlden.se

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DN Debatt

Varje år drabbas tusentals personer av åldersförändring i gula fläcken. En ny rapport visar att landstingen skulle spara mångmiljonbelopp om man började använda läkemedlet Avastin mot sjukdomen – ett läkemedel som fungerar lika bra som de betydligt dyrare alternativen. Men frågan är kontroversiell eftersom Avastin inte är godkänt för ändamålet.

– Du blir inte blind men du förlorar ditt centralseende. Du tappar förmågan att se färger och detaljer. Du kan orientera dig, se saker i periferin men i mitten ser du en mörk fläck.

Så beskriver läkaren Per Pohjanen ögonsjukdomen våt makuladegeneration eller så kallad åldersförändring i gula fläcken, den vanligaste orsaken till synnedsättning hos äldre i Sverige och västvärlden.

Länge fanns inget bra fungerande läkemedel mot sjukdomen. Men i början av 2000-talet upptäckte läkare att vissa cancerpatienter som behandlades med läkemedlet Avastin upplevde att de fick bättre syn. Det visade sig att just dessa cancerpatienter även hade åldersförändringen i gula fläcken – och att effekten av läkemedlet var orsaken till synförbättringen.

Läkemedelsbolaget bakom Avastin, amerikanska Genentech, tog då fram ett nytt snarlikt läkemedel – Lucentis – som registrerades som ett ögonpreparat hos Läkemedelsverket.

Henrik Sjövall, professor och universitetsöverläkare vid Sahlgrenska universitetssjukhuset och en av författarna till rapporten. Plötsligt fanns det ett godkänt, välfungerande ögonläkemedel på marknaden. Men till skillnad från cancerläkemedlet Avastin som numera kostar ett par hundralappar per dos, kostar Lucentis drygt 9 000 kronor per dos.

HTA-centrum vid Sahlgrenska universitetssjukhuset i Göteborg, som har uppdraget att granska och utvärdera nya behandlingsmetoder, publicerade nyligen en rapport där man undersökt effekten och biverkningarna av de två läkemedlen.

– Vi har gått igenom ett massivt forskningsmaterial av studier gjorda enligt konstens alla regler. Det vi hittade var väldigt intressant, det finns inga mätbara och kliniskt relevanta skillnader mellan de två läkemedlen över huvud taget. Helhetsbilden är för mig kristallklar – det finns inget stöd för att rutinmässigt använda det dyrare Lucentis i stället för Avastin, säger Henrik Sjövall, professor och universitetsöverläkare vid Sahlgrenska universitetssjukhuset och en av författarna till rapporten.

Det finns inga mätbara och kliniskt relevanta skillnader mellan de två läkemedlen i över huvud taget. Helhetsbilden är för mig kristallklar – det finns inget stöd för att rutinmässigt använda det dyrare Lucentis i stället för Avastin.

HTA-centrum räknade också på hur mycket pengar Västra Götalandsregionen skulle spara om ögonsjukvården gick över till att använda det billigare läkemedlet Avastin. Exakt vad landstinget betalar för läkemedlet vet man inte

eftersom det är en affärshemlighet, men vanligtvis får landstingen en viss rabatt på det officiella listpriset. Enligt HTA-centrums beräkningar handlar det om besparingar på 46–85 miljoner kronor per år beroende på läkemedelsrabatt.

Ungefär hälften av Sveriges landsting använder sig redan av Avastin. Redan 2012 presenterades en stor amerikansk studie som visade att de två läkemedlen hade samma effekt och därefter valde flera landsting och regioner att byta till det billigare preparatet.

– Vi sparar 7–8 miljoner per år genom att använda Avastin. Men vi räknar inte så, vi räknar på hur många ögon vi kan behandla. För varje öga som vi behandlar med ett dyrare läkemedel får 15–20 ögon stå tillbaka, säger Per Pohjanen, överläkare inom Ögonsjukvård Norrbotten.

Men det finns de som har invändningar mot att använda det billigare alternativet Avastin eftersom läkemedlet inte är godkänt för ändamålet.

– Det är inte så att vi avråder läkare från att använda Avastin, vi värnar den fria förskrivningsrätten som läkare har. Men vi kan bara förorda användningen av ett godkänt läkemedel, säger Kerstin Wickström, klinisk expert på Läkemedelsverket.

Att Avastin skulle godkännas för behandling av åldersförändringar i gula fläcken är heller inte troligt, säger Kerstin Wickström. Läkemedelsföretaget måste nämligen ansöka till myndigheten om att få läkemedlet godkänt för ögonbehandling. Och det är samma företag som tillverkar den aktiva substansen i det billigare icke-godkända Avastin och det dyrare godkända Lucentis.

– Företaget har alltså inte något incitament att ansöka om ett godkännande för Avastin, säger Kerstin Wickström.

Läs mer: ”Det handlar om att skapa jämlik vård.”

Fakta. Åldersförändring i gula fläcken

Gula fläcken kallas det område som finns i mitten av näthinnan. Det finns två typer av åldersförändringar i gula fläcken, torra eller våta. Torra förändringar är den vanligaste formen av sjukdomen och synen förändras långsamt. Mot det finns ingen effektiv behandling.

Våta förändringar är ovanligare. Våta förändringar beror på att det bildas blodkärl under gula fläcken som läcker blod och vätska, vilket gör att gula fläcken svullnar och syncellerna försämras.

Synen kan försämras snabbt, inom bara några veckor. Vanliga symptom är att man börjar se raka linjer som krokiga, att ansikten ser förvrängda ut och att det centrala synfältet går förlorat. I stället ser personen en suddig, mörk fläck i mitten.

Våta förändringar behandlas med läkemedel som sprutas in i ögats glaskropp. Läkemedlet bromsar bildandet av blodkärl under gula fläcken och gör så att mindre vätska läcker ut. Behandlingen botar inte sjukdomen, men kan bromsa den.

Källa: Vårdguiden 1177

Fakta. Läkemedlens pris

Lucentis och Eylea kostar ungefär 9 000 kronor per dos enligt listpris. Avastin kostar i sin tur omkring 3 300 kronor per förpackning. En förpackning räcker till cirka 30 doser dvs kostnad 110 SEK istället för 9000 SEK per patient.

När landstingen upphandlar får de rabatt på läkemedlen och vad varje landsting faktiskt betalar för respektive preparat är en affärshemlighet.

Källa: Tandvårds- och läkemedelsförmånsverket

Från www.dn.se

Nyhetsinfo 18 juli 2017
www red DiabetologNytt

20% Reduction in Total Mortality 12 Years Prospective Study With Greater Diet Quality. N Engl J Med

BACKGROUND

Few studies have evaluated the relationship between changes in diet quality over time and the risk of death.

METHODS

We used Cox proportional-hazards models to calculate adjusted hazard ratios for total and cause-specific mortality among 47,994 women in the Nurses' Health Study and 25,745 men in the Health Professionals Follow-up Study from 1998 through 2010. Changes in diet quality over the preceding 12 years (1986–1998) were assessed with the use of the Alternate Healthy Eating Index–2010 score, the Alternate Mediterranean Diet score, and the Dietary Approaches to Stop Hypertension (DASH) diet score.

RESULTS

The pooled hazard ratios for all-cause mortality among participants who had the greatest improvement in diet quality (13 to 33% improvement), as compared with those who had a relatively stable diet quality (0 to 3% improvement), in the 12-year period were the following: 0.91 (95% confidence interval [CI], 0.85 to 0.97) according to changes in the Alternate Healthy Eating Index score, 0.84 (95 CI%, 0.78 to 0.91) according to changes in the Alternate Mediterranean Diet score, and

0.89 (95% CI, 0.84 to 0.95) according to changes in the DASH score.

A 20-percentile increase in diet scores (indicating an improved quality of diet) was significantly associated with a reduction in total mortality of 8 to 17% with the use of the three diet indexes and a 7 to 15% reduction in the risk of death from cardiovascular disease with the use of the Alternate Healthy Eating Index and Alternate Mediterranean Diet.

Among participants who maintained a high-quality diet over a 12-year period, the risk of death from any cause was significantly lower — by 14% (95% CI, 8 to 19) when assessed with the Alternate Healthy Eating Index score, 11% (95% CI, 5 to 18) when assessed with the Alternate Mediterranean Diet score, and 9% (95% CI, 2 to 15) when assessed with the DASH score — than the risk among participants with consistently low diet scores over time.

CONCLUSIONS

Improved diet quality over 12 years was consistently associated with a decreased risk of death. Funded by the National Institutes of Health.

FROM THE ARTICLE

BACKGROUND

Some epidemiologic studies of nutrition focus on dietary patterns rather than single nutrients or foods to evaluate the association between diet and health outcomes.1 Accumulated evidence supports an association between healthy dietary patterns and a decreased risk of death.2-11 Results from recent studies suggest that improved diet quality, as assessed by means of the Alternate Healthy Eating Index–2010 score,12 the Alternate Mediterranean Diet score,10,13 and the Dietary Approaches to Stop Hypertension (DASH) diet score,14 was associated with reductions of 8% to 22% in the risk of death from any cause15,16 and reductions of 19% to 28% in the risk of death from cardiovascular disease and 11% to 23% in the risk of death from cancer.2-4,17

Given such consistent evidence, the 2015 Dietary Guidelines for Americans recommended the Alternate Healthy Eating Index, the Alternate Mediterranean Diet, and DASH as practical, understandable, and actionable diet plans for the public.18 Such guidelines are important in the United States and globally because unhealthy diets have been ranked as a major factor contributing to death and health complications.19 Evaluation of changes in diet quality over time in relation to the subsequent risk of death would be important. Here, we evaluated the association between 12- year changes (from 1986 through 1998) in the three diet-quality scores noted above and the subsequent risk of total and cause-specific death from 1998 through 2010 among participants in the Nurses' Health Study and the Health Professionals Follow-up Study. We also examined shortterm changes (baseline to 8-year follow-up, 1986–1994) and long-term changes (baseline to 16-year follow-up, 1986–2002) in diet quality in relation to total and cause-specific mortality.

Methods

Study Population and Design The Nurses' Health Study, a prospective study that was initiated in 1976, enrolled 121,700 registered nurses who were 30 to 55 years of age. The Health Professionals Follow-up Study, a prospective study that was initiated in 1986, enrolled 51,529 U.S. health professionals who were 40 to 75 years of age. Baseline and follow-up questionnaires were sent to participants every 2 years to update medical and lifestyle information over the follow-up period.20,21 In both studies, follow-up rates exceeded 90% in both cohorts.22

For the present study, the initial cycle was set at 1986, baseline was set at 1998 (changes in diet quality were calculated from 1986 through 1998), and the end of follow-up was 2010. We excluded participants who had a history of cardiovascular disease or cancer at or before baseline in 1998, missing information regarding diet and lifestyle covariates, or very low or high caloric intake (<800 kcal or >4200 kcal per day in men and <500 or >3500 kcal per day in women). We also excluded participants who died before 1998. The final analysis included 47,994 women and 25,745 men.

CONCLUSION

In the present study, we found consistent associations between improved diet quality over 12 years as assessed by the Alternate Healthy Eating Index, Alternate Mediterranean Diet, and DASH scores and a reduced risk of death in the subsequent 12 years. A 20-percentile increase in dietquality scores was associated with an 8 to 17% reduction in mortality.

In contrast, worsening diet quality over 12 years was associated with an increase in mortality of 6 to 12%. The risk of death from any cause was significantly lower (by 9 to 14%) among participants who maintained a high-quality diet than among those who had consistently low diet scores over time. Our results are consistent with those of recent meta-analyses showing that higher dietquality scores measured with the Alternate Healthy Eating Index, Alternate Mediterranean Diet, DASH, and the Healthy Eating Index–2010 were associated with a 17 to 26% reduction in the risk of death from any cause.15,16 We found a dose-dependent relationship between changes in diet quality over 12

years and total mortality.

These results underscore the concept that moderate improvements in diet quality over time could meaningfully decrease the risk of death, and conversely, worsening diet quality may increase the risk.

The change in the risk of death was more pronounced when longer-term (16 years) rather than shorter-term (8 years) changes in diet quality were considered.

Taken together, our findings provide support for the recommendations of the 2015 Dietary Guidelines Advisory Committee that it is not necessary to conform to a single diet plan to achieve healthy eating patterns.18 These three dietary patterns, although different in description and composition, capture the essential elements of a healthy diet. Common food groups in each score that contributed most to improvements were whole grains, vegetables, fruits, and fish or n– 3 fatty acids.

To improve our comparison of associations between the three scores that differ in scoring criteria and range, we evaluated the association with mortality using a 20-percentile increase in each score as a common unit for improving diet. For example, if we assume a causal relationship, a person with an increase of 22 of 110 points in the Alternate Healthy Eating Index score over a 12-year period could reduce his or her risk of death by nearly 20% in the subsequent 12 years. An increase in consumption of nuts and legumes from no servings to 1 serving per day and a reduction in consumption of red and processed meats from 1.5 servings per day to little consumption will result in an improvement of 20 points in the score. These findings are broadly consistent with those of previous meta-analyses of the association between consumption of nuts30 and red meat31 and mortality.

In line with other studies, stronger associations were seen when overall deaths and deaths from cardiovascular causes were analyzed, and null or weaker associations were observed for death from cancer.2,3,8,12,32 Our results with respect to improvement in the Alternate Healthy Eating Index and a reduction in the risk of death from cardiovascular disease were expected, given that the Alternate Healthy Eating Index is based on current knowledge of dietary factors contributing to cardiovascular disease.12 Evidence supports the inverse association between higher scores in the Alternate Healthy Eating Index2-4,6,8,16 or the Mediterranean-style diet10,11,13,32-34 and a lower risk of death from cardiovascular disease in various populations. We did not find significant associations between changes in the DASH score and death from cardiovascular causes. Although the DASH score shares some food and nutrient components with the two other scores, it does not include fish or specific fatty acids, which have been consistently associated with a reduced risk of cardiovascular disease.21,33 In addition, previous findings have shown that moderate alcohol intake is associated with a reduction in the risk of death from cardiovascular disease,21,35 and this component is not included in the DASH score. Although some studies have shown a significantly reduced risk of death from cancer with good adherence to some dietary patterns,4-6 other studies have not shown such associations.2,8,32

Our study did not provide consistent evidence that improving diet quality had a substantial effect on overall mortality from cancer.

The strengths of our study include the prospective design, large sample sizes, high rates of follow-up, repeated assessment of diet and lifestyle, and use of multiple diet-quality scores.

However, the study has certain limitations. Because dietary data were reported by the participants, measurement errors were inevitable. However, our food frequency questionnaires were extensively validated against diet records and biomarkers. Although we were able to adjust for many potential confounders, residual and unmeasured confounding could not be completely ruled out. We did not examine the association of each component of the scores and mortality because we considered that a high diet quality is a combination of multiple components that act synergistically. Finally, generalizability may be limited because participants were mostly white health professionals and we only included one third of the initial population because of our study design. However, our findings are broadly consistent with those from other populations.

In conclusion, among U.S. adults, we observed consistent associations between increasing diet quality over 12 years and a reduced risk of death.

Nyhetsinfo 14 juli 2017
www red DiabetologNytt

Better Quick Screening pathway could aid and speed up in diagnosis of monogenic diabetes (MODY), 98% sens, 85% spec. Diab Care

A biomarker-based screening method assessing levels of C-peptide and islet autoantibodies in patients with diabetes is an effective, inexpensive approach to identify patients with monogenic forms of the disease, including maturity-onset diabetes of the young, according to findings from a population-based assessment conducted in Britain.

"Identifying patients with monogenic diabetes, particularly [maturity-onset diabetes of the young], can be challenging," Beverley M. Shields, PhD,senior lecturer in medical statistics with the Institute of Biomedical and Clinical Science at the University of Exeter Medical School, United Kingdom, and colleagues wrote.

"Monogenic diabetes is confirmed by molecular genetic testing, but this is expensive, so testing all patients is not feasible. An approach that could be used to enrich for monogenic diabetes, increasing the proportion identified in those who undergo genetic testing, would be helpful."

Shields and colleagues tested a screening pathway using both C-peptide (via urinary C-peptide to creatinine ratio) and glutamic acid decarboxylase (GAD) and insulinoma-associated-2 autoantibodies (IA-2A) to exclude type 1 diabetes in two populations with previously high pickup rates of maturity-onset diabetes of the young (MODY) — patients diagnosed before age 30 years and currently younger than 50 years from the areas surrounding Royal Devon and Exeter NHS Foundation Trust (n = 716) and Ninewells Hospital (n = 702), both in the United Kingdom. For all patients negative for antibodies with significant endogenous insulin, DNA sequencing was performed for known MODY-related mutations.

Within the cohort, 1,365 had no known genetic cause for their diabetes, 34 had confirmed monogenic diabetes at baseline and eight had cystic fibrosis-related diabetes. After urinary C-peptide to creatinine testing, 979 (76%) had minimal endogenous insulin secretion, indicating type 1 diabetes, and received no further testing. Of the 386 patients then tested for GAD or IA-2A autoantibodies, 170 (44%) tested positive, also indicating type 1 diabetes, and received no further testing.

The remaining 216 patients underwent sequencing for the three most common MODY-related genes; eight tested positive, according to researchers. Of the 208 who tested negative for common MODY genes, additional testing by targeted, next-generation sequencing identified mutations in genes associated with monogenic diabetes in eight more patients. One additional patient had a MODY-related mutation identified through exome sequencing. The results suggested a prevalence of 3.6% (95% CI, 2.7-4.7) among the 1,407 recruited participants.

"A total of 199 out of 1,348 (15%) patients were put forward for genetic testing who were not found to have monogenic diabetes (ie, 15% false-positive rate, so 85% specificity)," the researchers wrote. "Assuming a 98% sensitivity and 85% specificity, the [positive predictive value] for the pathway is 20%, suggesting a 1-in-5 pickup rate for monogenic diabetes, a 5.6-fold increase in probability over the background prevalence alone."

The strength of the pathway, the researchers wrote, is in the integration of both C-peptide and islet autoantibodies, rather than relying on clinical features.

"This offers a simple approach that does not require specific clinician interpretation or complex algorithms of different combinations of features," the researchers wrote. "By combining the two biomarkers, we increase the discriminatory ability and allow the clinician to pick up even atypical cases and rarer forms of monogenic diabetes, which traditional criteria may miss. The use of clinical features, however, results in fewer cases being sent for genetic testing that are negative, which clearly has cost implications."

The most cost-effective approach will likely involve a combination of both biomarkers and clinical features, they noted, and further research is needed to determine whether the pickup rate could be improved by integrating the pathway with clinical features, such as the MODY calculator.

http://www.diabetesgenes.org/content/mody-probability-calculator

Disclosures: The authors report no relevant financial disclosures.
From https://www.healio.com

Abstract

Population-Based Assessment of a Biomarker-Based Screening Pathway to Aid Diagnosis of Monogenic Diabetes in Young-Onset Patients. https://doi.org/10.2337/dc17-0224. Beverley M. Shields,1,2 Maggie Shepherd,1,2 Michelle Hudson,1 Timothy J. McDonald,1,3 Kevin Colclough,4 Jaime Peters,5 Bridget Knight,1,2 Chris Hyde,5 Sian Ellard,1,4 Ewan R. Pearson,6 and Andrew T. Hattersley,1,2 on behalf of the UNITED study team.

OBJECTIVE

Monogenicdiabetes, a young-onset form of diabetes, is often misdiagnosed a stype1 diabetes, resulting in unnecessary treatment with insulin. A screening approach for monogenic diabetes is needed to accurately select suitable patients for expensive diagnostic genetic testing. We used C-peptide and islet autoantibodies, highly sen-sitive and specific biomarkers for discriminating type 1 from non–type 1 diabetes, in a biomarker screening pathway for monogenic diabetes.

RESEARCH DESIGN AND METHODS

We studied patients diagnosed aged 30 years or younger, currently younger than

50 years,intwoU.K. regions with existinghighdetectionofmonogenicdiabetes. The biomarker screening pathway comprised three stages:1) assessment of endogenous insulin secretion using urinary C-peptide/creatinine ratio (UCPCR); 2) if UCPCR was ‡0.2 nmol/mmol, measurement of GAD and IA2 islet autoantibodies; and 3) if negative for both autoantibodies, molecular genetic diagnostic testing for 35 mono-genic diabetes subtypes.

RESULTS

A total of 1,407 patients participated (1,365 with no known genetic cause, 34 with monogenicdiabetes,and8withcystic fibrosis–relateddiabetes).Atotalof386outof 1,365 (28%) patients had a UCPCR ‡0.2 nmol/mmol, and 216 out of 386 (56%) were negative for GAD and IA2 and underwent molecular genetic testing. Seventeen new casesofmonogenicdiabetes werediagnosed(8commonMaturityOnset Diabetesof the Young [Sanger sequencing] and 9 rarer causes [next-generation sequencing]) in addition to the 34 known cases (estimated prevalence of 3.6% [51/1,407] [95%CI 2.7–4.7%]). The positive predictive value was 20%, suggestinga one-in-five detection rate for the pathway. The negative predictive value was 99.9%.

CONCLUSIONS

Thebiomarker screeningpathwayfor monogenic diabetes isaneffective,cheap,and easily implemented approach to systematically screening all young-onset patients. The minimum prevalence of monogenic diabetes is 3.6% of patients diagnosed aged 30 years or younger.

From the article

BACKGROUND

Correct classification of a patient's diabe-tes is important to ensure he or she re-ceives the most appropriate treatment and ongoing management. The most common form of diabetes in children and young adults is type 1 diabetes, ac-counting for .90% of cases (1,2). Other forms of diabetes in this age group, such as monogenic diabetes (including Matu-rity Onset Diabetes of the Young [MODY]), or young-onset type 2, are not often con-sidered. It is estimated that at least 80% of patients with MODY are misdiagnosed (3), and other rarer forms of monogenic diabetes often go unrecognized because of lack of awareness (4). Patients with MODY or type 2 diabetes misclassified as type 1 diabetes will be treated with insulin, whereas noninsulin therapy would be more appropriate. Diet and metformin are the treatment of choice in young type 2 diabetes (5). Patients with MODY because of mutations in the HNF1A or HNF4A genes respond well to low-dose sulphonylureas (6,7), and those with MODY because of mutations in the GCK gene require no pharmacological treatment (8). Getting a correct diagnosis for all forms of monogenic diabetes has important implications for management of an individual's diabetes, a prognosis, and recognition of associated clinicalf eatures; it also allows appropriate counseling of other family members regarding likely inheritance (4).

Identifying patients with monogenic diabetes, particularly MODY, can be chal-lenging. Monogenic diabetes is confirmed by molecular genetic testing, but this is expensive, so testing all patients is not feasible. An approach that could be used to enrich for monogenic diabetes, increasing the proportion identified in those who undergo genetic testing, would be helpful. Clinical features can aid identification of those who may have an alternative diagnosis, and a prob-ability calculator has been developed to help determine which patients are likely to have the most common forms of MODY (9). However, this will not pick up other forms of monogenic diabetes, and its performance is weaker for detecting MODY in insulin-treated patients com-pared with non–insulin-treated patients.

An alternative approach to enrich for monogenic diabetes is to use biomarkers that have been shown to discriminate well between type 1 and other forms of young-onset diabetes. Type 1 diabetes is characterized by autoimmune destruc-tion of the b-cells in the pancreas, leading to absolute ▶

insulin deficiency, so two tests that could be used to diagnose type 1 di-abetes are is let autoantibodies (markers of the autoimmuneprocess) and C-peptide (a marker of insulin deficiency). C-peptide has been shown to be ahighly sensitiveand specific biomarker for discriminating be-tween type 1 and type 2 diabetes and MODY 3–5 years after diagnosis (10,11).

Urine C-peptide/creatinine ratio (UCPCR) canbeusedtoremovetheneedforblood samples, which may be of particular concern in the pediatric population, and means that the sample can easily be taken at home and posted to the labora-tory (12). GAD and IA2 islet autoanti-bodies also discriminate well between type 1 and MODY, with cross-sectional studies showing they are present in 80% of patients with type 1 diabetes and in ,1% of patients with MODY (13).

These biomarkers have been used to screen for MODY in other studies (14,15), but have been limited to pediatric cases only. Given the median age at diagnosis for MODY is 20 years (from U.K. refer-rals data [3]), and there is on average a delay of 13 years from diabetes diag-nosis to a confirmed genetic diagnosis (16), it is crucial to study adults as well.

Furthermore, the combined diagnostic performance of the two biomarkers as a screening pathway has not been formally assessed.

By excluding those with type1 diabetes using these two biomarkers, we can obtain a smaller percentage of patients in whom diagnostic molecular testing for monogenic diabetes could be per-formed. We tested a screening pathway using both C-peptide and islet autoanti-bodies to exclude type 1 diabetes in two populations with previously high pickup rates of MODY (3) and performed genetic testing on all patients with significant en-dogenous insulin and absence of islet autoantibodies. This allowed us to deter-mine the prevalence of all monogenic di-abetes subtypes in those diagnosed at 30 years or younger and to calculate the positive predictive values (PPVs) and neg-ative predictive values (NPVs) for the pathway.

CONCLUSIONS

The biomarker screening pathway for monogenic diabetes is a systematic, cheap (U.K. UCPCR cost of £10.80 and antibodies cost of £20), and easily imple-mented approach to screening all pa-tients with young-onset diabetes in a clinic or population that helps identify suitable patients for molecular diagnostic genetic testing. The pathway picked up new cases of monogenic diabetes, even in areas of existing high detection be-cause of research interests in the regions. We found 3.6% of patients diagnosed at younger than 30 years of age have monogenic diabetes. In areas in which no cases have been identified, we estimate that 1 in 5 patients referred for genetic testing because of the pathway will have monogenic diabetes, which is a 5.6-fold higher detection rate than if all patients in this age range received genetic testing. The high NPV of 99.9% indicates it is an extremely effective approach for ruling out monogenic diabetes.

There have been relatively few studies that have systematically screened whole populations for monogenic diabetes. The majority of studies have been in pediatric populations only (14,15,22–26), with only two studies that have screened adults (27,28).Noother studyhas systematically screened a whole population of both adults and children together. Only 8 out of 51 (16%) of patients with a genetic diagnosis of monogenic diabetes in our cohort were in the pediatric age range (younger than 20 years) at the time of recruitment, highlighting the importance of looking for monogenic diabetes in adult diabetes clinics. This may explain why the prevalence we find is higher thananyofthepreviouspediatricstudies. The strength of our pathway is the in-tegration of two biomarkers (C-peptide and islet autoantibodies [both GAD and IA2]), rather than relying on clinical fea-tures. This offers a simple approach that does not require specific clinician inter-pretation or complex algorithms of different combinations of features.Weshowed that by using clinical features alone, over half of the cases of monogenic diabetes would be missed.

By combining the two biomarkers, we increase the discrimina-tory ability and allow the clinician to pick up even atypical cases and rarer forms of monogenic diabetes, which tra-ditional criteria may miss. The use of clin-ical features, however, results in fewer cases being sent for genetic testing that are negative, which clearly has cost impli-cations.Themostcost-effectiveapproach is likely to involve a combination of bio-markers and clinical features. Further studiesareneeded to determinewhether the pickup rate could be further improved by integrating the pathway with clini-cal features, such as the MODY calcula-tor, or whether this would result in moremissedpatientsbecause ofreduced testing.

In this study, we also systematically tested all known genes for monogenic diabetes, rather than just the most com-mon MODY genes (GCK, HNF1A, and HNF4A).Nineout of17 (53%) of the cases identified as part of our cohort had mu-tations identified through additional testing on the targetedcapture,and17outof 51 (33%) of all of the monogenic diabetes cases found in total had mutations in other genes, highlighting the advantage of further testing using targeted next-genera-

tion sequencing.

Health economic evaluation of the path way for detecting the common forms of MODY (GCK, HNF1A, and HNF4A) has been carried out as a separate project, which has shown the pathway to be cost-saving(20,21).Thecost-effectiveness of additional testing for other forms of monogenic diabetes has not been as-sessed. Because of the rarity of other monogenic diabetes, there are few data available to inform such analyses. Treat-ment change from insulin to sulphonylur-easisstillpossibleincasesdiagnosedwith ABCC8 and KCNJ11 (29,30), and for other genes for which treatment change is not an option, a confirmed diagnosis can still help with management, prognosis, and advice on risk to other family members (4). The decision whether to pay for the more expensive, but more comprehen-sive, next-generation sequencing, rather than Sanger sequencing for MODY genes only, would depend on assessing the tradeoffs of additional costs with long-term benefits to the patient. The pres-ence of additional clinical features (e.g., renal cysts associated with HNF1B) may also point to specific monogenic diagno-ses and increase the likelihood of a posi-tive genetic test result.

A limitation of our study was that we had small numbers of patients with monogenic diabetes on which to evaluate the sensitivity of the pathway. Consider-ably larger studies have shown the biomarkers individually to be highly sen-sitive for monogenic diabetes (99% for UCPCR [10,11] and .99% for islet auto-antibodies [13]), and by using both of these markers in a pathway, the number of missed cases should be minimal at a population level (2% of 3.6% = 0.07%, reflected in the NPV of 99.9%). Although there have been reports of MODY pa-tients who are positive for islet autoanti-bodies (reviewed in Ref. 13), these are rare and likely to be cases with coinciden-tal type 1 diabetes. Previous studies re-porting high prevalence of positive autoantibodies in their cohort have in-cluded clinically defined, rather than ge-netically confirmed, MODY (31) or use low cutoffs for antibody positivity, which can be inappropriate (32), and are likely to represent an overestimate. There is also the potential for missed cases based onUCPCR,butagain,thenumberofthese patients will be small, and as they have insulin levels suggestive of type 1 diabe-tes (33), they are unlikely to be able to transfer off insulin even if a genetic diag-nosis is made.

A further limitation is that despite screening using C-peptide and antibody testing, the PPV is still fairly low at 20%, indicating four out of five screened will not have a monogenic cause identified on diagnostic molecular genetic testing. However, the aim of our screening path-way is that it is used purely as a tool to narrow down those individuals who would be more appropriate for genetic testing. This approach is a vast improve-ment over no screening represent a PPV at the background prev-alence rate of 3.6%), misses fewer cases than using clinical features alone, and is at a level that has been shown to be cost-effective (20,21). Furthermore, the screening pathway still provides useful test results for this age group that of-fer additional information to support patient care. Patients with severe insulin deficiency, as determined by very low C-peptidevalues, will not respond to non-insulin therapy (33). Positive C-peptide and negative antibody results are impor-tantclinicallytohighlightatypical casesof type1diabetesorinwhichother forms of diabetes, such as young-onset type 2 di-abetes, should be considered. Patients with very high endogenous insulin with out is let auto antibodies andnomutations in monogenic diabetes genes are likely to have type 2 diabetes and may be able to manage on noninsulin treatment.

Finally, this study comprised a 98% white population and assesses patients at a median of 14 years after diagnosis. Assessment of the pathway in other racial groups and in patients close to diagnosis is needed.

In conclusion, we have demonstrated a simple, cheap, effective screening path-way that could be implemented at a pop-ulation level to help correctly diagnose patients with monogenic diabetes.

Nyhetsinfo 14 juli 2017
www red DiabetologNytt

Swedish Diabetes Summit will take place November 21-22 in Gothenburg. See Program and More Info. No Cost for Registration, Free

The Second Swedish Diabetes Summit will take place November 21-22 in Gothenburg.

This is a unique national diabetes research meeting with speakers representing as many as 8 different Swedish universities as well as guest speakers from abroad.

The preliminary programme with the confirmed speakers is attached (presentation titles TBA).

This symposium is targeted to basic and clinical diabetes researchers, researchers from industry, clinically active medical doctors/ health care personnel and patient organization representatives.

We welcome abstracts to the poster session. Two abstracts submitted to the poster session will be selected for a short (10 min) oral presentation.
http://neurophys.gu.se/english/Research/second-swedish-diabetes-summit/abstract-posters

Abstract submission to the poster session - Institute of Neuroscience and Physiology, University of Gothenburg, Sweden neurophys.gu.se

Abstract - Poster

Registration to the event is free of charge on a first come first serve basis. Registration to the Second Swedish Diabetes Summit.

Conference delegates must care for their own lodging. A list of recommended hotels where subsidized prizes will be offered can be found on the symposium website below.
http://neurophys.gu.se/english/Research/second-swedish-diabetes-summit/accommodation

More information: http://neurophys.gu.se/english/Research/second-swedish-diabetes-summit

Welcome!

On behalf of the organisers led by Associate Professor Charlotta Olofsson, University of Gothenburg. Please, spread the word!

Preliminary programme

Second Swedish Diabetes Summit 21st –22nd November 2017, Gothenburg

Tuesday

09.00–09.30	Registration, coffee
09.30–09.40	Welcome address
09.40–11.50	Treating metabolic disease
09.40–10.20	Roy Taylor, Newcastle University
10.20–10.50	Fredrik Bäckhed, University of Gothenburg
10.50–11.20	Lena Carlsson, University of Gothenburg
11.20–11.50	Olov Andersson, Karolinska Institutet
11.50–13.00	Lunch, poster setup
13.00–15.00	Type 1 diabetes
13.00–13.30	Knut Dahl-Jörgensen, University of Oslo
13.30–14.00	Johan Jendle, Örebro University
14.00–14.30	Daniel Espes, Uppsala University
14.30–15.00	Helena Fadl, Örebro University
15.00–15.30	Coffee
15.30–17.00	Adipose tissue
15.30–16.00	Peter Strålfors, Linköping University
16.00–16.30	Ingrid Dahlman, Karolinska Institutet
16.30–17.00	Ingrid Wernstedt Asterholm, University of Gothenburg
17.00–19.00	Buffet dinner with poster viewing

Wednesday

07.45–08.00	Coffee available
08.00–10.10	Genetics
08.00–08.40	Steve O'Rahilly, University of Cambridge
08.40–09.10	Charlotte Ling, Lund University
09.10–09.40	Anders Rosengren, Lund University/ University of Gothenbur
09.40–10.10	Carina Ämmälä, AstraZeneca, Mölndal
10.10–10.40	Coffee
10.40–11.40	Nutrition and exercise
10.40–11.10	Christian A Drevon, University of Oslo.
11.10–11.40	Anna Krook, Karolinska Institutet
11.40–12.40	Lunch
12.40–14.40	Islets
12.40–13.10	Helena Edlund, Umeå university
13.10–13.40	Per-Olof Berggren, Karolinska Institutet
13.40–14.10	Patrik Rorsman, University of Oxford/University of Gothenburg
14.10–14.40	Sebastian Barg, Uppsala University
14.40–15.10	Coffee
15.10–16.10	Neural Control of metabolism
15.10–15.40	Tore Bengtsson, Stockholm University
15.40–16.10	Karolina Skibicka, University of Gothenburg
16.10–16.40	Closure of meeting (including 2x10min poster presentations)

Nyhetsinfo 11 juli 2017
www red DiabetologNytt

Diabetes Mellitus More Prevalent In Psychiatric Patients Than General Population, Meta-analysis 32 Studies. Journal of Gen Hosp

The prevalence of diabetes and impairment in glucose metabolism are noticeably higher in psychiatric patients.

Diabetes mellitus (DM) appears to be more prevalent in the psychiatric setting than in the general population, according to the results of a recent meta-analysis from the United Kingdom published earlier this year in General Hospital Psychiatry.1 Both inpatients and outpatients with psychiatric conditions were more likely to have a diagnosis of DM, or to have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) than patients without a psychiatric condition.2,3

The investigators evaluated 36 studies from Europe, Asia, and North America involving 42 psychiatric cohorts for the prevalence of multiple impairments of glucose metabolism. Unspecified DM was reported in 10% of all patients evaluated from 31 studies (95% CI, range 9-12), while the prevalence of type 1 DM was 1% (0-1) and type 2 DM was 9% (613) reported in 5 and 13 studies, respectively. The prevalence of IFG was 18% (8-28, 7 studies), and of IGT 22% (16-28, 3 studies).

This meant that 1 of every 10 psychiatric patients studied was diagnosed with DM, 1 in 5 with IFG, and 1 in 5 with IPG. The prevalence rates did not vary by continent or by type of inpatient setting.

The range of psychiatric diagnoses included schizophrenic or schizoaffective disorders, mood disorders, and substance abuse disorders, with little variation in prevalence of unspecified DM by psychiatric category (11% across all inpatient disorders, 95% CI, 10-12).

The etiology of this increased prevalence was not clear, although the investigators suggested that links to antipsychotic medication use in these patients could be a factor.4,5 "The study did not set out to examine the etiology of abnormal glucose metabolism in these patients, but to document its prevalence in these settings," study co-investigator, Emmert Roberts, MA, BM-BCh, MRCP (UK), MRCPsych, DFSRH, of the Institute of Psychiatry, Psychology and Neuroscience at King's College London, in the United Kingdom, told Psychiatry Advisor.

The study findings indicated a need for psychiatrists to give attention to their patients' glucose metabolism status. "We would recommend that routine screening take place in psychiatric inpatient settings for not only DM but also pre-diabetic states of abnormal glucose metabolism," Dr. Roberts said. The researchers contend that such screening would present opportunities for timely intervention with metabolic issues that might be contributing to psychiatric illnesses. "A prevalence of 1 in 5 for IFG or IGT is higher than estimates for number of inpatients with bipolar affective disorder and some personality disorders across all inpatient settings, suggesting that abnormal glucose metabolism should be an essential part of psychiatric postgraduate examination, training and expertise," they concluded.

RELATED ARTICLES

Mental Health, Behavioral Screenings Vital for Pediatric Patients With T1DOSA Linked to Sight-Threatening Diabetic Retinopathy in Type 2 Diabetes-Concomitant Use of Antidepressants, Antipsychotics Linked to T2D Risk Antipsychotics Have Few Negative Long-term Effects on Schizophrenia OutcomesSchizophrenia Symptoms May Benefit From Specific Kind of Talk Therapy

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From wwww.psychiatryadvisor.com/

Nyhetsinfo 11 juli 2017
www red DiabetologNytt

ADA Report. Metformin particularly effective in those with history of GDM, 41% reduced risk for T2DM after 15 years. Dpp diabetes prevention program

SAN DIEGO — Long-term use of metformin shows a particularly strong effect in preventing the development of type 2 diabetes among women who've had gestational diabetes, according to data presented at the American Diabetes Association (ADA) 2017 Scientific Sessions.

These latest findings come from the Diabetes Prevention Program (DPP) and its extension phase.

After 15 years from the start of DPP, women with a history of gestational diabetes taking metformin still had a 41% reduced risk of type 2 diabetes, compared with an 11% reduction in parous women with no history of gestational diabetes.

This contrasts with an overall effect of metformin in reducing the risk of type 2 diabetes by 18% in the study cohort as a whole.

"The overall results reinforce the long-lasting efficacy of metformin in reducing the development of diabetes and support its more widespread use as a prevention measure in those at high risk," said David M Nathan, MD, director of the Diabetes Center at Massachusetts General Hospital, Boston, the study chair of DPP, who presented these latest results at the conference.

Asked for comment, Shubhada Jagasia, MD, professor of medicine and vice chair of clinical affairs in the department of medicine, Vanderbilt University Medical Center, Nashville, Tennessee, told Medscape Medical News that these new data should help doctors to target metformin treatment to those who will benefit most.

DPP: An Ongoing Investigation

DPP started in 1996 and followed individuals who were at high risk of diabetes on the basis of body mass index (BMI) and impaired glucose tolerance. They were randomized to one of three groups: intensive lifestyle interventions with diet and exercise, 850-mg metformin twice a day, or placebo. DPP ran through 2002 and compared the incidence of diabetes — defined as a fasting plasma glucose of 126 mg/dL or greater, or a 2-hour oral glucose tolerance test of 200 mg/dL or more — in each of the groups.

As has already been reported, those in the placebo group developed diabetes at a rate of 11% per year, while the lifestyle intervention was associated with a 58% decrease in the risk of diabetes and metformin was linked to a 31% reduction in risk.

In that original analysis, metformin reduced the risk of future diabetes by 51% in women with a history of gestational diabetes. Two other subgroups of patients also seemed to gain greater benefit from metformin — those younger than 60 years of age and those with a BMI >35 kgm2.

At the conclusion of the DPP, the placebo was stopped, and all patients were offered a slightly different lifestyle intervention. In addition, metformin continued to be provided to the people in the original metformin group. This extension phase — known as the Diabetes Prevention Program Outcomes Study (DPPOS) — was started in 2003 and is still ongoing, with 88% of the original volunteers still participating.

Over time, the 31% reduction in diabetes risk initially seen with metformin waned to 18% by 10 years and has remained stable, so "an 18% reduction is the overall result, compared with people in the original placebo group," Dr Nathan pointed out.

At 15 years, the differences between the subgroups in the benefits of metformin also waned, so that the effects of metformin were for the most part no longer significantly different in these subgroups, with the exception of the women with a history of gestational diabetes.

Clinical Implications

When considering which of their patients should receive metformin, clinicians should now "be more likely to prescribe it" to women with a history of gestational diabetes, "who were shown in this study to have the biggest impact in terms of diabetes reduction," said Dr Jagasia.

"These are the patients in whom we would be more likely to go the metformin route if for any reason intensive lifestyle modification or a 5% to 10% reduction in body weight is not possible," she added.

However, lifestyle modification should always be tried first, she stressed to Medscape Medical News. "Whenever clinicians prescribe medication for diabetes, it is always in addition to lifestyle changes."

Dr Nathan reports no relevant financial relationships. Disclosures for the coauthors are listed in the abstract. Dr Jagasia disclosed no relevant financial relationships.

American Diabetes Association 2017 Scientific Sessions. June 11, 2017; San Diego, California. Abstract 169-OR

From www.medscape.com

Nyhetsinfo 7 juli 2017
www red DiabetologNytt

Diabetesutbildningar i höst i Sverige för läkare och sjuksköterskor.

När? Var? Hur? - Inkretiner – Insuliner, för diabetesteam, 1 dag

http://www.fokusdip.se/utbildningar-moten/dip-nar-var-hur

Dagen bygger på aktivitet från deltagarna med diskussioner och grupparbeten. Utbildningen innehåller därför praktiska övningar och verkligheten: Bakgrund och patofysiologi, Behandlingsarsenalen, Målvärden, Inkretiner

Novo Nordisk Trollhättan 23 maj
Skövde 31 maj
Karlstad 28 sep
Västerås 11 oktober
DIP Öppen finns kurstilfällen beslutad

Sanofi Balans

En interaktiv utbildning för diabetesteam. 3 heldagar vid 3 olika tillfällen
http://www.sanofi.se/l/se/sv/layout.jsp?scat=35E60207-9B1F-4427-83D1-

Steg 1 (Heldag)
Diagnostik och klassifikation, screening, prevention, fysisk aktivitet och maten. Glukoskontroll-mål-tablettbehandling

Steg 2 (Heldag)
Insulin och kombinationsbehandling samt patientinformation vid insulinbehandling. Produktinformation om våra insuliner.

Steg 3 (Heldag)
Kardiovaskulära komplikationer, retino-, neuro- och nefropati och diabetesfoten.

Kontakta utbildningsansvarig Annelie Jörnvik Karlsson, e-post: annelie.jornvik.karlsson@sanofi.com.

Uppdatering diabetes typ 2 för läkare

https://distriktslakare.com/utbildning/

En praktisk klinisk inriktad utbildning för distriktsläkare. 2 dagar

Hur ska vi individualisera diabetesbehandlingen, Nyheter, Insulin, ”nya” läkemedel, Njuren, Fotsår, Lipider. Utbildningen utgår mycket från patientfall. Den är oberoen- de av producent och läkemedelsindustri.

diabeteshandboken.se i samarbete med distriktsläkare.com
Stockholm 19 - 20 oktober Göteborg 9 - 10 november Malmö 23 - 24 november

Lilly Academy

https://www.lillyacademy.com/se/news/news.aspx Utbildningar mm från Lilly

Uppdatering diabetes för allmänläkare anställda i Närhälsan samt ST.

https://www.narhalsan.se/om-narhalsan/for-vardgivare/KursDoktorn/kurser2/kurser/uppdatering-diabetes/

Kurs i första hand typ-2-diabetes och utgår ifrån verkliga primärvårdsfall som allmänläkaren träffar i sin kliniska vardag. Utredning, diagnostik, utformning av individualiserad behandling, vanliga komplikationer och förebyggande arbete.

Nyhetsinfo 7 juli 2017
www red DiabetologNytt

Sveriges första tv-gala till förmån för diabetes 14/11 TV3

Diabetes är en av våra stora folksjukdomar, ändå får sjukdomen inte den uppmärksamhet som de drabbade förtjänar.

Därför kan vi nu stolt avslöja att vi sänder Sveriges första direktsända TV-gala till förmån för diabetes, den 14 november kl. 20.00 på TV3, Viafree och Viaplay.

Galan sänds direkt från Vinterträdgården på Grand Hôtel i Stockholm och görs i samarbete med MTG.

Från www patientföreningen Svenska Diabetesförbundet

Nyhetsinfo 1 juli 2017
www red DiabetologNytt

Many people with type 1 diabetes still make some insulin surprising finding hints at potential future therapy. Swedish Study, Diab Care

Almost half of people with type 1 diabetes are still producing some insulin more than a decade after being diagnosed with the disease.

The new findings challenge previous assumptions that people with type 1 diabetes lose the ability to produce any insulin -- a hormone that helps usher sugar to cells to be used as fuel -- over time.

Researchers at Sweden's Uppsala University, led by post-doctoral researcher Daniel Espes, reached their conclusions after studying more than 100 patients with type 1 diabetes.

The investigators found that people who still produced insulin despite their long-standing type 1 diabetes had higher levels of a protein called interleukin-35. This protein appears to play an important role in the immune system.

Past research had shown that both newly diagnosed people with type 1 diabetes and those who've had the disease for some time had lower average levels of interleukin-35 compared to healthy people.

Type 1 diabetes is an autoimmune disease that causes the body's immune system to mistakenly attack healthy cells in the pancreas that make insulin.

This leaves people without enough insulin to meet the body's daily needs. To survive, people with type 1 diabetes must replace that lost insulin through multiple daily injections or through a tiny tube inserted under the skin every few days and then attached to an insulin pump.

The Uppsala researchers have launched a new study to see if they may be able to boost insulin production in those people with type 1 diabetes who are still making insulin.

The study appears in the June issue of Diabetes Care.

Nyhetsinfo 7 juli 2017
www red DiabetologNytt

Marcus Lind, Sahlgrenska Akademin, får hedervärt Jubileumspris från Sv Läkaresällskapet för sin forskning kring diabetes typ 1 och 2. 150 000 SEK

I år går Svenska Läkaresällskapets stora Jubilemspris till forskare inom diabetesområdet. Det händer kanske vart 5:e år - och nog nu framöver än mer ofta.

Foto Anette Juhlin

Priset delas ut på Svenska Läkaresällskapet 14/11. Av en händelse är det samtidigt Världsdiabetesdagen med events world wide, i Sverige, nationellt, regionalt och nationellt, för awareness-kampanj och uppmärksamma diabetes

Press release Svenska Läkaresällskapet 170629 09.45

"Behandling mot diabetes, inte om utan när!"

Diabetesforskare Marcus Lind, Göteborgs universitet, får Svenska Läkaresällskapets Jubileumspris, 150 000 kronor, för banbrytande kliniska prövningar inom typ 1- och typ 2-diabetes i syfte att förbättra behandlingarna för dessa sjukdomar. Han har utfört nationella och internationella epidemiologiska studier i världsklass för att bättre förstå prognosen vid typ 1- och typ 2-diabetes och hur sjukdomarna bör behandlas för att minska risken för organskador och uppnå normal livslängd.

- Jag är oerhört glad och känner mig mycket hedrad att få ta emot detta fina pris. Det känns mycket unikt då det går till en pristagare inom hela det medicinska området och det finns så många discipliner. Jag känner mig oerhört stimulerad för framtida forskningsprojekt. Priset är mycket anrikt med dess långa tradition ända sedan 1800-talet. Jag hoppas det kommer ge spin-off-effekter inom diabetesvården och diabetesforskningen"

Marcus Lind har med sin forskning bidragit till kunskap och utveckling av så kallad kontinuerlig blodsocker-mätning, en subkutan sensor som många patienter med typ 1-diabetes idag använder för behandling av sin sjukdom.

Behandlingen innebär att blodsockret blir bättre och riskerna för låga blodsockervärden mindre. Den leder också till ökad livskvalitet och trygghet i behandlingen. Inom typ 2-diabetes har Marcus Lind utfört studier inom bland

annat inkretinbaserad behandling. Han var till exempel den förste att i en placebo-kontrollerad studie visa att patienter med svårbehandlad typ 2-diabetes, som behöver flera insulininjektioner per dag, har nytta av denna behandling.

Inom det epidemiologiska området har Marcus Lind utfört nyckelstudier såväl i Sverige som i andra länder, däribland Kanada och Storbritannien för att bättre förstå prognosen vid typ 1- och typ 2-diabetes.

Han har bland annat visat hur dödligheten skiljer sig vid typ 1- och typ 2-diabetes jämfört med övriga befolkningen och vilka nivåer på riskfaktorer som behöver nås för att få en bättre prognos. Vidare var han en av de första att studera effekter på hjärtsvikt vid typ 1-diabetes i populationsbaserade studier.

Marcus Linds studier har under de senaste åren publicerats i samtliga av världens ledande kliniska vetenskapliga tidskrifter som New England Journal of Medicine, Lancet, Journal of American Medical Association (JAMA) och British Medical Journal (BMJ).för frågor om hans forskning.

Marcus Lind är lektor och docent i Diabetologi, Sahlgrenska Akademin, Göteborgs Universitet, samt överläkare i Diabetologi, NU-Sjukvården, Uddevalla.

PRISUTDELNING

Priset kommer att delas ut vid Läkaresällskapets Årshögtid den 14 november 2017.

Svenska Läkaresällskapet är läkarkårens oberoende vetenskapliga och professionella organisation och arbetar för en förbättrad hälsa och sjukvård i samhället. Vi är en politiskt och fackligt obunden ideell förening med cirka 10 500 medlemmar. Vi arrangerar konferenser, seminarier och debatter och stödjer medicinsk forskning. Mer information hittar du på www.sls.se

Nyhetsinfo 7 juli 2017
www red DiabetologNytt

Vilket bröd ska vi helst äta? Avhandling Pernilla Sandvik, Uppsala

Brödvalet en klassfråga

Vilket bröd vi väljer att äta som vuxna påverkas av både utbildningsnivå och vilket bröd vi fick när vi var barn. Yngre personer föredrar mindre hälsosamt bröd och äldre föredrar hälsosammare bröd. Det visar en ny avhandling om råg från Uppsala universitet.

Det är känt att rågbröd på många sätt är hälsosammare än bröd bakat på vete. Rågbröd ger en jämnare blodsockernivå, en längre mättnad, skapar viktkontroll, motverkar typ 2-diabetes och är positivt för tarmfloran. Ändå äter vi i Sverige mycket mindre råg jämfört med andra nordiska länder, bara drygt 11 kg per person och år jämfört med Finlands 16 kilo per person och år.

Men viktigast när vi väljer vilket bröd vi ska äta är ändå att det smakar gott. Men gott är inte alltid det mest hälsosamma, skriver Pernilla Sandvik, forskare vid institutionen för kostvetenskap vid Uppsala universitet, i sin nya avhandling. Hon har undersökt hur människor uppfattar olika bröd när det gäller smak och hälsosamhet, och vad de själva väljer att äta. 398 personer alla mellan 18 och 80 år var med och provsmakade bröden.

Smaktest

I provsmakningen användes färdigpackade bröd från stora bagerier som säljs i livsmedelsbutiker över hela Sverige.

Smaken på 24 bröd kartlades med hjälp av en tränad sensorisk panel, sedan valdes ett representativt urval av 9 olika bröd ut till konsumenttestet. I konsumenttestet provsmakades bröden blint, det vill säga utan information om vilket bröd det var. Smaken på de mest hälsosamma bröden stick i stäv med den yngre gruppens smakpreferenser. Personer mellan 18 och 44 år föredrar bröd med en mild smak, lågt tuggmotstånd, utan fullkorn och med ett lågt innehåll av råg, medan den äldre (45-80 år) oftare föredrog smaken av bröden med mycket fullkornsråg.

- I båda åldersgrupperna var det tydligt att de som i större utsträckning föredrog ljust, mjukt bröd med mer sötma hade en lägre utbildningsnivå och hade i större utsträckning ätit vitt bröd under uppväxten, säger Pernilla Sandvik.

Ska vara bra för magen

I avhandlingen tycker konsumenterna att ett hälsosamt bröd ska vara bra för magen, bidra till ett balanserat blodsockersvar och vara mättande. Råg och surdeg uppfattas som hälsosamt i bröd. Många upplever att det är svårt att veta vilket bröd som är hälsosamt, men tycker att ett rågbröd ska innehålla 70 procent råg.

En kartläggning av 24 mjuka rågbröd på den svenska marknaden visar att även om det står råg eller surdeg på förpackningen kan innehållet vara lågt. Idag finns inte heller några godkända märkningar som hjälper konsumenten välja till exempel ett bröd som bidrar till en jämn blodsockernivå.

Tuggmotstånd

En studie av mjukt bröd i Sverige, innehållande 15-100 procent råg visar att vi kan ta hjälp av vårt smaksinne för att hitta det hälsosammare rågbrödet. Bröd som bidrog till mer jämna blodsockernivåer karaktäriserades av en kompakt textur, ett högt tuggmotstånd och eller en tydligt syrlig smak. Om brödet är mörkt eller ljust spelar mindre roll.

- Även om man kan lära sig tycka om nya smaker även i vuxen ålder, visar studien på vikten av att tidigt vänja sig vid olika smaker men också på potentialen för brödindustrin att utveckla bröd med en hög andel siktad råg. Det ger en mildare smak, mjukare textur och kan samtidigt stabilisera blodsockerhalten. En ökad rågbrödkonsumtion skulle kunna ha en positiv effekt på folkhälsan men först måste de vara tillgängliga och smaka gott, säger Pernilla Sandvik.

Källa: Pressmeddelande från Uppsala universitet

Nyhetsinfo 28 juni 2017
www red DiabetologNytt

TLV kan lära av Frankrike. Se utvärdering och konklusion av Libre. Nationell reimbursement T1DM och T2DM med flerdosinsulin

Se nedtill hur TLVs motsvarighet i Frankrike arbetar

Kanske kan TLV lärdom hur en motsvarande process kring medicinteknik i Sverige kan ske.

Frankrikes har fokuserat på den behandling patienterna faktiskt behöver.

1. Först gjorde man en en HTH-analys via Haute Autorité De Santé.

2. Sedan gjorde man en nationell prisförhandling.

3. Utfallet blev estimerat 300 000 individer med diabetes dvs flerdosbehandlade T1 och T2 DM.

Nyhetsinfo
www red DiabetologNytt

Haute Autorité De Santé HAS National Committee for the Evaluation of Medical Devices and Health Technologies

CNEDiMTS Review 12th July 2016 Following the inspection dated 28th June 2016, CNEDiMTS adopted the draft review on 12th July 2016

Conclusions

FREESTYLE LIBRE Flash Glucose Monitoring System
Applicant: ABBOTT France S.A.S. Manufacturer: ABBOTT (USA)

Retained Indications:

Measuring interstitial glucose levels in the treatment of patients with type 1 or type 2 diabetes (adults and children aged at least 4 years) undergoing intensified insulin therapy (using an external insulin pump or ≥ 3 injections per day) and performing self-monitoring of blood glucose (SMBG) several times a day (≥ 3 per day).

The FREESTYLE LIBRE system is especially designed for patients who have received therapeutic education and specific training on the use of the flash interstitial glucose monitoring system.

Actual Benefit (AB):

Sufficient, due to:
· The diagnostic value of the FREESTYLE LIBRE system
· The interests of public health due to the seriousness of complications caused by type 1 or type 2 diabetes

Retained Comparator:

Self-monitoring of blood glucose using a single capillary blood glucose meter
Added Clinical Value (ADV)
ASA Level III

Type of Inclusion on Reimbursement List:

Brand name
Duration of Inclusion: 5 years

Analyzed Data:

- Two prospective non-randomized, multi-center studies to evaluate the performance of the FREESTYLE LIBRE system in terms of accuracy and precision, compared to the values of capillary blood glucose on 75 patients, and 89 adult patients aged 4-17 years, treated with insulin.

- A randomized controlled study, to evaluate, in 239 patients with type 1 diabetes on insulin pumps or on multiple daily injections (IMPACT study), the impact of using FREESTYLE LIBRE on the time spent in hypoglycemia (< 70 mg/dl), compared to a control group performing capillary blood glucose monitoring.

- A randomized controlled study to compare, in 224 patients with type 2 diabetes on insulin (REPLACE study), the level of HbA1c at 6 months in the FREESTYLE LIBRE group, compared to the clinical control group performing capillary blood glucose monitoring.

Factors Determining the Actual Benefit:

Technical Specifications:

No additional requirements proposed by the manufacturer with respect to the technical specifications.

Warranty period:

- The FREESTYLE LIBRE Reader: 4 years
- The FREESTYLE LIBRE Sensor: 14 days

In case of the product failing within the warranty period, the defective Reader shall be replaced with a new one within 3 working days.

Prescription and Terms of Use:

Prescription:

The initial prescription of the FREESTYLE LIBRE system must be ensured by a diabetologist or a pediatric diabetologist.

Initiation phase:

Before issuing a long-term prescription, the arrangements shall allow the provision of the FREESTYLE LIBRE system for:

- A trial period of a minimum of one month for every patient candidate of the FREESTYLE LIBRE system. This period should allow patients who are capable of using the FREESTYLE LIBRE and wearing the Sensor to be selected.

The criteria for termination of the trial may in particular be related to the patient's own choice and/or that of his caregivers, poor skin tolerance to the Sensor, and the inability to wear a Sensor at all times.

- Towards the end of the trial period, patients who continue to use the FREESTYLE LIBRE system should undergo an evaluation at 3 months to assess whether or not to continue to use the system.

This assessment is based on the aforementioned criteria, in addition to a clinical assessment pertaining to the objectives set a priori (severe hypoglycemia, ketoacidosis decompensation, time spent above or below a certain hypoglycemic threshold), and/or biological (HbA1c).

Renewal:

Renewal is ensured by any doctor.
Patient-specific education and/or their caregivers:

Prior to prescription, patients should receive specific education to provide them with the necessary skills and knowledge to apply the Sensor and to interpret and use the information provided by the FREESTYLE LIBRE system to optimize their treatment. The patient should also be informed of the lower reliable results of the FREESTYLE LIBRE system 1st day after sensor application. This training is provided by a pump center or any other center that provides care for diabetic patients and is involved in therapeutic education programs validated by the Regional Health Agencies (ARS)[1]. It is essential to plan this SMBG with the patient and/or his caregivers, by determining its frequency, the targets and therapeutic decisions to be taken based on results.

Terms of reimbursement :

FREESTYLE LIBRE includes a capillary blood glucose meter. Terms of reimbursement for this device does not include any other capillary blood glucose meter. Terms of reimbursement of the FREESTYLE LIBRE system should allow the provision of the FREESTYLE LIBRE system elements, as a part of a long-term prescription: a Reader and Sensor (wearing time 14 days), following a 3-month initial period.

· The wearing time of the Sensor being 14 days, the total number of Sensors to maintain per year and per patient is limited to 28 Sensors.

· In clinical situations, where the manufacturer recommends measuring blood glucose, the capillary blood glucose meter test strips and lancets must be limited to 100 test strips and 100 lancets, per patient, per year.

Terms of Use:

Measuring interstitial glucose using the FREESTYLE LIBRE system requires patient intervention via a scan of the Reader over the Sensor to get a current glucose reading. In the case of occasional scanning (> 8 hours), the first values become lost. The device is designed to replace the capillary blood glucose measurement, except in the cases listed below where the manufacturer recommends the use of a capillary blood glucose meter to check the results of the glucose levels.

The different cases are as follows:

- In the case of rapidly changing glucose levels, the level of interstitial glucose, as measured by the Sensor and reported as actual, may not accurately reflect blood sugar levels. When glucose levels are rapidly dropping, the results of interstitial glucose levels measured with the Sensor may be higher than the blood glucose levels. Conversely, when glucose levels are rapidly increasing, interstitial glucose results measured with the Sensor may be lower than the blood glucose levels.

- In order to confirm hypoglycemia, or impending hypoglycemia, as reported by the Sensor.

- If symptoms do not match the FREESTYLE LIBRE system readings. Symptoms that may be caused by hypoglycemia or hyperglycemia should not be ignored.

No on-call duty 24/7 is required in case of system failure.

No preventive maintenance is required for the FREESTYLE LIBRE system.

Renewal Conditions:

Updating data as recommended by the practice guidelines for inclusion in the reimbursement list of products and services.

Target Population:

Approximately 300,000 patients.

Definitive Review 1

EVIDENCE REVIEW

01 NATURE OF THE APPLICATION

Application for inclusion on the list of products and services qualifying for reimbursement, mentioned under article L 165-1 of the Social Security Code (referred to as LPPR in the rest of the document).

01.1. Models and references

01.2. Packaging

The system comes in a Reader Kit and a Sensor Kit.

The Reader Kit includes:

1 Freestyle libre reader 1 usb cable 1 power adapter quick start guide user manual

The sensor kit includes:

1 Sensor pack 1 sensor applicator 1 alcohol wipe product leaflet

01.3. Claimed indication

Measuring interstitial glucose levels for the treatment of patients with type 1 or type 2 diabetes (adults and children aged at least 4 years) undergoing intensified insulin therapy (using an external insulin pump or multiple injections).

01.4. Claimed comparator

Self-monitoring of blood glucose by capillary sampling (reference method).

02 Reimbursement history

This is the first application for inclusion on the lppr for freestyle libre.

03 Characteristics of the product

03.1. Ce marking

Class iib, notification by the british standards institution (no. 597686), United kingdom.

03.2. Description

The Flash Interstitial Glucose Monitoring System FREESTYLE LIBRE consists of two main parts:

- A Reader that is used to get the interstitial glucose readings from the Sensor by scan (scan of the Reader above the Sensor). Scanning can be done over clothing and requires a maximum distance of 4 cm between the Reader and Sensor to obtain readings.

With every scan, the user receives a reading of the current interstitial glucose level, the last 8 hours of glucose data and an arrow indicating the direction and rate of the glucose change. A glucose pattern and variability report can be generated.

The Reader holds up to 90 days of data, providing a historical snapshot of glucose levels over time; as well as the notes entered by the user about his daily activities, such as taking insulin, eating food or exercising.

The Reader also allows the measurement of blood glucose and blood ketones of capillary blood sampling. It works using the glucose and blood ketone electrodes FREESTYLE OPTIUM.

- A Sensor that is inserted by the patient subcutaneously on the back of the upper arm with a simple applicator unit (only); it measures and stores interstitial glucose levels.

It comprises a sterile, flexible filament (0.4 mm thick), which is inserted 5 millimeters under the skin, into the interstitial fluid. The filament is connected to a small, 5 mm high and 30 mm diameter round disc and held in place on the skin with a small medical adhesive.

The Sensor can be worn for up to 14 days. It is water-resistant up to 1 meter (3 feet) of water for a maximum of 30 minutes. No calibration is recommended by the manufacturer within 14 days of usage.

The manufacturer also indicated that the Sensor can be used to check the glucose level 60 minutes after start-up.

The Sensor automatically measures and continuously stores glucose readings and stores up to 8 hours of glucose readings at 15 minute intervals. Therefore, in order to obtain all glucose data over a typical day, the patient should scan over the Sensor at least every 8 hours. In the event of scans spaced apart over a longer period (> 8 hours), the initial data is lost.

The operating temperature (Sensor and Reader) is between 10 and 45 degrees Celsius.

03.3. Functions provided

Interstitial glucose measurement.

04 Expected benefit of the product or service

04.1. Benefit of the product

04.1.1. Data analysis: assessment of the therapeutic effect /adverse effects and risKS

LINKED TO USE

04.1.1.1. Specific data

The IMPACT Study, unpublished[2], was an open, multicenter (23 centers) randomized controlled study. The purpose of the study was to assess the impact, after completion of 6-months use of FREESTYLE LIBRE on the time spent in hypoglycemia [number of hours per day <70 mg/dL], compared to a control group performing self-monitoring of blood glucose (SMBG) by capillary sampling. The patients analyzed were diabetic adults with type 1 diabetes, using intensive insulin treatment with either an insulin pump or multiple daily injections, (N= 239) with an HbA1c level of 6.74 ± 0.56% (144/239 patients (60.3%) had an HbA1c <7.0%).

The time spent in hypoglycemia was significantly lower in the FREESTYLE LIBRE group compared to the control group (mean difference -1.24 ± 0.239 hours per day (p <0.0001), at 6 months).

The results obtained after the completion of multiple analyses in favor of FREESTYLE LIBRE tackled the time spent in the target range (70 to 180 mg/dL) with a mean difference of 1 ± 0.30 hours per day (p = 0.0006) between the groups at 6 months; time spent in hyperglycemia (> 240 mg/dL) with a difference of -0.37 ± 0.163 hours per day (p = 0.0247); maximum satisfaction score [in the Diabetes Treatment Satisfaction Questionnaire (DTSQ)]; and the treatment satisfaction score in the [Diabetes Quality of Life questionnaire (DQoL)].

The results did not show any difference between the FREESTYLE LIBRE group and the control group tackled concerning the mean reduction in HbA1c at 3 and 6 months; the time spent in hyperglycemia > 180 and 300 mg/dL; the other dimensions of the DTSQ and DQoL scores, the HFS scores (Hypoglycemia Fear Survey) and the DDS (Diabetes Distress Screening) scores.

With respect to the number of tests in the intervention group, the mean number self-monitoring blood glucose (SMBG) jumped from 5.5 ± 2 tests per day (between 0 and 15 days) to 0.6 ± 0.1 tests per day at 6 months. The mean number of scans decreased from 18.5 ± 9.4 tests per day to 14.5 ± 9.8 tests per day at 6 months.

In the control group, the mean frequency of self-monitoring of blood glucose (SMBG) went from 5.8 ± 1.7 tests per day (between 0 and 15 days) to 5.6 ± 2.2 test per day at 6 months. The Sensor wearing time in the FREESTYLE LIBRE (between day 15 and day 208) was between 40% and 99%, with an average of 92.8 ± 7.3%.

The study is explained in detail in the Appendix.

The REPLACE Study, unpublished[3], is an open, multicenter (26 centers), randomized controlled study. The purpose was to compare the HbA1c (glycated hemoglobin A1c) level at 6 months between FREESTYLE LIBRE group (N.of patients = 149) and a control group (N. of patients= 75), performing self-monitoring of blood glucose (SMBG) by capillary sampling. Patients included in the study were adults with type 2 diabetes on insulin (N= 5/224 (2.2%), either treated with prandial insulin alone, N= 207/224 (92.4%), or with prandial and basal insulin; and 12 patients (5.4%) treated by insulin pump, with an HbA1c level between 7.5% and 12.0% (average 8.68%).

The results indicated no statistically significant difference between both groups in terms of reducing HbA1c at 6 months (average of 0.03% ± 0.114, p = NS).

With respect to the quality of life questionnaires, the results were in favor of FREESTYLE LIBRE on the maximum satisfaction score in the DTSQ (Diabetes Treatment Satisfaction Questionnaire) and the treatment satisfaction score in the DQoL (Diabetes Quality of Life) questionnaire.

Other dimensions of the DQoL and the DDS (Diabetes Distress Screening) scale showed no difference between the groups.

With respect to the number of tests in the intervention group, the mean number self-monitoring blood glucose (SMBG) was 0.3 ± 0.7 tests per day and the mean number of scans 8.3 ± 4.3 tests per day (between day 15 and day 208). In the control group (N = 51), the mean number self-monitoring blood glucose (SMBG) was 3.0 ± 1.1 tests per day. The Sensor wearing time in the FREESTYLE LIBRE group (between day 15 and day 208) was between 48% and 99%, with an average of 88.7 ± 9.2%.

The study is explained in detail in the Appendix.

The BAILEY et al. Study is a prospective, non-randomized, multicenter (involving 4 centers in the US) study using the FREESTYLE LIBRE device in hidden mode.

The purpose of this study was to evaluate the performance and usability of the FREESTYLE LIBRE Flash glucose monitoring system compared with capillary blood glucose (BG) results.

In total, 75 adult patients with type 1 or 2 diabetes treated with insulin were selected; the follow-up period was 14 days.

The primary endpoint was the percentage of paired points (FREESTYLE LIBRE / SMBG) found within Consensus Error Grid Zone A. (zone corresponding to clinically accurate readings, which is clarified as having “no effect on clinical action.”).

The analysis indicated that 86.7% of the results achieved by the FREESTYLE LIBRE device were found within Consensus Error Grid Zone A[4], compared ▶

with the results obtained by capillary sampling. On the first day of use, 72% of the results were within Consensus Error Grid Zone A.

The BEAGLE, Edge et al. Study, unpublished[5], is a prospective, non-randomized, multicenter (involving 9 centers in the UK), using the FREESTYLE LIBRE device in hidden mode.

The objective of this study was to assess the accuracy of the readings on the FREESTYLE LIBRE device on children in ambulatory use.

A total of 89 patients were included in the study. Patients were aged 4-17 years, with type 1 or 2 diabetes and were treated with insulin.

The primary endpoint was the percentage of paired points (FREESTYLE LIBRE / SMBG) found within Consensus Error Grid Zone A (zone corresponding to clinically accurate readings, which is clarified as having "no effect on clinical action").

The analysis indicated that 83.8% of the results achieved by the FREESTYLE LIBRE device were found within

Consensus Error Grid Zone A, compared with the results obtained by capillary sampling.

04.1.1.2. MATERIOVIGILANCE

FREESTYLE LIBRE has been marketed and distributed since September 2014. 17 materiovigilance (post-market surveillance) statements have been received by the National Agency for the Safety of Medicines and Health Products (L'Agence Nationale de Sécurité du Médicament et des Produits de Santé or ANSM) between 2014-2015.

Materiovigilance statements included skin reactions (N = 9) and result discrepancies between the scan and capillary blood glucose (N = 8). The number of Readers sold is 17,174, including samples (between September 2014 to May 2016).

The application is based on two specific randomized, controlled clinical studies (one specific to type 1 diabetics and the other to type 2 diabetics) and two accuracy studies. The data highlights the feasibility of usage of the FREESTYLE LIBRE device in terms of accuracy.

The first study (IMPACT) evaluates the clinical benefit of the FREESTYLE LIBRE device in adult patients with type 1 diabetes using intensive insulin treatment with either an insulin pump or multiple daily injections, with an average HbA1c level of 6.74 %. The time spent in hypoglycemia (<70 mg/dL) was significantly lower in the FREESTYLE LIBRE group compared to the control group (average difference -1.24 hours per day at 6 months. There was no difference in terms of the mean reduction in HbA1c levels between the groups.

The second clinical study (REPLACE) targets a population of adult patients with type 2 diabetes using insulin with an average HbA1c level of 8.68%. This study did not reveal any difference in terms of HbA1c reduction at 6 months. The study was not specific to patients using intensive insulin therapy.

In these two clinical studies, the results from the diabetes quality of life questionnaire (DQoL) were in favor of the FREESTYLE LIBRE, in terms of patient satisfaction.

With respect to safety and tolerance data, adverse events in clinical trials were primarily related to reactions around the Sensor insertion site (skin rash, infections, allergies, erythemas and necrosis). The number of incidents reported in the context of a materiovigilance (post-market surveillance) statement was low.

The available data does not allow assessment of the impact of the FREESTYLE LIBRE device on the frequency of prevented events or their consequences. However, the decrease of time spent in hypoglycemia (<70 mg/dL) and increased time spent in the target range are likely to protect the patient from the occurrence of severe hypoglycemia. Interpretation of the results obtained from the secondary endpoints of the studies was limited, given the multiplicity of the criteria being evaluated.

The National Professional Council for Endocrinology, Diabetes and Metabolic Diseases and the Federation of Associations of patients with diabetes in France were interviewed by the Commission. They confirmed the actual benefit of the FREESTYLE LIBRE system in the indications and defined the conditions for its prescription and use. Reliable results of the FREESTYLE LIBRE system as of the first day of set-up have however been brought to the attention of the Commission.

04.1.2. ROLE IN THE DIAGNOSTIC STRATEGIES

Glycemic control is the main objective of medical care for patients with diabetes to prevent long-term vascular complications and acute metabolic complications.

Pharmacological treatment of glycemic control in insulin-dependent type 1 and type 2 diabetes is based on an insulin therapy that mimics the normal physiologic pancreatic insulin secretion due to a basal/ bolus regimen, obtained either by multiple injections or by pump.

The choice between intensive insulin treatment with either an insulin pump or multiple daily injections is primarily based on patient preferences.

Self-monitoring of blood glucose is essential in insulin-treated patients. It should be performed daily using a capillary blood glucose meter (at least 4 times per day). This reading would allow patients to adjust treatment and is an am-

bulatory reference method.

Continuous measurement of interstitial glucose constitutes a new tool in the therapeutic arsenal against the disease. It complements conventional monitoring of capillary blood glucose but not a substitute.

Measuring interstitial glucose using the FREESTYLE LIBRE system requires patient intervention via a scan of the Reader over the Sensor to get a current glucose reading. In the case of occasional scan (> 8 hours), the first values become lost. The device is designed to replace the capillary blood glucose measurement, except in the cases listed below where the manufacturer recommends the use of a capillary blood glucose meter to check the results of the glucose levels.

The different cases are as follows:

-In the case of rapidly changing glucose levels, the level of interstitial glucose, as measured by the Sensor and reported as actual, may not accurately reflect blood sugar levels. When glucose levels are rapidly dropping, results of interstitial glucose levels measured with the Sensor may be higher than the blood glucose levels. Conversely, when glucose levels are rapidly increasing, the interstitial glucose results measured with the Sensor may be lower than blood glucose levels.

- In order to confirm hypoglycemia or impending hypoglycemia as reported by the Sensor.

- If symptoms do not match the FREESTYLE LIBRE system readings. Symptoms that may be caused by hypoglycemia or hyperglycemia should not be ignored.

Systematic monitoring of HbA1c concentrations should be done 4 times per year. Measurement of fasting blood glucose carried out in a medical laboratory, allows self-monitoring of blood glucose (SMBG) and should be carried out once a year.

Continuous measurement of glucose levels (3 -5 days test) using a Continuous Glucose Monitoring System (CGMS) Holter-style Sensor system, provides a posteriori analysis by the doctor of glycemic excursions; it can be used to complement capillary blood glucose.

These last two readings are useful to the doctor to check the patient's glycemic control.

Given the data, the Committee considers that the FREESTYLE LIBRE system is beneficial in the management of diabetes and constitutes a new tool in the self-monitoring of blood glucose, according to interstitial glucose data, but does not completely replace it.

04.1.3. CONCLUSION ON THE BENEFIT OF THE PRODUCT

Given the available data and according to the National Professional Council for Endocrinology, Diabetes and Metabolic Diseases and the Federation of Associations of Patients with Diabetes in France, the Committee underscores the benefit of the FREESTYLE LIBRE device for the self-monitoring of interstitial glucose, within the provided indications and conditions for use.

04.2. PUBLIC HEALTH BENEFIT

04.2.1. SEVERITY OF THE PATHOLOGY

Diabetes is a serious condition due to the associated complications.

Acute complications of diabetes are metabolic emergencies (discomfort or coma) due to hyperglycemia, ketoacidosis or hypoglycemia.

Chronic and degenerative complications of diabetes are the leading cause of morbidity and death with this disease. They include the microvascular complications (retinopathy, glomerular disease and neuropathy) and macrovascular complications (coronary heart disease, cerebrovascular and peripheral artery disease [PAD]).

Diabetes is a serious disease due to complications that may occur but are preventable when the metabolic control of blood sugar is permanently achieved.

04.2.2. EPIDEMIOLOGY OF THE PATHOLOGY

Results of the 2007-2010 Entred survey have estimated that 2.4 million adults in France suffer from diabetes. In 2013, the French Institute for Public Health Surveillance (InVS) estimated that over 3 million patients are being treated for diabetes.

Type 2 diabetes is the most common form (92%, or 2.76 million people in France). Patients with type 2 diabetes treated with insulin account for 17% of type 2 diabetes patients (469,200 patients).

Patients with type 1 diabetes account for 5.6% of diabetic patients, i.e. approximately 168,000 patients.

According to Entred, there are approximately 12,000 children with diabetes; they mainly suffer type 1 diabetes.

The total number of diabetic patients who have type 1 diabetes account for 170,000 patients. The total number of patients with type 2 diabetes treated with insulin is estimated at 470,000.

04.2.3. IMPACT

Blood glucose monitoring is provided by capillary blood glucose meters. No interstitial blood glucose scanner is currently listed on the LPPR.

This type of medical device constitutes a new tool in the arsenal of diabetes self-monitoring devices.

04.2.4. CONCLUSION ON PUBLIC HEALTH BENEFITS

Due to the expected reduction of the occurrence of long-term complications from diabetes and severe hypoglycemia; and given the severity of the pathology, the Committee estimates that the FREESTYLE LIBRE system provides a public health benefit.

In conclusion, the National Committee for the Evaluation of Medical Devices and Health Technologies (CNEDiMTS) believes that Actual Benefit is sufficient for inclusion on the list of products and services qualifying for reimbursement mentioned under article L 165-1 of the Social Security Code.

The Commission recommends inclusion of the product under brand name and retains the following indications:

Measurement of interstitial glucose levels for the treatment of patients with type 1 or type 2 diabetes (adults and children aged 4 years) undergoing intensified insulin therapy (using an external insulin pump or ≥ 3 injections per day) and performing the self-monitoring of blood glucose (SMBG) several times a day (≥ 3 per day).

The FreeStyle Libre System is especially designed for patients who have received therapeutic education and specific training on the use of the flash interstitial glucose monitoring system.

05 FACTORS DETERMINING THE ACTUAL BENEFIT

05.1. MINIMUM TECHNICAL SPECIFICATIONS

No additional requirements with respect to the technical specifications proposed by the manufacturer.

Warranty period:

- The FREESTYLE LIBRE Reader: 4 years
- The FREESTYLE LIBRE Sensor: 14 days

05.2. TERMS OF USE AND PRESCRIPTION

Prescription:

The initial prescription of the FREESTYLE LIBRE system must be ensured by a diabetologist or a pediatric diabetologist.

Initiation phase:

Before issuing a long-term prescription, the arrangements shall allow the provision of the FREESTYLE LIBRE system for:

- A trial period of a minimum of one month for every patient eligible for FREESTYLE LIBRE system. This period should allow the selection of patients who are capable of using the FREESTYLE LIBRE and wearing the Sensor.

The criteria for termination of the trial may in particular be related to the patient's choice and/or his caregivers, poor skin tolerance to the Sensor, or the inability to wear a Sensor at all times

- Towards the end of the trial period, patients who continue to use the FREESTYLE LIBRE system should undergo an evaluation at 3 months to assess whether or not to continue to use the system.

This assessment is based on the aforementioned criteria, in addition to a clinical assessment pertaining to the objectives set a priori (Severe hypoglycemia, ketoacidosis decompensation, time spent above or below a certain hypoglycemic threshold), and/or biological (HbA1c).

Renewal:

Renewal is ensured by any doctor.

Patient-specific education and/or their caregivers:

Prior to prescription, patients are supposed to receive specific education to provide them with the necessary skills and knowledge to apply the Sensor and to interpret and use the information provided by the FREESTYLE LIBRE system to optimize their treatment. The patient should also be informed of the lowest reliability of the FREESTYLE LIBRE system's results upon installation. This training is provided by a pump center any other center that provides care for diabetic patients and is involved in therapeutic education programs validated by the Regional Health Agencies (ARS)[6]. It is essential to plan this SMBG with the patient and/or his caregivers, by determining its frequency, the targets and therapeutic decisions to be taken based on results.

Conditions for support:

FREESTYLE LIBRE includes a

capillary blood glucose meter. Providing support and maintenance for this device does not include any other capillary blood glucose meter. The conditions for support of the FREESTYLE LIBRE system should allow the provision of the FREESTYLE LIBRE system elements, as a part of a long-term prescription: a Reader and Sensor (wearing time 14 days), following a 3-month initial period.

The wearing time of the Sensor being 14 days, the total number of Sensors to maintain per year and per patient is limited to 28 Sensors. In clinical situations, where the manufacturer recommends measuring blood glucose, the capillary blood glucose meter test strips and lancets must be limited to 100 test strips and 100 lancets, per patient, per year.

Terms of Use:

Measuring interstitial glucose using the FREESTYLE LIBRE system requires patient intervention via a scan of the Reader over the Sensor to get a current glucose reading. In the case of occasional scanning (> 8 hours), the initial values will become lost. The device is designed to replace the capillary blood glucose measurement, except in the cases listed below where the manufacturer recommends the use of a capillary blood glucose meter to check the results of the glucose levels.

The different cases are as follows:

- In the case of rapidly changing glucose levels, the level of interstitial glucose as measured by the Sensor and reported as actual may not accurately reflect blood sugar levels. When glucose levels are rapidly dropping, results of interstitial glucose levels measured with the Sensor may be higher than the blood glucose levels. Conversely, when glucose levels are rapidly increasing, interstitial glucose results measured with the Sensor may be lower than blood glucose levels.

- In order to confirm hypoglycemia or impending hypoglycemia as reported by the Sensor.

- If symptoms do not match the FREESTYLE LIBRE system readings. Symptoms that may be caused by hypoglycemia or hyperglycemia should not be ignored.

No on-call duty 24h/24h is required in the case of system failure.

No preventive maintenance is required for the FREESTYLE LIBRE system.

06 ADDED CLINICAL VALUE (ACV)

06.1. RETAINED COMPARATOR

Self-monitoring of blood glucose using a single capillary blood glucose meter.

06.2. ACV LEVEL

The Commission emphasizes that patient comfort and improved quality of life due to lower capillary blood glucose by finger prick test improved with the FREESTYLE LIBRE system.

The Commission decided on a moderate Added Clinical Value (ACV III) of the FREESTYLE LIBRE versus Self-Monitoring of Blood Glucose (SMBG) by capillary blood glucose Reader alone.

07 CONDITIONS OF RENEWAL AND DURATION OF INCLUSION

07.1. RENEWAL CONDITIONS

Updating data, as recommended by the practice guidelines for inclusion in the reimbursement list of products and services.

07.2. DURATION OF INCLUSION

5 years.

08 TARGET POPULATIONS

The population using the FREESTYLE LIBRE device was estimated based on analysis of individual data on the reimbursement of healthcare expenses.[7]

The selection criteria were as follows:

- At least one insulin treatment reimbursed during 2015 (ATC code: A10A)

Associated to

- At least one capillary blood glucose meter strip reimbursed during 2015 (LPPR code: 1173487, 1136894, 1186722, 1180441, 1187408, 1177611, 1179337 and 1172861).

Results indicated that the number of individuals treated with insulin and using testing strips for capillary blood glucose meter in 2015 was:

- 288,963 based on a minimum of 1,095 strips reimbursed (which reflects a mean daily consumption of 3 strips or more).

-136,127 based on a minimum of 1,460 strips reimbursed (which reflects a mean daily consumption of 4 strips or more).

- 72,540, based on a minimum of 1,825 strips reimbursed (which reflects a mean daily consumption of 5 strips or more).

Bearing in mind that individual reimbursement reflects the actual use of the product and that the frequency of use of capillary blood glucose meter strips is linked to insulin injections, it is estimated that the number of patients performing at least 3 insulin injections per day would be approximately 300,000 per year.

ANNEX 1
CLINICAL DATA

All studies published in detail with results and conclusions

[1] Two decrees (D2010-904 and D2010-906) and two bylaws dated 2nd August 2010, setting the authorization procedures of patient education by the regional health agencies and the skills required to deliver these programs, have been published in the Official Gazette on 4th August 2010.
According to these texts, any implemented therapeutic education program must submit for authorization from the Regional ▶

Health Agencies (ARS).
[2] IMPACT Study Report 'Randomized Controlled Study to Evaluate the Impact of Novel Glucose Sensing Technology on Hypoglycemia in Type 1 Diabetes' – 25th January 2016.
[3] REPLACE Study Report 'Randomized Controlled Study to Evaluate the Impact of Novel Glucose Sensing Technology on HbA1c in Type 2 Diabetes'- 23rd October 2015.
4 Bailey T., Bode B., Christiansen M., Klaff L., Alva S. et al. 'The performance and Usability of a Factory-Calibrate Flash Glucose Monitoring System.' 'Diabetes Technol The.' 2015; 17(11).
[4] Parkes JL et al, 'A New Consensus Error Grid to Evaluate the Clinical Significance of Inaccuracies in the Measurement of Blood Glucose; Diabetes Care' 23:1143-1148,2000.
[5] Edge J.A., Acerini C., Campbell F., Hamilton-Sheild J., Moudiotis C. 'Clinical Accuracy Evaluation of the FREESTYLE LIBRE Flash Glucose Monitoring System When Used by Children and Young People with Diabetes'.
[6] Two decrees (D2010-904 and D2010-906) and two bylaws dated 2nd August 2010, setting the authorization procedures of patient education by the regional health agencies and the skills required to deliver these programs, have been published in the Official Gazette on 4th August 2010.
According to these texts, any implemented therapeutic education program must apply for authorization from the Regional Health Agencies (ARS).
[7] According to the Inter-scheme Consumption Data (données de consommation inter-régimes [DCIR]) database of Health Insurance; which compiles data on healthcare expenses paid to beneficiaries in France.
[8] Diabetes Treatment Satisfaction Questionnaire : 8 questions on a scale of 0 to 6, highest score = high satisfaction
[9] Diabetes Quality of Life: 46 items (on a scale of 0 to 5).
[10] Diabetes Distress Screening Scale
[11] Hypoglycemia Fear Survey

Nyhetsinfo 25 juni 2017
www red DiabetologNytt

NT-rådets rekommendation angående Freestyle Libre vid diabetes typ 2:

"NT-rådet rekommenderar landstingen - att avstå från att använda flashglukosmätaren Freestyle Libre vid typ 2-diabetes"

NT-rådet (Nya Terapi-Rådert), SKL, Sveriges Kommuner och Landsting

NT-rådets yttrande till landstingen gällande kontinuerlig glukosmätning med FreeStyle Libre vid typ 2-diabetes

Bakgrund

Enligt önskemål från landstingens hälso- och sjukvårdsdirektörsnätverk ska kontinuerliga glukosmätare och flashglukosmätare för diabetiker, inom ramen för ett pilotförsök, genomgå samma process för nationellt ordnat införande som nya läkemedel.

TLV uppdrogs därför att inom sitt medicinteknikuppdrag göra en bedömning av kostnadseffektiviteten för flashglukosmätaren FreeStyle Libre, som skulle ligga till grund för en rekommendation från NT-rådet. Uppdraget omfattade både användning vid diabetes typ 1, vid vilken FreeStyle Libre sedan tidigare används, samt vid diabetes typ 2, där FreeStyle Libre ännu inte är införd.

Omkring år efter att detta uppdrag påbörjades, har företaget Abbot valt att inte häva sekretessen gällande hälsoekonomiska beräkningar och resultat och därmed kan inte FreeStyle Libre längre utvärderas inom medicinteknikuppdraget, vilket TLV kommunicerat.

NT-rådets bedömning

För att en fullständig bedömning av behandlingens värde med hänvisning till den etiska plattformen ska kunna göras krävs en utvärdering av kostnadseffektivitetet.

Det är NT-rådets förhoppning att företaget kan tillgängliggöra ett hälsoekonomiskt underlag till TLV och bidra till att en sådan bedömning kan göras.

I avsaknad av underlag för bedömning, rekommenderar NT-rådet landstingen att avstå från använda flashglukosmätaren Freestyle Libre vid typ 2-diabetes.

Eftersom FreeStyle Libre sedan tidigare är införd vid diabetes typ 1 ger NT-rådet ingen rekommendation, men uppmärksammar landstingen på att ingen bedömning av kostnadseffektiviteten gjorts varför en noggrann klinisk värdering av vilka patienter som har det största behovet av produkten bör göras innan den sätts in.

För NT-rådet,
Gerd Lärfars, ordförande
Referenser:
https://www.tlv.se/Medicinteknik/Medicinteknikuppdraget/

https://www.tlv.se/press/ovriga-nyheter/Ingen-utvardering-av-FreeStyle-Libre/

Om NT-rådets beslut

http://www.janusinfo.se/Nationellt-inforande-av-nya-lakemedel/Nationellt-inforande-av-nya- lakemedel/NT-radets-rekommendationer-grunder-till-beslut/

Närvarande vid beslut: Gerd Lärfars, ordförande NT-rådet; Lars Lööf, Uppsala/Örebro sjukvårdsregion; Johannes Blom, sjukvårdsregion Stockholm/Gotland; Anna Lindhé, Västra regionen; Maria Landgren, Södra regionen; Mårten Lindström, Sydöstra sjukvårdsregionen; Anders Bergström, Norra regionen

Jäv: Ingen ledamot deklarerade någon intressekonflikt för det aktuella ärendet.

Nyhetsinfo 21 juni 2017
www red DiabetologNytt

TLV tar semester utan att leverera hälsoekonomiskt dokument för FGM

Ett års arbete

Publicerad 13 juni 2017. Ingen utvärdering av FreeStyle Libre. Nedan är utlagt på TLVs www

”TLV har inte möjlighet att publicera en hälsoekonomisk utvärdering av den kontinuerliga glukosmätaren FreeStyle Libre, eftersom företaget som marknadsför produkten valt att inte bidra med nödvändigt underlag.

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– Det är viktigt att rätt patienter får FreeStyle Libre så det är olyckligt att vi nu inte har möjlighet att publicera en hälsoekonomisk utvärdering, säger Malin Blixt, enhetschef.

TLV:s utvärdering inom medicinteknikuppdraget skulle legat till grund för en nationell rekommendation från landstingens NT-råd. Syftet med rekommendationen var att ge förutsättningar för en jämlik tillgång till FreeStyle Libre.

Bakgrund

TLV påbörjade en hälsoekonomisk utvärdering av FreeStyle Libre sommaren 2016. På hösten samma år ansökte företaget som marknadsför produkten om att den skulle ingå i läkemedelsförmånerna och utvärderingen till NT-rådet avbröts.

I mars 2017 återkallade företaget sin ansökan och TLV återupptog då utvärderingen som skulle ligga till grund för NT-rådets rekommendation. Företaget har nu valt att inte bidra med materialet från ansökan och TLV kan därför inte publicera den utvärdering som gjorts.

För att TLV ska kunna återuppta arbetet krävs att företaget bidrar till en utvärdering.”

https://www.tlv.se/press/ovriga-nyheter/Ingen-utvardering-av-FreeStyle-Libre/

Nyhetsinfo 21 juni 2017
www red DiabetologNytt

TLV
TANDVÅRDS- OCH
LÄKEMEDELSFÖRMÅNSVERKET

FDA panel supports cardiovascular indication for Novo’s diabetes drug Victoza for T2DM, Can Lower CV Risks in High-Risk Patients

Following a daylong meeting on Tuesday, an FDA expert panel voted to recommend a label update for Novo’s blockbuster diabetes drug Victoza stating the med can lower cardiovascular risks for high-risk Type 2 diabetes patients.

By a 17-2 vote, the panel concluded that an outcomes trial dubbed Leader provides significant evidence demonstrating the CV benefit for Novo’s blockbuster’s GLP-1 diabetes medication.

In that trial, Victoza reduced major adverse cardiovascular events by 13% compared to placebo. The Novo drug reduced cardiovascular deaths by 22%, any deaths by 15%, and advanced diabetic kidney disease by 22%.

Ahead of the committee’s vote, FDA reviewers published briefing documents raising no major qualms about those results. The FDA doesn’t have to follow panel recommendations, but it typically does.

While the FDA reviewers noted that two clinical studies are usually needed in order to approve a new indication, the agency can rely on one study when the trial has shown a “highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.”

Further, the reviewers pointed out that the agency approved a CV indication for Eli Lilly and Boehringer Ingelheim’s SGLT-2 drug Jardiance on a single study, Empa-Reg.

FDA committee members took two votes on Tuesday, one ▶ on whether the Leader trial esta-

blishes that use of Victoza in Type 2 diabetes patients isn't associated with excess CV risks, and the second on whether the trial shows that Victoza reduces CV risks. The committee voted "yes" unanimously on the first question.

In its own briefing document published ahead of the meeting, Novo touted the data as supporting "a cardiovascular benefit of liraglutide in both primary and secondary cardiovascular prevention." Liraglutide is the generic name for Victoza, a GLP-1 med that was first approved in 2010.

Victoza is already approved in Type 2 diabetes in combination with diet and exercise, but the Danish drugmaker wants an addition to the label stating its med can lower the risk of major CV events in patients with high cardiovascular risks. In its document, Novo said the new indication would "provide important guidance to prescribers considering their options to treat" patients.

From www.fiercepharma.com

Nyhetsinfo 21 juni 2017
www red DiabetologNytt

Antioxidant i broccoli vid T2DM? Science Translational Medicine. Forskning Lund, Göteborg

Nya forskningsresultat ger hopp åt patienter med diabetes typ 2

Lantmännen har genom sin forskningsstiftelse kunnat bidra till forskning som visar positiva effekter hos patienter med typ 2-diabetes. I fokus står en vanlig grönsak som odlas på de svenska åkrarna.

Genom ett forskningsprojekt som finansieras av Lantmännen har forskare vid Lunds Universitet och Sahlgrenska akademin nu lyckats identifiera en naturlig substans som har en positiv effekt på patienter med diabetes typ 2.

Det aktiva ämnet - en antioxidant som finns i broccoli – har visat sig ge lägre blodsockernivåer hos vissa personer med diabetes typ 2. Den mängd av antioxidanten som behövs dagligen motsvarar 4-5 kg broccoli och dosen ges därför som ett koncentrat.

Typ 2-diabetes är redan idag ett gigantiskt hälsoproblem och Världshälsoorganisationen WHO uppskattar att 500 miljoner människor kommer att ha typ 2-diabetes år 2030. I Sverige står sjukdomen för 10% av vårdkostnaderna.

– Diabetes är en aktuell och global utmaning. Att ta ansvar är viktigt för Lantmännen, som har ett stort fokus på hälsosamma livsmedelsprodukter och en ambition att bidra till ett bättre hälsoläge i världen, säger Mats Larsson, forskningsdirektör på Lantmännen.

Diabetesstudien har pågått under tolv veckor och resultaten publiceras nu i tidskriften Science Translational Medicine. I studien ingick 100 patienter med diabetes, och resultatet visar att en viss antioxidant i broccoli kan motverka leverns förhöjda produktion av glukos – och därmed bli ett viktigt tillskott för diabetiker.

– Mycket talar för att det här kan bli ett värdefullt tillägg till existerande läkemedel, säger Anders Rosengren, docent vid Sahlgrenska akademin.

Planen är att livsmedelsprodukter innehållande den aktiva antioxidanten skall finnas tillgängligt på marknaden så snart utvecklingsarbetet är klart.

– Forskning är viktigt för Lantmännen och för våra ägare. Vår forskningsstiftelse är central för oss, och vi är stolta över att se så tydliga och fina resultat, som på sikt kan göra verklig skillnad för konsumenten, säger Per Olof Nyman, vd och koncernchef på Lantmännen.

Läs mer om studien på

http://www.gu.se/omuniversitetet/aktuellt/nyheter/detalj//broccoli-i-fokus-nar-ny-substans-mot-diabetes-identifierats.cid1475132

Nyhetsinfo 21 juni 2017
www red DiabetologNytt

Artificiell intelligens ska göra diabetesvården vid T2DM bättre – och mer kostnadseffektiv. I Skåne.

Christina Bjartell och Mattias Jönsson verksamhetschef på Capio i Malmö deltar i projektet som leds av Damon Tojjar .

Kan artificiell intelligens bidra till smartare användning av sjukvårdens resurser och leda till en bättre diabetesvård? Tillsammans med Region Skåne tar Lunds universitet täten i en satsning på e-hälsa och diabetes.

– Vinnare är både patienten och samhället, säger Damon Tojjar som leder projektet.

Efter att ha fått diagnosen typ 2-diabetes väntar för det mesta en krokig väg till bästa behandlingen kantad av många olika läkemedel. I dagens riktlinjer saknas specifik vägledning i vilket preparat som bäst passar den enskilde patienten. Samtidigt har såväl antalet patienter som nya godkända produkter ökat i antal de senaste åren. Resultatet är att allt fler läkemedel skrivs ut till allt fler patienter, utan adekvat uppföljning och utvärdering.

Ger rekommentationer

Ett intelligent digitalt beslutsstöd ger läkare behandlingsrekommendationer anpassade till varje enskild patient. Detta genom att verktyget samlar in och tolkar patientdata. Patienten kan med sin app få större möjlighet att förstå och följa sin behandling, och därigenom få bättre kontroll över sin diabetes.

Christina Bjartell (tv) och Mattias Jönsson verksamhetschef på Capio i Malmö (i mitten) deltar i projektet som leds av Damon Tojjar (th). Foto: www.med.lu.se

Lösningen bygger på artificiell intelligens vilket innebär att behandlingsrekommendationerna som presenteras bygger på en kombination av en ansenlig mängd data och variabler som den enskilda läkaren normalt sätt inte kan hantera.

Trettiotal vårdcentraler

Under 2017 deltar ett trettiotal vårdcentraler i projektet med Region Skåne som huvudman.

– Detta kan innebära en stor vinst och ökad trygghet för patienten samtidigt som det löser en viktig utmaning för sjukvården, säger Mattias Jönsson verksamhetschef vid Capio citykliniken i Malmö som deltar i projektet.

Professor Patrik Midlöv vid Centrum för primärvårdsforskning är koordinerande prövare:

- Det är mycket på gång inom e-hälsa men det är viktigt att dessa innovationer utvärderas vetenskapligt i en rigorös klinisk studie såsom vi gör i detta projekt innan de införs på bred front.

”Först i världen”

– Vi är först i världen med denna lösning, tack vare vårt fantastiska team av experter från klinik, akademi och industri, inom både medicin och teknik. Vi bygger lösningar som löser sjukvårdens utmaningar och är på god väg att bygga ut systemet mot flera andra viktiga folksjukdomar i närtid, säger Damon Tojjar som är forskande läkare vid Lunds universitets Diabetescentrum som själv varit med om att framgångsrikt utveckla och få godkänt läkemedel i Europa, USA och andra delar av världen.

Fakta/Diabetes

Diabetes är den snabbast växande folksjukdomen i världen. År 2040 beräknas fler än 640 miljoner människor vara drabbade. Typ 2-diabetes utgör 90 procent av alla fall. Utan behandling leder sjukdomen till svåra följdsjukdomar och kan leda till njursvikt, blindhet, amputationer, hjärtinfarkt och stroke.

Möt oss i Almedalen!

Medverkande på seminariet i Almedalen: Göran Hägglund (moderator), Johan Assarsson (Inera), Heidi Stensmyren (Sveriges läkarförbund), Anders Åkesson (Region skåne), Niklas Eklöf (eHälsomyndigheten), Janeth Leksell (Uppsala universitet) och Damon tojjar (Lunds universitet).

Intresserad av att veta mer? Välkommen till vårt seminarium i Almedalen onsdagen den 5 juli kl 16-17, Hästgatan 13, Visby

Hur kan artificiell intelligens bidra till en bättre, mer jämlik och personcentrerad diabetesvård?

Utvecklingen inom e-hälsa går rasande fort och nya evidensbaserade lösningar som kan förbättra läkemedelsbehandlingen och livskvaliteten för personer med diabetes är redan här. På vilket sätt bidrar de till en bättre diabetesvård? Hur tar vi vara på dessa initiativ och hur kan de implementeras?

Läs mer om seminariet
http://www.almedalsveckan.info/event/user-view/47364?redir=%23eidx_2

Nyhetsinfo 20 juni 2017
www red DiabetologNytt

TLV beslutar att Fiasp, mer snabbverkande än Novorapid, i beredningsform Fiasp Flextouch

Snabbverkande Novorapid, Fiasp, finns nu i beredningsformen Flextouch, till engångspenna, och till samma pris som för Humalog och Apidra.

Förhoppningsvis kan TLV och Novo Nordisk komma överens om, efter sommaren, också ett pris för Fiasp som penfil och flaska till insulinpump.

Det är framförallt sprut-Fiasp till insulinpump, som är intressant, ett extra snabbverkande insulin. 11,8 min snabbare i pump mot 8 min snabbare i penna jämfört med Novorapid.

Tandvårds- och läkemedelsförmånsverket, TLV, avslår ansökan om att Fiasp injektionsvätska lösning i cylinderampull, 5 x 3 ml ska få ingå i läkemedelsförmånerna.

Tandvårds- och läkemedelsförmånsverket, TLV, avslår ansökan om att Fiasp injektionsvätska, lösning flaska, I x IO ml ska få ingå i läkemedelsförmånerna.

Tandvårds- och läkemedelsförmånsverket, TLV, beslutar att Fiasp i beredningsformen och styrkan nedan ska ingå i läkemedelsförmånerna från och med 2017-06-16 till i tabellen angivna priser. TLV fastställer det alternativa försäljningspriset till samma belopp som AIP.

Nyhetsinfo 21 juni 2017
www red DiabetologNytt

TLV har diskvalificerat sig själv som hälsoekonomisk utredare. Debattinlägg, Jan Bolinder, prof, Karolinska

Det bidde inte ens en tumme.

Efter att under lång tid ha förhalat en önskvärd nationell samordning för användning av FGM kastar nu TLV in handduken.

Ett minst sagt märkligt och uppseendeväckande agerande, som nu riskerar att bidra till fortsatt ojämlik subvention och förskrivning i landet med stora regionala olikheter.

Detta trots att flera länder i Europa – senast i raden Frankrike – beslutat om obegränsad subvention för alla med typ 1 diabetes och typ 2 diabetes med multipel insulin-behandling.

Man frågar sig om inte TLV nu diskvalificerat sig själv i sin självpåtagna roll som hälsoekonomisk utredare; i den uppgiften borde väl rimligen ingå att i egen regi ta fram nödvändiga underlag, och samverka med motsvarande organ inom EU.

Jan Bolinder. Professor/överläkare
Kliniken för Endokrinologi,
Metabolism och Diabetes
Karolinska Universitetssjukhuset
Huddinge

TLV tar semester utan att leverera hälsoekonomiskt dokument för FGM.

Ett års arbete. Ingen utvärdering av FreeStyle Libre. Nedan är utlagt på TLVs www.

”TLV har inte möjlighet att publicera en hälsoekonomisk utvärdering av den kontinuerliga glukosmätaren FreeStyle Libre, eftersom företaget som marknadsför produkten valt att inte bidra med nödvändigt underlag.

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Nyhetsinfo 18 juni 2017
www red DiabetologNytt

Exercise management in type 1 diabetes: a consensus Statement. The Lancet jan 2017. Peter Adolfsson m fl

Michael C Riddell, Ian W Gallen, Carmel E Smart, Craig E Taplin, Peter Adolfsson, Alistair N Lumb, Aaron Kowalski, Remi Rabasa-Lhoret, Rory McCrimmon, Carin Hume, Francesca Annan, Paul A Fournier, Claudia Graham, Bruce Bode, Pietro Galassetti, Timothy W Jones, Inigo San Millan, Tim Heise, Anne L Peters, Andreas Petz, Lori M Laffel

Abstract

Type 1 diabetes is a challenging condition to manage for various physiological and behavioural reasons. Regular exercise is important, but management of different forms of physical activity is particularly difficult for both the individual with type 1 diabetes and the health-care provider. People with type 1 diabetes tend to be at least as inactive as the general population, with a large percentage of individuals not maintaining a healthy body mass nor achieving the minimum amount of moderate to vigorous aerobic activity per week. Regular exercise can improve health and wellbeing, and can help individuals to achieve their target lipid profile, body composition, and fitness and glycaemic goals. However, several additional barriers to exercise can exist for a person with diabetes, including fear of hypoglycaemia, loss of glycaemic control, and inadequate knowledge around exercise management. This Review provides an up to date consensus on exercise management for individuals with type 1 diabetes who exercise regularly, including glucose targets for safe and effective exercise, and nutritional and insulin dose adjustments to protect against exercise-related glucose excursions.

Introduction

Despite tremendous advances since the discovery of insulin almost 100 years ago, management of type 1 diabetes remains challenging.1,2 The majority of patients living with type 1 diabetes do not have a healthy body weight (about 60% are overweight or obese), about 40% have hypertension, about 60% have dyslipidaemia,3 and most do not engage in enough regular physical activity.4 Regular exercise can help patients achieve several goals: it improves the cardiovascular disease risk profile in paediatric patients5 and reduces HbA1c by about 0.3% in the paediatric population.6 Body composition, cardiorespiratory fitness, endothelial function, and blood lipid profile (ie, triglycerides and total cholesterol) all improve with regular physical activity in children and young people with type 1 diabetes.6 These cardiometabolic improvements are all important, given that cardiovascular disease is the leading cause of morbidity and mortality in young people with type 1 diabetes.7,8 In adults, both retinopathy and microalbuminuria are less common in those who are physically active than in those who are not.9 Active adults with type 1 diabetes tend to have better chance of achieving their HbA1c and blood pressure targets, and a healthier BMI, than do inactive patients.3 Regular exercise also decreases total daily insulin needs.10 Having a high exercise capacity in adulthood is associated with a reduced risk of coronary artery disease, myocardial ischaemia, and stroke, regardless of whether a person has diabetes or not.11 In a large cross-sectional study of 18 028 adults with type 1 diabetes,3 patients who were categorised as being most physically active (exercising two or more times per week) had better HbA1c concentrations, a more favourable BMI, less dyslipidaemia and hypertension, and fewer diabetes-related complications (retinopathy and microalbuminuria), than those who were less habitually active. The study also showed that patients with type 1 diabetes who are more active tend to have less diabetic ketoacidosis and a reduced risk of developing severe hypoglycaemia with coma.3 However, older women who are physically active have higher rates of severe hypoglycaemia (with coma) than those who are inactive.3 Several barriers to exercise might exist, including a fear of hypoglycaemia, loss of glycaemic control, insufficient time, access to facilities, an absence of motivation, issues around body image, and a general scarcity of knowledge around exercise management.12–14 For all adults living with diabetes, including those living with type 1 diabetes, 150 minutes of accumulated physical activity is recommended each week, with no more than two consecutive days of no physical activity.15 Resistance exercise is also recommended two to three times a week.15 Getting this much exercise is difficult for many patients; results from a large cross-sectional study showed that less than 20% of patients manage to do aerobic exercise more than two times per week, and about 60% of patients do no structured exercise at all.3 For children and young people, at least 60 minutes of physical activity should be done per day.16 Physical inactivity and prolonged sitting times increase gradually

with age and are linked to high HbA1c concentrations in young people with type 1 diabetes,17 and physical inactivity appears to be more common in women than in men.3 Regular exercise should be encouraged and supported by health-care professionals for many reasons, but primarily because the overall cardiometabolic benefits outweigh the immediate risks if certain precautions are taken. In this Review, the basic categories of exercise are described from a physiological perspective, as are the starting points for nutritional and insulin dose adjustments to keep patients in a targeted glycaemic range. This Review summarises the authors' consensus on the available strategies that help incorporate exercise safely into the daily management plan for those adults with type 1 diabetes who are regularly engaging in exercise, sports, or competitive events. We hope these new guidelines for exercise management will improve glycaemic control and encourage more individuals with type 1 diabetes to increase their physical activity.

Physiology of physical activity and exercise

Modalities of exercise

An understanding of the metabolic and neuroendocrine responses to the various types of exercise done by people with type 1 diabetes is essential for determination of appropriate nutritional and insulin management strategies. Exercise is generally classified as aerobic or anaerobic, depending on the predominant energy systems used to support the activity, although most exercise activities include a combination of energy systems. Aerobic exercise (eg, walking, cycling, jogging, and swimming) involves repeated and continuous movement of large muscle groups that rely primarily on aerobic energy-producing systems. Resistance (strength) training is a type of exercise using free weights, weight machines, body weight, or elastic resistance bands that rely primarily on anaerobic energy-producing systems. High intensity interval training involves alternation between brief periods of vigorous exercise and recovery at low to moderate intensity (eg, from 20 s to 4 min intervals of exercise and rest, for up to ten cycles).18 Both aerobic and anaerobic activities are recommended for most people living with diabetes,15,16 and guidelines now also incorporate high intensity interval training as a training modality with established benefits for individuals with prediabetes or type 2 diabetes.15 In some studies, high intensity interval training has been shown to be more effective than continuous aerobic training in improvement of cardiovascular fitness and various parameters related to glucose metabolism, including insulin sensitivity and glycaemic control in type 2 diabetes.19 At present, it is unclear what the most effective forms of exercise for improvement of cardiometabolic control in type 1 diabetes are.20

Neuroendocrine and metabolic responses to exercise

Individuals without diabetes

The metabolic responses to different forms of exercise are distinct. However, in almost all forms of exercise, regardless of the intensity or duration, blood glucose concentrations are normally held within a tight range (4–6 mmol/L). During aerobic exercise, insulin secretion decreases and glucagon secretion increases in the portal vein to facilitate release of glucose from the liver to match the rate of glucose uptake into the working muscles.21 Exercise can increase glucose uptake into muscle by up to 50 times—a phenomenon that occurs independently of insulin signalling—22 so the decrease in circulating insulin does not restrict glucose provision to the working body. Although the main determinant of glucose production during aerobic exercise is an increase in glucagon concentrations, neural control of glucose release and other counter-regulatory hormones also have a supportive role.23 An extended duration of exercise leads to reduced reliance on muscle glycogen as fuel and increased reliance on lipid oxidation and glucose derived from plasma.24 If insulin concentrations do not fall during prolonged aerobic exercise (eg, walking, jogging, or cycling), the rise in counter-regulatory hormones is less effective than when they do fall in the promotion of hepatic glucose production.21 When the intensity of exercise increases above 50–60% of maximal oxygen consumption (VO2max), fat oxidation decreases, particularly in those who are untrained, and carbohydrates become the preferred fuel.25 Prolonged high intensity exercise is supported by use of both muscle glycogen and blood glucose, with minimal contributions from lipid and protein.26 During predominantly anaerobic activities such as springing,27 and during a high intensity interval training session,28 circulating insulin concentrations do not decrease as markedly as in purely aerobic activities, in part because the duration of activity is typically shorter. High rates of external power output during high intensity interval training increase reliance on muscle phosphagens and glycogen, with lactate concentrations rising markedly in the circulation.28 Insulin concentrations increase above baseline concentrations in early recovery from a high intensity interval training session to offset the rise in glucose caused by the elevations in counter-regulatory hormones and other metabolites.27

Dysglycaemia during exercise in individuals with type 1 diabetes In

type 1 diabetes, the glycaemic responses to exercise are influenced by the location of insulin delivery, the amount of insulin in the circulation, the blood glucose concentration before exercise, the composition of the last meal or snack, as well as the intensity and duration of the activity29 (figure 1).

During aerobic exercise, blood glucose concentrations fall in most individuals with type 1 diabetes , unless they ingest carbohydrates, because insulin concentrations cannot be decreased rapidly enough at the start of the activity and might rise in the systemic circulation,30 perhaps because of increased blood flow to subcutaneous adipose tissue during exercise.31 Even if basal insulin infusion rates are halved 60 min before the start of exercise in patients on continuous subcutaneous insulin infusion, circulating free insulin concentrations do not decrease sufficiently upon commencement of exercise and concentrations tend to increase transiently during the activity.32 Increased insulin concentrations in the circulation during exercise promote increased glucose disposal relative to hepatic glucose production, and might delay lipolysis—another feature that increases the reliance of muscles on glucose as a fuel. Hypoglycaemia develops in most patients within about 45 min of starting aerobic exercise.33–35 Trained individuals with type 1 diabetes have greater reductions in blood glucose concentrations during aerobic exercise than do individuals with reduced physical fitness,36 possibly because the overall work rate is higher in those who are more aerobically conditioned than those who are not. As such, both trained and untrained individuals with type 1 diabetes typically require an increased carbohydrate intake [A: before commencing aerobic exercise?] or an insulin dose reduction, or both, for prolonged aerobic exercise. High intensity interval sprint training promotes the increased oxidative capacity of skeletal muscle in type 1 diabetes and attenuates the rates of glycogen breakdown,37 which might, in theory, protect against hypoglycaemia after exercise. Perhaps in line with this, individuals who are aerobically conditioned have lower glucose variability than do those who are unconditioned.38 Low insulin concentrations due to aggressive reductions in insulin administration or a skipped insulin dose can cause hyperglycaemia before and during aerobic exercise,39 and even mild activity could lead to development of ketosis.40

Resistance exercise is associated with better glucose stability than continuous moderate intensity aerobic exercise,41 although resistance exercise could cause a modest rise in glycaemia in some individuals.42 Compared with aerobic exercise, a high intensity interval training session attenuates the decrease in glycaemia,43 as does resistance exercise done before aerobic exercise,44 possibly because of increased concentrations of counterregulatory hormones and various metabolites that restrict glucose disposal.45 In situations of brief and intense anaerobic exercise (eg, sprinting, weight lifting, and some competitive sports),42,46 or during high intensity interval training,28 glucose concentrations typically rise. Dysglycaemia after exercise in individuals with type 1 diabetes Glucose uptake into muscle decreases immediately after aerobic exercise, but overall glucose disposal remains elevated for several hours in recovery from exercise to help replenish glycogen stores.47 The risk of hypoglycaemia is elevated for at least 24 h in recovery from exercise, with the greatest risk of nocturnal hypoglycaemia occurring after afternoon activity.48 As mentioned above, weight lifting, sprinting, and intense aerobic exercise can promote increase in glycaemia that could last for hours in recovery. Although a conservative insulin correction after exercise might be prudent in some situations,49 over-correction with insulin can cause severe nocturnal hypoglycaemia and lead to death.50 High intensity interval training has been associated with a higher risk of nocturnal hypoglycaemia than continuous aerobic exercise in some51—but not all—52,53 studies.

Exercise goals and glycaemic targets

Individuals with type 1 diabetes should engage in exercise for various health reasons. The evidence on ▶

whether regular exercise improves metabolic control in adults with type 1 diabetes is somewhat scarce,20,54 although exercise appears to be helpful in young people with type 1 diabetes.6 Exercise readiness questionnaires, such as Physical Activity Readiness Medical Examination (ePARmed-X+) and Physical Activity Readiness Questionnaire for Everyone (PAR-Q+), are available online for adults with diabetes who might be at increased risk of developing adverse events. Patient goals for exercise (eg, metabolic control, prevention of complications, fitness, weight loss, or competition and performance) should be considered before decisions on diabetes management are made. This is an important element of the diabetes management plan. For example, exercise for weight loss requires strategies that focus on reduction of insulin concentrations during and after exercise, as opposed to consumption of additional carbohydrates. By contrast, if maximisation of sports and exercise performance is the primary goal, then nutritional guidance specific to the sporting activity is needed and a modified insulin plan to match the increased nutritional requirements should be considered.55 For all patients, blood glucose monitoring before, during, and after exercise is essential to inform strategies and maintain stable and safe glycaemia.

The appropriate blood glucose concentration at the start of exercise should be tailored to the individual. Based on our consensus, a reasonable starting range for most patients doing aerobic exercise lasting up to an hour is 7–10 mmol/L. This range balances performance considerations against the risk of hypoglycaemia. Concentrations higher than 7–10 mmol/L might be acceptable in some situations where added protection against hypoglycaemia is needed. Achieving and maintaining circulating glucose concentrations in this range is challenging. The glycaemic response to exercise is variable and based on several factors, including the duration and intensity of exercise,45,56 the starting level of glycaemia,34 the individual's aerobic fitness,36 and the amount of insulin in circulation57,58 (figure 1). Anaerobic exercise and a high intensity interval training session can be initiated with a lower starting glucose concentration (5–7 mmol/L) because glucose concentrations tend to remain relatively stable and fall to a lesser extent than with continuous aerobic exercise, or rise slightly (figure 1). Strategies to cope with a range of glucose concentrations before the start of exercise are provided in panel 1, bearing in mind that for aerobic activities lasting longer than 30 min, additional carbohydrates are likely to be needed (table 1). If glucose concentrations are too high because of insulin omission, ketosis and further hyperglycaemia can occur,40 and perceived exercise or work effort probably increases. Although it is unclear if there is an optimal glycaemic range for exercise performance, clinical experience and data from a field study in adolescents62 suggest that maintenance of a concentration of about 6.0–8.0 mmol/L might be ideal.

Contraindications and cautions for exercise

Although few exercise restrictions should be placed on patients, some considerations are important, and are highlighted below.

Elevated ketones

Elevated blood ketones (≥1.5 mmol/L) or urine ketones (2+ or 4.0 mmol/L) [A:OK?] before a bout of exercise should be addressed before the start of the session via insulin administration with carbohydrate feeding if necessary (ie, relativity euglycaemic but ketotic; see panel 1). [A:OK?] The cause of elevated ketone concentrations should be identified (illness, diet manipulation, a recent bout of prolonged exercise, insulin omission, etc). Prolonged endurance type activities (eg, marathons and trekking) and diets very low in carbohydrate can elevate blood ketone concentrations in patients and blood glucose might not be markedly elevated. The health-care professional should therefore define appropriate protocols for ketone monitoring and strategies for what to do when blood or urine ketones are elevated. Blood ketone concentrations of 3.0 mmol/L or more should be managed immediately by a qualified health-care professional (eg, a hospital emergency department or physician).

Recent hypoglycaemia

Severe hypoglycaemia (defined here as blood glucose ≤2.8 mmol/L or a hypoglycaemic event requiring assistance from another individual) within the previous 24 h is a contraindication to exercise, because of the substantially increased risk of a more serious episode during exercise.63 In situations where minor hypoglycaemia (blood glucose 2.9–3.9 mmol/L, with the ability to self-treat) has occurred, the increased risk of recurrence must be taken into account.64 Vigilance around monitoring should be stressed and exercise should be avoided if the setting is deemed particularly unsafe (eg, Alpine skiing, rock climbing, swimming or trekking alone).

Diabetes-related complications

Overall, the health benefits of being physically active outweigh the risks of being sedentary for people with diabetes. Those with complications can derive several health benefits from low intensity physical activities, with little risk of any

adverse events.65 In individuals with long-standing disease or with HbA1c concentrations well above the target, vigorous exercise, activities involving lifting of heavy weights, and competitive endurance events are contraindicated, particularly if the patient has unstable proliferative retinopathy, severe autonomic dysfunction, or renal failure.65

Inadequate preparation for exercise-associated hypoglycaemia

In preparation for exercise, individuals with type 1 diabetes should be aware of their starting glucose concentrations, and should also have blood glucose monitoring equipment and snacks to treat hypoglycaemia. They should also be advised to wear or carry some form of diabetes identification.

Nutritional management

Goals for nutritional management Nutritional management for people with type 1 diabetes should incorporate strategies that optimise glycaemic control while promoting long-term health.66 The main strategies around nutrition for exercise and sport discussed in this section primarily aim to maximise athletic performance and are based largely on studies done in highly trained healthy individuals without diabetes,59 with few studies done in people with type 1 diabetes. Application of these strategies to people with type 1 diabetes must consider the individual's insulin management plan and include specific advice focused on nutrition for both athletic performance and glycaemic management. A registered dietitian with specialist diabetes and sports knowledge is the most qualified to help active people with type 1 diabetes. An individualised meal planning approach is central to improvement of performance and glycaemic outcomes. Daily carbohydrate intake should relate to the fuel cost of training in the athletic subpopulation and ensure prevention of hypoglycaemia for all active people. Balancing insulin dose to carbohydrate intake during exercise is essential. Various carbohydrate and insulin adjustment strategies can be used, such as reduction of the pre-exercise bolus insulin dose by 30–50% up to 90 min before aerobic exercise,67 consumption of carbohydrates with a high glycaemic index during sport (30–60 g/h), or replacement of carbohydrates after anaerobic exercise. Personal tolerance of ingested carbohydrate, particularly during exercise, is a key factor in tailoring of recommendations. The distribution of macronutrient intake over the day should take into account the timing of exercise so that liver and muscle glycogen stores are maximised before the activity and replenished in early recovery.59 This strategy should include carbohydrate feeding well before exercise (~4 h) and early in recovery.59,68Daily energy and macronutrient balance Athletes with type 1 diabetes need sufficient energy to meet the demands of their daily activities. These demands will vary with age, sex, body composition, and activity type.69 Total energy requirements differ with individual aims. Predictive equations can be used to estimate resting energy expenditure;70 however, they should serve only as a guide, as they could overestimate or underestimate actual requirements. An appropriate macronutrient balance and micronutrient intake,59 coupled with a glycaemic control strategy, is required to maximise performance. The optimal macronutrient distribution will vary depending on the individualised assessment and exercise goals. A guide to the nutritional distribution of the total daily energy intake is as follows: 45–65% carbohydrate, 20–35% fat, and 10–35% protein, with higher protein intakes indicated for individuals wanting to lose weight.71 The major nutrients required to fuel performance are carbohydrates and lipids, while the addition of protein is needed to help foster recovery and maintain nitrogen balance.59,72 Protein requirements range from 1.2 to 1.6 g per kg body weight per day, and will vary with training type and intensity, and carbohydrate availability.59,73 Higher intakes might be needed for recovery from injury or for individuals on energy-restricted diets74 to maintain lean body mass.

Carbohydrate needs before, during, and after exercise

A distinction should be made between carbohydrate needs for performance and carbohydrate intake required for hypoglycaemia prevention (table 1). Carbohydrate requirements will alter insulin management strategies and vice versa. Most studies in type 1 diabetes have investigated the amount and distribution of carbohydrate required to prevent hypoglycaemia rather than to optimise performance, although the two might be at least partially related.34,67,75,76 For example, although only 15–20 g/h of carbohydrate might be required to prevent hypoglycaemia in people who reduce their insulin concentrations in anticipation of exercise, this amount of carbohydrate could be insufficient for performance. Implementation of increased carbohydrate supplementation (up to 75 g/h) is possible for prolonged activity lasting longer than 2.5 hours (eg, marathons and other endurance type races) without having an adverse effect on glycaemia, as long as the insulin dose is titrated appropriately.55 In general, carbohydrate requirements during shorter, intermittent, high-intensity, and anaerobic activities can be considerably decreased (table 1).

Nutritional needs for recovery

Nutrition requirements to maximise muscle recovery and muscle protein synthesis after exercise have been well studied in the athletic population without diabetes.77 For replenishment of glycogen content after exercise, carbohydrate intake is essential.59 For athletes with type 1 diabetes, rapid and adequate replenishment of muscle and liver glycogen stores is essential to help prevent late onset hypoglycaemia. Glycogen replacement strategies could also be important in prevention of euglycaemic ketosis in exercise recovery.78 Ingestion of protein (~20–30 g) in addition to carbohydrate in the period after exercise is beneficial for muscle protein synthesis, but protein ingestion does not appear to facilitate glycogen replenishment in athletes who do not have diabetes.59 Role of high and low glycaemic index foods for maintenance of euglycaemia The glycaemic index of a carbohydrate-rich food can be used to assist with the selection of the carbohydrate type for exercise; sports drinks and energy gels with a high glycaemic index provide rapidly released carbohydrate to increase blood glucose concentrations during endurance events and can treat or prevent hypoglycaemia. Consumption of foods with a low glycaemic index before exercise could sustain carbohydrate availability and maintain euglycaemia, whereas consumption of meals and snacks with a high glycaemic index after exercise could enhance recovery. Snacks with a low or moderate glycaemic index could also be preferred for long-distance activities such as trekking and long-distance cycling at low to moderate workloads. Consumption of a carbohydrate with a low glycaemic index (isomaltose) 2 hours before a high intensity run in adults with type 1 diabetes showed better blood glucose responses during exercise than did consumption of a carbohydrate with a high glycaemic index (dextrose).79 In adults with type 1 diabetes, consumption of a meal and bedtime snack with a low glycaemic index after midday exercise prevented postprandial hyperglycaemia more effectively than consumption of a meal and snack with a high glycaemic index after exercise, with both meal types being protective against hypoglycaemia for about 8 h.80 [A: OK as edited?] The protection provided by a snack was not sustained beyond 8 h, and the risk of hypoglycaemia remained high for at least 24 h.80

Fluid replacement

Adequate fluid intake before, during, and after exercise is necessary for prevention of dehydration and optimisation of performance.68 Water is the most effective drink for low-intensity and short-duration sports (ie, ≤45 min), as long as glucose concentrations are 7 mmol/L or higher. Sports beverages containing carbohydrate (6–8%) and electrolytes are useful for athletes with type 1 diabetes exercising for a longer duration; they are also useful as a hydration and fuel source for higher intensity exercise, and for prevention of hypoglycaemia.34,81 However, overconsumption of these beverages can result in hyperglycaemia. Milk-based drinks containing carbohydrate and protein can assist with recovery after exercise and prevent delayed hypoglycaemia.76Low-carbohydrate high-fat diets and exercise People with type 1 diabetes can choose a low carbohydrate high fat diet for various reasons. A review on low carbohydrate high fat diets and sports performance in individuals without type 1 diabetes concluded that, despite increasing the ability of muscles to utilise fat over time, no evidence was available to suggest performance benefits.82 Long-term studies have yet to be done on the health, glycaemia, or performance effects of low carbohydrate high fat diets in people with type 1 diabetes. A concern with these diets is that they could impair the capacity for high-intensity exercise.83 Variation in carbohydrate intake (ie, periodisation throughout the training cycle according to fuel needs and performance) has been suggested by some researchers as a way to help promote adaptation of skeletal muscle to training.84 Additionally, various exercise-nutrient protocols are used to manipulate carbohydrate availability, such as training in a fasting state or withholding carbohydrate intake at a meal before or after exercise. These approaches have not been studied in individuals with type 1

diabetes, in whom manipulation of dietary carbohydrate as part of training presents unique challenges for insulin therapy and requires careful glucose monitoring. Sports nutritional aids and type 1 diabetes The use of ergogenic aids is a widespread performance enhancement strategy used by athletes, but little evidence is available on their use in athletes with type 1 diabetes. Caffeine intake in athletes without diabetes has shown improvements in endurance capacity and power output.85 Caffeine intake (5–6 mg per kg body mass) before exercise attenuates decrease in glycaemia during exercise in individuals with type 1 diabetes, but it might increase the risk of late onset hypoglycaemia.86 Recommendations for management of glycaemia Blood glucose responses to the various forms and intensities of exercise show high variability between and within individuals (figure 1). Glycaemic management is therefore based on frequent glucose monitoring, adjustments to both basal and bolus insulin dosing, and consumption of carbohydrates during and after exercise. These recommendations are intended to serve as a starting point for insulin adjustments and carbohydrate intake that can then be individualised (figure 2). Clinical management strategies should be built around exercise types and individual aims, and implementation of these strategies should take into account the factors summarised in panel 2. Generally, sustained aerobic exercise requires more substantial reductions in insulin dose and a higher carbohydrate intake than a short-term high intensity interval training session. By contrast, brief anaerobic exercise (eg, sprinting or weight lifting) could require increased insulin delivery, which is typically given in early recovery rather than before exercise for obvious safety reasons.49 Strategies for insulin dose adjustments and carbohydrate intake during and after planned exercise are presented in table 2 and table 3.

Insulin adjustment for prolonged activities: bolus insulin approaches

Reductions in the bolus insulin dose accompanying the meal before exercise or consumption of additional carbohydrate during exercise are typically needed to avoid hypoglycaemia during prolonged exercise (>30 min).34,56,67,102–104 Bolus dose reductions require planning in advance and are probably only appropriate for exercise with a predictable intensity performed within 2–3 h after a meal. As shown in table 3, the extent of a mealtime dose reduction is proportional to both the intensity and duration of the physical activity. This approach is safe and effective; even reducing the bolus insulin dose by as much as 75% does not appear to increase ketone production during exercise.104 Another strategy is to combine a 75% reduction of the bolus insulin dose before exercise with ingestion of a snack or meal with a low glycaemic index.105 This method also reduces the risk of hyperglycaemia before exercise. However, this approach will not protect against hypoglycaemia if the exercise is performed an hour or more after consumption of the snack.105 As such, this combined approach might be preferable only for postprandial exercise done soon after a meal.

Basal insulin approaches

Late postprandial hypoglycaemia (>4 h after a meal) following aerobic exercise is driven partly by circulating basal insulin concentrations. Elevated insulin sensitivity after exercise, and possibly a blunting of glucose counter-regulation, appear to place individuals at risk for at least 12 h. Reduction of circulating basal insulin concentrations can ameliorate this risk. For patients on multiple daily insulin injections, clinical observations and limited experimental data106 show that reduction of long-acting basal (as well as prandial) insulin concentrations before exercise reduces the risk of hypoglycaemia during and after the activity, but might promote hyperglycaemia at other points during the day. Therefore, reduction in the basal insulin dose for patients on multiple daily insulin injections should not be routinely recommended but can be a therapeutic option for those engaging in considerably more planned activity than usual (eg, camps or tournaments). In general, basal insulins with a short half-life, such as NPH insulin or insulin detemir, seem to lead to less hypoglycaemia in conjunction with exercise than do basal insulins with a longer half-life, such as insulin glargine,107 although the mechanism through which this occurs is unclear. Although ultra-long-acting insulins (eg, insulin degludec, with a 25 h half-life) pose similar risks of hypoglycaemia with endurance exercise to those of insulin glargine,108 dose reductions for exercise would have to be implemented at least 48 h before planned exercise. We do not recommend this, as it would compromise overall glycaemic control.

Continuous subcutaneous insulin infusion offers the flexibility to modify basal infusion delivery and obtain a quick effect (within ~1–2 h).109 Suspension of basal insulin infusion at the onset of 60 min exercise reduces the risk of hypoglycaemia during the activity, but it could increase the risk of hyperglycaemia after exercise.110 Moreover, glucose concentrations could still decrease by 2–3 mmol/L over 30–60 min even when basal insulin is dramatically reduced (or completely suspen- ▶

ded),67,110,111 because of the lag time in the change in circulating insulin concentrations. Where practical, a basal rate reduction, rather than suspension, should be attempted 60–90 min before the start of exercise. An 80% basal reduction at the onset of exercise helps mitigate hyperglycaemia after exercise more effectively than does basal insulin suspension, and appears to be associated with a reducedrisk of hypoglycaemia both during and after the activity.67

However, the optimal timing of basal rate reductions for aerobic and high intensity exercise activities and the maximal safe duration for insulin pump suspension have yet to be determined and remain open to debate. To limit the risk of compromised glycaemic control and ketosis, we propose a time limit of less than 2 h on the basis of rapid-acting insulin pharmacokinetics.109 Hyperglycaemia commonly occurs in patients after intense exercise, particularly if insulin concentrations are reduced. Continuous subcutaneous insulin infusion seems to offer advantages over multiple daily insulin injections in the management of early onset112 and late onset hypoglycaemia after exercise,113 because of the increased flexibility around basal insulin adjustments. Overcorrection of hyperglycaemia after exercise via repeated insulin dose administration results in an increased risk of severe late onset hypoglycaemia, which could even be fatal.50 Strategies to reduce the risk of late onset hypoglycaemia after exercise Increased insulin sensitivity lasts up to 24–48 h following exercise.47 Few studies have tested various nutrient or insulin dose adjustments to prevent hypoglycaemia after exercise. Nocturnal hypoglycaemia after exercise commonly occurs in individuals with type 1 diabetes,114 with an increased risk after afternoon exercise.48,115 Immediate increases in insulin sensitivity after exercise can be addressed through a reduction of about 50% in the bolus insulin dose administered at meal after exercise, along with consumption of a snack with a low glycaemic index at bedtime.80 In one study of 16 young people using an insulin pump, a temporary basal rate reduction of about 20% at bedtime for 6 h reduced the risk of nocturnal hypoglycaemia.113 Similarly, in another study of ten men on multiple daily insulin injections, a 20% basal rate reduction on the day of exercise along with provision of a free carbohydrate snack at bedtime (0.4 g carbohydrate per kg body mass) reduced the risk of nocturnal hypoglycaemia.106 Individuals at high risk ofsevere nocturnal hypoglycaemia (eg, those with recurrent hypoglycaemia and those sleeping alone) should take additional preventive measures, including blood glucose checks at 0200 h or 0300 h, or the use of a real time continuous glucose monitoring system with alarms and automatic pump suspension.116 Consumption of a snack alone, without changing basal insulin therapy, does not appear to entirely eliminate the risk of nocturnal hypoglycaemia,80 and alcohol intake might increase the risk.98

Emerging tools for exercise management

Several treatment regimens exist for people with type 1 diabetes. Continuous subcutaneous insulin infusion offers better flexibility in basal insulin adjustments and management of exercise-associated hyperglycaemia than other methods of insulin delivery.117 Continuous subcutaneous insulin infusion is associated with reduced hyperglycaemia after exercise compared with multiple daily insulin injections,112 but can create frustrating challenges for sports that might require disconnection of the insulin pump (for example, combat sports, diving, and some team sports such as football, soccer, field hockey, or basketball).118 Continuous subcutaneous insulin infusion could also contribute to a greater sense of being diseased and social stigma in some individuals by drawing undue attention to their condition.118 Prolonged disconnection of the pump (>60 min) should be managed by reconnecting, testing, and reconnection of the pump if necessary, or by switching to basal insulin provision by needle. Continuous glucose monitoring provides comprehensive information on blood glucose concentrations, real-time trends, and rates of change, which can be used to prevent low concentrations during exercise,119 even in unique settings where self-monitoring of blood glucose is difficult.120 Existing sensors are reasonably accurate for exercise;96,121 however, the lag time in glucose equilibrium with the interstitial space and the rapid turnover in glucose during exercise might affect accuracy (ie, overestimate blood glucose when concentrations are dropping and underestimate it when concentrations are rising).97,122 Structured educational sessions can be implemented by downloading data on self-monitoring of blood glucose, continuous glucose monitoring, and continuous subcutaneous insulin infusion.123 Continues glucose monitoring systems now offer the option to add followers who can view glucose concentrations in real time and potentially alert the patient while they are playing sports. Threshold suspension of insulin delivery in continuous subcutaneous insulin infusion could offer additional protection against exercise-associated hypoglycaemia, according to some data.124 The development of a fully artificial pancreas for exercise remains an elusive goal.125

Conclusion

Regular physical activity should be a routine objective for patients with type 1 diabetes, for various health and fitness reasons. Considerable challenges remain for people with type 1 diabetes, and their health-care team, in management of exercise and sports. Several small observational studies and a few clinical trials have been published to date that help to inform the consensus recommendations presented here. More studies are needed to determine how to best prevent exerciseassociated hypoglycaemia with basal rate insulin dose adjustments and how to manage glycaemia in the recovery period after exercise. In general, aerobic exercise is associated with reductions in glycaemia, whereas anaerobic exercise might be associated with a transient increase in glucose concentrations. Both forms of exercise can cause delayed-onset hypoglycaemia in recovery. A sound understanding of the physiology of different forms of exercise and the variables that can influence glycaemia during exercise and sport should underpin the implementation of safe and effective glycaemic management strategies. For aerobic exercise, reductions in insulin administration before the activity (ie, reductions in basal or bolus insulin, or both) can help ameliorate the risk of hypoglycaemia, as can increasing carbohydrate intake to 60 g per h or more. For anaerobic exercise, conservative insulin dose corrections might be required, although this too might increase the risk of nocturnal hypoglycaemia, particularly if the exercise is performed late in the day. In all instances, additional vigilance around glucose monitoring is needed before, during, and after the physical activity.

Panel 1: Blood glucose concentrations before exercise commencement and recommended glucose management strategies

The carbohydrate intakes shown here aim to stabilise glycaemia at the start of exercise. Blood glucose at the start of exercise must also be viewed within a wider context. Factors to consider include directional trends in glucose and insulin concentrations, patient safety, and individual patient preferences based on experience. Carbohydrate intake will need to be higher if circulating insulin concentrations are high at the onset of exercise. Starting glycaemia below target (<5 mmol/L) Ingest 10–20 g of glucose before starting exercise Delay exercise until blood glucose is more than 5 mmol/L (90 mg/dL) and monitor closely for hypoglycaemia Starting glycaemia near target (5–6·9 mmol/L) Ingest 10 g of glucose before starting aerobic exercise Anaerobic exercise and high intensity interval training sessions can be started Starting glycaemia at target levels (7–10 mmol/L) Aerobic exercise can be started Anaerobic exercise and high intensity interval training sessions can be started but glucose concentrations could rise Starting glycaemia slightly above target (10·1–15·0 mmol/L) Aerobic exercise can be started Anaerobic exercise can be started but glucose concentrations could rise Starting glycaemia above target (>15 mmol/L) If the hyperglycaemia is unexplained (not associated with a recent meal), check blood ketones. If ketones are modestly elevated (up to 1·4 mmol/L), exercise should be restricted to a light intensity for only a brief duration (<30 min) and a small corrective insulin dose might be needed before starting exercise. If blood ketones are elevated (≥1·5 mmol/L), exercise is contraindicated and glucose management should be initiated rapidly as per the advice of the health-care professional team. Mild to moderate aerobic exercise can be started if blood ketones are low (<0·6 mmol/L) or the urine ketone dipstick is less than 2+ (or <4·0 mmol/L). [A: OK as edited?] Blood glucose concentrations should be monitored during exercise to help detect whether glucose concentrations increase further. Intense exercise should be initiated only with caution as it could promote further hyperglycaemia

Panel 2: Factors that to consider before adjustments are made for exercise in individuals with type 1 diabetes

Subcutaneous insulin injection and its adjustments Differences in the site and depth of insulin injection affect absorption charac-

teristics87,88 Lipodystrophy can lead to increased fluctuation in blood glucose and unpredictable hypoglycaemia Inadequate understanding of insulin pharmacokinetics often leads to inappropriate insulin adjustments, including excessive insulin corrections (stacking), which could be particularly dangerous after exercise Rapid acting,30 regular, and intermediate acting,89,90 but probably not long acting,91 insulin absorption rates are increased with exercise Carbohydrate intake Variation in carbohydrate quantity (including inaccuracy in measurement of intake) and type will affect glycaemic excursions92 Self-monitoring of capillary blood glucose and continuous glucose monitoring Errors in self-monitored blood glucose sampling or measurement errors during self-monitoring or continuous glucose monitoring could result in inappropriate insulin dose estimations93,94 Although the accuracy of continuous glucose monitoring is improving, it can be compromised by poor accuracy in self-monitoring and calibrations methods95 The lag time in continuous glucose monitoring could affect accuracy during exercise96,97 Medications and alcohol Insulin sensitivity might be affected98 as might glucose monitoring tools94 Physiological cycles Diurnal endocrine variation, the menstrual cycle, and pregnancy affect insulin sensitivity and glycaemic patterns99 Changes in work and sleep patterns Such changes require adjustments in timing of basal insulin dose administration The timing of exercise should be considered relative to insulin sensitivity and the risk of nocturnal hypoglycaemia48 Intercurrent illness and stress Intercurrent illness or stress might necessitate changes in both basal and bolus insulin dose100 Vigorous exercise is contraindicated 5

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Nyhetsinfo 18 juni 2017
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Avhandling kring socioekonomiska konsekvenser av typ-1 diabetes. Sofie Persson, Lund

8/6 försvarade IHE:s Sofie Persson sin avhandling kring socioekonomiska konsekvenser av typ-1 diabetes.

Disputationen ägde rum vid Ekonomihögskolan, Lunds universitet, den 8 juni 2017.

Avhandlingens titel är "Socioeconomic Consequences of Childhood Onset Type 1 Diabetes – a case study of the impact of an early life health shock" och undersöker de socioekonomiska konsekvenserna av typ-1 diabetes och hur en hälsochock tidigt i livet kan påverka socioekonomisk status som vuxen.

Hela vhandlingen som free https://lup.lub.lu.se/search/publication/2fdf7492-311e-4a0c-bf94-3fa2b8456d51

Nyhetsinfo 17 juni 2017
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Sverige ett innovativ land. Regeringens utredare Anders Lönnberg säljer in Sverige i USA som bioteknik intressant

Sverige behåller andraplatsen i global innovationsrankning

De fem nordiska länderna finns bland de 25 högst rankade länderna i Global Innovation Index 2017,

Sverige behåller sin position som världens näst mest innovativa land, enligt Global Innovation Index 2017,

Schweiz är för sjätte året i rad det mest innovativa landet. Nederländerna är i år rankat som nummer tre, och har avancerat fem positioner framför allt tack var de insatser som gjorts för att öka tillgängligheten till data i landet.

Sverige har förbättrat sin placering i flera av rankningens undergrupper. I gruppen länkade innovationer (innovation linkage) avancerade Sverige elva positioner, i gruppen kunskapspåverkan (knowledge impact) tio positioner och sju positioner i gruppen informations- och kommunikationsteknik, IKT.

Generellt finns Sverige med bland de tio högst rankande länderna i de olika undergrupperna, med undantag för gruppen kreativa resultat (creative output) där Sverige är rankat elva.

Samtliga nordiska länder finns bland de 20 högst rankade länderna.

Bland de kluster som rankats för sin innovationsförmåga ligger Stockholm på plats 13, Malmö på plats 62 och Göteborg på plats 69. De högst rankade klustren är Tokyo–Yokohama i Japan, Shenzhen–Hongkong i Kina, San Jose–San Francisco i USA och Seoul i Sydkorea.

Rapporten presenteras i dag i Genève av Cornell University, The Business School for the World (Insead) och världspatentorganisationen World Intellectual Property Organization (Wipo).

Världens mest innovativa länder, enligt GII 2017 (förra årets placering inom parentes).

1. Schweiz (1)
2. Sverige (2)
3. Nederländerna (9)
4. USA (4)
5. Storbritannien (3)
6. Danmark (8)
7. Singapore (6)
8. Finland (5)
9. Tyskland (10)
10. Irland (7)

Lönnberg säljer in svensk life science på Bio i San Diego

I samband med den internationella bioteknikkonferensen Bio i San Diego i USA 19–22 juni kommer svensk life science att företrädas av Anders Lönnberg, regeringens nationella samordnare på området.

Anders Lönnberg är en av talarna under ett seminarium med temat ”Är vi redo att digitalisera kliniska prövningar” (Are we ready for clinical trials to go digital?), enligt ett pressmeddelande från organisationen Business Sweden i dag.

”Ett av mina deluppdrag handlar om att främja förutsättningar för att innovationer omsätts i nya produkter och tjänster som leder till nya exportintäkter. Jag är övertygad om att Sverige har en hel del att erbjuda när det gäller nya lösningar och samarbeten, inte minst inom digitalisering i vården men även när det gäller utveckling av nya läkemedel och jag ser fram emot en givande diskussion”, säger Anders Lönnberg i en presskommentar. Han refererar till en nyligen publicerad studie i tidskriften Lancet och där svensk sjukvård rankas på fjärde plats bland 195 undersökta länder.

”Den höga rankingen stämmer väl överens med mitt eget intryck från andra internationella events som jag deltagit i. Jag har där funnit att det finns ett stort intresse för svensk life science och för vårt sjukvårdssystem”, säger Anders Lönnberg.

Under bioteknikkonferensen – som enligt Business Sweden är världens största i sitt slag – diskuteras befintliga och nära förestående teknologiska genombrott och hur dessa kan bidra till bättre kvalitet samt kostnads- och tidsbesparingar inom vården.

Andra ämnen som kommer att diskuteras:

* Hur kan digitalisering hjälpa patienterna att aktivt bidra till bättre behandlingsresultat?
* Hur behöver det regulatoriska ramverket för godkännande av nya läkemedel förändras, så att digitaliseringens alla fördelar kan utnyttjas?

Business Sweden har tagit fram en broschyr och en webbplats för att lyfta fram Sveriges komparativa fördelar inom life science. Informationsmaterialet finns här http://lifescience.business-sweden.com/?utm_campaign=Läkemedelsmarknaden_170615_Sverige%20behåller%20andraplatsen%20i%20global%20innovationsrankning&utm_medium=email&utm_source=Eloqua&elqTrackId=ebe65877f4346508066a307f7b4dd6e&elq=f2e151cd8ecd42d4acc70563d49e77e0&elqaid=8507&elqat=1&elqCampaignId=5999

Nyhetsinfo 17 juni 2017
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ADA Report. DEVOTE full text free article N Engl J Med

DEVOTE: Tresiba as Safe as Glargine With Less Severe Hypoglycemia

SAN DIEGO — For the treatment of type 2 diabetes, the ultra-long–acting, once-daily basal insulin degludec (Tresiba, Novo Nordisk) is as safe in cardiovascular terms as insulin glargine and is associated with much lower rates of severe hypoglycemia, new data confirm.

Full results from the Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) were reported by a number of investigators here at the American Diabetes Association (ADA) 2017 Scientific Sessions and were simultaneously published in the New England Journal of Medicine, with lead author Steven P Marso, MD, of the Research Medical Center, Kansas City, Missouri.

The top-line results of DEVOTE had already been reported by the company in November last year, and it recently applied to the Food and Drug Administration (FDA) to update the Tresiba label with these data.

"For me, this is a robust demonstration of the cardiovascular safety of degludec — and a dramatic and unimpeachable demonstration of the relatively lower rate of severe hypoglycemia" with degludec compared with glargine, senior investigator of DEVOTE, John B Buse, MD, PhD, of University of North Carolina School of Medicine, Chapel Hill, told Medscape Medical News.

"The former is of regulatory significance and the latter is of meaningful clinical significance," he added.

The number of patients who would need to be treated with degludec rather than glargine to avert one severe hypoglycemic event was 40, the DEVOTE paper indicates.

Hypoglycemia: What's the Significance?

"There's always been this theory, demonstrated over and over again, that severe hypoglycemia is a big risk for subsequent cardiovascular events," Dr Buse explained to Medscape Medical News. "Whether it's related to the fact that the people who have severe hypoglycemia are also people who have cardiovascular events — because they are frail and have lots of comorbidities — or whether there is a causal relationship is still uncertain."

Asked by Medscape Medical News why — if there is a relationship between hypoglycemia and CVD — would he not have expected the rate of CVD to be significantly lower with degludec than with glargine in DEVOTE, Dr Marso said: "The short answer is no. There may well be a causal relationship between hypoglycemia and CV mortality, but in my opinion, if true, it's a small part of what drives cardiovascular events in people with diabetes.

"As cardiologists, we tend to be focused on the [atherosclerotic] plaque, I think too much focused, and I think in the diabetes world they tend to be too much focused on the hypoglycemia, and I think it's going to be much more complicated than just one or the other."

Meanwhile, discussant of the trial at ADA, Elizabeth R Seaquist, MD, from the University of Minnesota, Minneapolis, said there remain some unanswered questions in DEVOTE.

For instance, "data on moderate hypoglycemia were not collected, so the impact on the most common type of hypoglycemia experienced by patients cannot be addressed," she observed. And data were not collated on events when blood glucose was 54 mg/dL (3mmol/L) or lower, "so impact on the development of impaired awareness of hypoglycemia" again could not be assessed, she noted.

And finally, because investigators in DEVOTE could modify the titration process based on clinical judgment, "it isn't clear if this modification process was applied equally in both arms." Any differential application of this process could have affected the hypoglycemia outcomes.

DEVOTE Details

The US FDA insisted that Novo Nordisk conduct the DEVOTE trial before it would approve insulin degludec, despite the fact that the product was already approved in the European Union. In the end, the US agency approved insulin degludec in November 2015 on the basis of interim results from DEVOTE.

In the trial, 7637 patients with type 2 diabetes were randomized to receive either insulin degludec (n = 3818) or insulin glargine U100 (n = 3819) once daily between dinner and bedtime in a double-blind, treat-to-target fashion.

Dr Buse explained that insulin glargine was chosen as the comparator insulin because of the ORIGIN trial, which indicated no increased risk of cardiovascular events with glargine, "so that's why we picked it as a comparator."

Of the patients in DEVOTE, 85.2% had established cardiovascular disease, chronic kidney disease, or both. Mean age was 65 years, the mean duration of diabetes was 16.4 years, and mean HbA1c was 8.4%

The primary composite outcome was the first occurrence of an adjudicated major cardiovascular event (death from CV causes, nonfatal myocardial infarction, or ▶

nonfatal stroke). Severe hypoglycemia, as defined by the ADA, was the prespecified secondary outcome.

The primary outcome occurred in 325 patients (8.5%) in the degludec group and in 356 (9.3%) in the glargine group (hazard ratio, 0.91; 95% CI, 0.78 — 1.06; P < .001 for noninferiority).

At 2 years, the mean HbA1c was 7.5% in each group, but the mean fasting plasma glucose level was significantly lower in the degludec group than in the glargine group (128 vs 136 mg/dL; P < .001).

Severe hypoglycemia occurred in 187 patients (4.9%) in the degludec group and in 252 (6.6%) in the glargine group, for an absolute difference of 1.7 percentage points (rate ratio, 0.60; P < .001 for superiority).

Rates of adverse events did not differ between the two groups.

Is Insulin the Right Treatment for Type 2 Diabetes?

It is almost impossible to assess how the cost of different insulins compare with each other, both within one country and from country to country.

In the United States, there has been an uproar about the cost of insulin, and Dr Buse said that, as a clinician, he's in the dark.

He also questions whether insulin is even "the ideal drug" for the treatment of type 2 diabetes. "It's probably not. It is an acceptable drug, its cardiovascular safety is well established, but it's not empagliflozin, it's not liraglutide."

N Engl J Med. Published online June 12, 2017. Article

http://www.nejm.org/doi/full/10.1056/NEJMoa1615692?query=featured_home#t=article

From www.medscape.com

Nyhetsinfo 17 juni 2017
www red DiabetologNytt

ADA Report. More about CANVAS - the article in N Engl J Med in full text free. Dagens Medicin Björn Eliasson

SAN DIEGO — The sodium–glucose cotransporter 2 (SGLT2) inhibitor canagliflozin (Invokana, Janssen Pharmaceuticals) reduces cardiovascular events by 14% and cuts the rate of renal decline by 40% but also doubles the risk for lower-limb amputation, new cardiovascular-outcomes trial data indicate.

Combined results from the Canagliflozin Cardiovascular Assessment Study (CANVAS) and the CANVAS renal-end-points trial (CANVAS-R) were presented here at the American Diabetes Association (ADA) 2017 Scientific Sessions today and were simultaneously published in the New England Journal of Medicine.

These data represent the second time cardiovascular benefit has been demonstrated in a US Food and Drug Administration–mandated cardiovascular outcomes trial for an SGLT2 inhibitor, with the first being the landmark Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), which demonstrated a major reduction in both all-cause and cardiovascular death among high-risk patients taking empagliflozin (Jardiance, Boehringer Ingelheim/Lilly) in September 2015.

Now, the CANVAS data suggest that cardiovascular and renal benefits are a class effect, lead investigator Bruce Neal, MB, ChB, PhD, professor of medicine, University of New South Wales Sydney, and senior director, the George Institute for Global Health, Sydney, Australia, told Medscape Medical News.

"Here's a second drug with clear protection. Things bounce around in terms of the individual outcomes, as you'd expect with relatively small numbers, but I think it will be viewed — and should be viewed — as a big piece of new evidence that basically says this is a great class of drugs for people with diabetes."

However, the CANVAS data also revealed a significant doubling in the risk for amputations, primarily of the toe or metatarsal (6.3 vs 3.4 cases per 1000 patient-years; hazard ratio, 1.97). That risk, already identified, led to a boxed warning for canagliflozin from the US Food and Drug Administration, and a warning on the labels of all SGLT2 inhibitors by the European Medicines Agency.

In addition, cardiovascular death was not significantly reduced in CANVAS, as it was in both EMPA-REG and the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial of the glucagonlike peptide-1 (GLP-1) agonist liraglutide (Victoza, Novo Nordisk)

"Prescribers and patients will need to balance the positive and negative events from the CANVAS trial in clinical decision-making. Certainly it is a more complicated calculus than with the results of the EMPA-REG trial," LEADER principal investigator John Buse, MD, of the University of North Carolina, Chapel Hill, told Medscape Medical News.

Cardiovascular Protection, but at a Cost?

The so-called "CANVAS program" combined data from two trials, CANVAS and CANVAS-R,

involving a total 10,142 patients with type 2 diabetes and high cardiovascular risk. The CANVAS patients were randomized 1:1:1 to canagliflozin 300 mg or 100 mg or placebo, and the CANVAS-R patients to 100 mg (with option to increase to 300 mg after week 13) or placebo. Mean follow-up was 188 weeks (median, 126.1 weeks).

Unlike EMPA-REG and LEADER, in which all subjects had established cardiovascular disease, in CANVAS two-thirds did and the rest did not.

CANVAS Program Primary and Secondary Outcomes
Outcome Canagliflozina(n=5795) Placeboa(n=4347) Hazard ratio 95% CI P
Primary outcome (CV death, nonfatal MI, or nonfatal stroke 26.9 31.5 0.86 0.75–0.97 0.02 for superiorityb
All-cause death 17.3 19.5 0.87 0.74–1.01
CV death 11.6 12.8 0.87 0.72–1.06
Hospitalization for heart failure 5.5 8.7 0.67 0.52–0.87
Albuminuria progression 89.4 128.7 0.73 0.67–0.79
Renal composite (40% eGFR reduction, renal replacement therapy, or death) 5.5 9.0 0.60 0.47–0.77
Amputationsc 6.3 3.4 1.97 1.41–2.75 Not tested

Number of participants per 1000 patient-yearP< .001 for noninferiority Primarily at the toe or metatarsal level

Dr Neal presented an analysis indicating that use of canagliflozin reduces the risk of major cardiovascular adverse events (MACE) per 1000 patients over 5 years by 23, risk of hospitalization for heart failure by 17 per 1000, and renal events by 16.

At the same time, amputations will occur in 15 more patients per 1000 over 5 years.

"It's fair to say we're clearly preventing more major cardiovascular events than we're going to be causing amputations. I think the balance of benefits vs risks is going to fall pretty heavily in favor of SGLT2 inhibition, even with an amputation risk," Dr Neal told Medscape Medical News.

Whether the amputation risk is a class effect is still an open question. Amputation data weren't reported in EMPA-REG, although a post hoc analysis has not detected a signal with empagliflozin compared with placebo, according to the study's lead investigator Silvio Inzucchi, MD, of Yale University, New Haven, Connecticut.

But Dr Neal pointed out that it's a relatively infrequent complication and "certainly something under intense scrutiny." He also said that "there might be challenges collecting the data retrospectively" from EMPA-REG.

In February 2017, the European Medicines Association said in a statement: "An increased [amputation] risk has not been seen in studies with other medicines in the same class, dapagliflozin and empagliflozin. However, data available to date are limited and the risk may also apply to these other medicines. Further data are expected from ongoing studies with canagliflozin, dapagliflozin, and empagliflozin."

New Engl J Med. Published online June 12, 2017. Article in full text free

http://www.nejm.org/doi/full/10.1056/NEJMoa1611925?query=featured_home

LÄS DAGENS MEDICIN
DIABETES VETENSKAP
HJÄRTA-KÄRL

Kardiovaskulärt skydd av ytterligare ett diabetesläkemedel

Läkemedlet kanagliflozin minskar risken för kardiovaskulära komplikationer bland patienter med typ 2-diabetes, enligt en ny studie som presenterades på diabetesmötet ADA som pågår i USA.

Maria Gustavsson www.dagensmedicin.se

Björn Eliasson är adjungerad professor vid Sahlgrenska universitetssjukhuset i Göteborg.

– Fynden är i linje med förväntningarna. Det här blir ytterligare en bekräftelse på att det finns en kardiovaskulär nytta med läkemedelsgruppen. Kanagliflozin ser även ut att ha gynnsamma effekter på njurfunktionen, säger Björn Eliasson som är adjungerad professor vid Sahlgrenska universitetssjukhuset i Göteborg.

Resultaten är även publicerade i tidskriften New England Journal of Medicine. Fynden kommer från två studier som sammantaget inkluderar fler än 10 000 personer med typ 2-diabetes samt hög risk för kardiovaskulär sjukdom. De lottades till att antingen få placebo eller kanagliflozin (Invokana), som är en så kallad SGLT2-hämmare.

Deltagarna följdes i snitt i 188 veckor och det primära utfallsmåttet var en kombination av död i kardiovaskulär sjukdom, icke-dödlig stroke eller icke-dödlig hjärtinfarkt.

Någon av dessa händelser inträffade för 31,5 personer per 1 000 personer och år i placebogruppen. Motsvarande siffra var lägre bland deltagare på kanagliflozin, 26,9 per 1 000 patienter och år. Forskarna skriver även att läkemedlet kan ha en skyddande effekt på njurfunktionen och exempelvis minska risken att proteiner läcker ut i urinen.

Till skillnad från tidigare studier av läkemedlet fann dock forskarna att patienter på kanagliflozin drabbades av amputationer i högre utsträckning – främst av fötter och tår.

– Frågan är om det är en ef- ▶

fekt av läkemedlet i sig eller av läkemedelsklassen. Det är något som kommer att diskuteras vidare framöver. För studien Empa-reg antydde inte problem med amputationer, säger Björn Eliasson.

Empa-reg är en studie som berör en annan SGLT2-hämmare som heter Jardiance (empagliflozin). Även här sågs en minskad risk att dö i hjärt-kärlsjukdom bland patienter med typ 2-diabetes.

SGLT2-hämmare är en läkemedelsklass som sänker glukoshalten i blodet genom att öka utsöndringen av glukos i urinen. Deltagarna i den aktuella studien var i snitt 63 år gamla och majoriteten var män. Studien är sponsrad av läkemedelsföretaget Janssen.

Tidigare har det inte gått att visa om blodsockersänkande läkemedel mot typ 2-diabetes även sänker risken för så kallade makrovaskulära komplikationer av diabetessjukdomen. Men efter att resultaten för ovan nämnda studie Empa-reg publicerades 2015 har en motsvarande effekt också visats för två läkemedel i klassen GLP1-analoger.

År 2016 utsåg Dagens Medicin kardiovaskulär effekt av diabetesläkemedel som det årets främsta forskningsnyhet.

Just nu pågår ytterligare en studie med ett annat läkemedel av klassen SGLT2-hämmare som kallas Forxiga (dapagliflozin) på patienter med typ 2-diabetes. Det resultatet förväntas komma om något år.

Bruce Neal med flera. Canagliflozin and cardiovascular and renal events in type 2 diabetes. The New England Journal of Medicine, publicerad online den 12 juni. DOI: 10.1056/NEJMoa1611925

Nyhetsinfo 13 juni 2017
www red DiabetologNytt

ADA Report. A New Era for SGLT2-I in the Treatment of T2DM. CANVAS. 14% mindre risk för CVD, hjärtsvikt 33%, njurskada 40%. Kommentar Peter Nilsson.

Studien CANagliflozin cardioVascular Assessment Study (CANVAS) har idag just presenterats på American Diabetes Association (ADA) mötet.

Det är en stor randomiserad studie som testade två doser av canagliflozin, SGLT2-hämmare, mot placebo hos patienter med typ 2 diabetes, både med och utan tidigare kardiovaskulär sjukdom.

Resultaten anger

- att den samlade risken för kardiovaskulära händelser minskade med 14%,
- risken för hjärtsvikt minskade med 33%
- risken för att få allvarlig njurskada pga diabetes minskade med 40%

”Detta är i linje med resultaten från den tidigare publicerade EMPA-REG OUTCOME studien (N Engl J Med 2015) och antyder klinisk nytta med SGLT2-hämning, således mera av en klasseffekt, säger prof Peter Nilsson.

Detta öppnar dörren för vidgad behandling.

Dock måste man även beakta att risken för amputation fördubblades i CANVAS, och detta kan betyda att försiktighet bör iakttas för förskrivning till patienter med svår perifer artärsjukdom.

Svenska riktlinjer från Socialstyrelsen 170529 har redan idag en positiv skrivning om nyttan med empaglflozin Jardiance® med prio vid T2DM med etablerad hjärt- och kärlsjukdom - och detta kommer sannolikt framöver även att gälla för närbesläktade canagliflozin.

Dock väntar vi ännu på studiedata av liknande slag för ett tredje läkemedel inom gruppen, dapagliflozin”, säger Peter M Nilsson, professor och överläkare vid SUS i Malmö.

I USA förskrivs canafliflozin Invokana® mest. I Sverige förskrivs mest Jardiance® empa och på plats 2 Forxiga® dapa. Fynden publiceras idag i N Engl J Med.

Comment

Professor Neal: We do not know why there was an increased risk of amputation, but further work is needed in this area. But now we urge caution in prescribing this drug to people at increased risk of suffering amputations

The study of more than 10 000 patients with T2DM in 30 countries also found that the drug offered protection not just for people already suffering cardiovascular disease, but for all with T2DM

Nyhetsinfo 12 juni 2017
www red DiabetologNytt

ADA Report. DEVOTE trial. Tresiba versus Lantus. No increased risk of major cardiovascular events. Reduction in severe hypoglycemia.

Tresiba® demonstrated no increased risk of major cardiovascular events and significant reduction in rates of severe hypoglycaemia compared to insulin glargine U100 in the DEVOTE trial

San Diego, US, 12 June 2017 - Novo Nordisk today announced the primary results from DEVOTE - the first randomised, double-blind, treat-to-target, event-driven trial comparing two basal insulins, Tresiba® (insulin degludec injection 100 U/mL) and insulin glargine U100, in adults with type 2 diabetes at high risk of cardiovascular (CV) disease. The trial demonstrated that Tresiba® met the primary endpoint of non-inferiority compared with insulin glargine U100 for major adverse CV events (MACE) with a hazard ratio (HR) of 0.91 (95% confidence interval [CI]: 0.78; 1.06, p=0.209). Additionally, the findings for each component of MACE were consistent with the primary endpoint, including first occurrence of CV death (HR=0.96, 95% CI: 0.76; 1.21, p=0.714), non-fatal myocardial infarction (HR=0.85, 95% CI: 0.68; 1.06, p=0.150) or non-fatal stroke (HR=0.90, 95% CI: 0.65; 1.23, p=0.502).1

Results from the trial, involving 7,637 people with type 2 diabetes followed for approximately two years, were presented at the American Diabetes Association's 77th Scientific Sessions (ADA 2017) and also published simultaneously in the New England Journal of Medicine.1

Results from the secondary endpoints of the trial showed a significant reduction in the rate of severe (40%) and nocturnal severe (53%) hypoglycaemia with Tresiba® vs. insulin glargine U100 (both p<0.001).* Additionally, post hoc analyses showed: similar levels of glycaemic control with an end of trial HbA1c estimated treatment difference of 0.01% (p=0.779) between the two treatment groups and significantly lower fasting plasma glucose levels with Tresiba® after 2 years vs. insulin glargine U100 (estimated treatment difference -7.2 mg/dL, p<0.001).1

"In the DEVOTE trial degludec demonstrated no increase in the risk of major cardiovascular events and significant reductions in the rates of severe and nocturnal severe hypoglycaemia compared to insulin glargine U100," said Dr Bernard Zinman of the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada and member of the DEVOTE Steering Committee. "Risk of cardiovascular disease and hypoglycaemia are important concerns for those with type 2 diabetes and the results from DEVOTE add to the mounting evidence that will play an important role in treatment decisions."

The safety profile of Tresiba® in DEVOTE was generally consistent with previous Tresiba® clinical trials.1 In DEVOTE, systematic collection of adverse events was limited to serious adverse events, adverse events leading to permanent discontinuation of investigational product (5.2% of patients in the Tresiba® arm and 5.8% of patients in the insulin glargine U100 arm), medication errors leading to serious adverse events and adverse events related to technical complaints.

*Severe hypoglycaemia was defined as an episode requiring assistance of another person, and nocturnal severe defined as between the hours of 00:01-05:59, inclusive.1

About DEVOTE

DEVOTE is a long-term, multi-national, randomised, double-blind and event-driven trial conducted to confirm the CV safety of Tresiba® (insulin degludec) compared to insulin glargine U100. In the trial, 7,637 people (Tresiba®: n=3,818, insulin glargine U100: n=3,819) with type 2 diabetes at high risk of CV disease were randomised to treatment with either Tresiba® or insulin glargine U100 in vial in addition to standard of care.1 The primary endpoint in DEVOTE was time from randomisation to the first occurrence of a three-component composite CV outcome comprising CV death, non-fatal myocardial infarction or non-fatal stroke. Secondary endpoints included severe hypoglycaemia, nocturnal severe hypoglycaemia, HbA1c and fasting plasma glucose.1

Nyhetsinfo 12 juni 2017
www red DiabetologNytt

ADA Report. T1DM Prevention; Trial.Net Org with Oral Insulin and DiAPREV-iIT-trial with Alum-GAD. No positive effects in prevention

Delaying T1DM is important. It means a longer period of time without the day to day extra job or living with T1DM.

This is the largest trial ever performed using oral insulin. Oral insulin did not delay clinical diagnosis of T1DM in the main strata of 389 peiple, or when all the strata were combined.

However, in a secondary analysis of the subgroup of 55 people there was a 31 month delay in median time to clinical T1DM. This further supports that not everyone develops T1DM in the same way and is a step towards targeted therapies.

T1DM Diabetes TrialNet has 3 other ongoing studies to determine whether we can delay or stop disease progression. "Since relatiuves hav a 15x increased risk of disiease we urge relatiuves of those with T1DM to stop T1DM trialNet.org

DIAPREV-it trial with Alunm-GAD Helena Elding Larsson, Lund university, Sweden

In this first study of antigen-specific therapy with Alumn-GAD in young children with mulltiple islet autoantibodies, we found it is safe to use,

The results shows that Alun-GAD given alone coukld not in the current doseing, delay or prevent T1DM in their cohort. Other dosing or combination with immunomodulatiory agents or other antigens may be tested. Immunological samples will be analysed to further investigate the mechanisms.

Nyhetsinfo 12 juni 2017
www red DiabetologNytt

ADA Report. Many CV-Outcomes Trials in T2DM Must Drive Guideline Change Rapid

SAN DIEGO — The recent results of large outcomes trials showing cardiovascular benefit with type 2 diabetes drugs must be properly incorporated into treatment guidelines, such as those issued by the American Diabetes Association and other national guidelines all over the world, implores one expert.

"This is a very big deal. I think it's time now to apply the evidence and incorporate it into the guidelines for cardiologists, and endocrinologists and professional societies have to take the lead," cardiologist Steve Nissen, MD, of the Cleveland Clinic, Ohio, told a packed auditorium here at the American Diabetes Association (ADA) 2017 Scientific Sessions yesterday.

And, he emphasized, for this to happen, "we need close collaboration between cardiologists and diabeto-endocrinologists. We take care of the same patients, so coming together to determine how best to treat these patients is incredibly important."

The past few years have illustrated "a triumph of evidence-based medicine," he stressed, "and now it's very important for changes in the guidelines to reflect contemporary knowledge, but we will still have a way to go with that. We've got to overcome clinical inertia," he stressed.

Referring specifically to landmark results with the sodium-glucose cotransporter-2 (SGLT-2) empagliflozin (Jardiance, Boehringer Ingelheim) in EMPA-REG OUTCOME and the glucagonlike peptide-1 (GLP-1) agonist liraglutide (Victoza, Novo Nordisk) in LEADER — which both showed impressive reductions in cardiovascular end points in patients with type 2 diabetes at high risk of cardiovascular events, he said that the most important outcome seen in both of these trials was the reduction in cardiovascular death.

"The one thing we want to do for our patients, whether they have heart disease or diabetes [or both], is to keep them alive," Dr Nissen asserted.

But if the results of these trials are not rapidly translated into changes in guidelines, there is a danger that the same thing that happened with statins will happen in diabetes, he said, noting, "It took years for the adoption of the pivotal trial results with statins, it was just too slow."

And he stressed that, since statins, "it's been hard to come up with therapies that reduce cardiovascular death. And now we have the most robust results with diabetes drugs on the end point that is toughest to achieve — death."

CV-Outcomes Trials Show Not All Drugs in Class Are the Same
Dr Nissen explained how, prior to the current crop of CV-outcomes trials, there had historically been little progress in preventing diabetes patients from dying from cardiovascular disease — the biggest killer in this condition.

While nondiabetic patients saw tumbling death rates from CVD in past decades, the rate had stagnated among diabetes patients and even increased in women with diabetes, he explained.

"It's taken some shock waves to wake the medical community from a 50-year slump — the realization that merely lowering blood glucose is not a guarantee of improving health outcomes [in diabetes]," he added.

He then went on to outline the history behind the cardiovascular-outcomes trials for diabetes drugs, which were mandated by the FDA in 2008 as a result of the rosiglitazone debacle — in which Dr Nissen played a key role.

"There was a lot of pushback, a lot of whining, when we first suggested these CV-outcomes trials," he noted. "But we've gotten some really big bonuses from doing them. These drugs are not all the same. and before we label something as a 'class effect,' we have to look carefully. We only find out what they actually do when we study them."

And while he acknowledged that the aim of the cardiovascular-outcomes trials was initially to demonstrate lack of CV harm with diabetes drugs, there was some anticipation of positive effects, he said.

For example, with the dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs, when these were introduced, "people said it's going to be a revolution. Every single [prior analysis] suggested DPP-4 inhibitors would lower CV outcomes," he told the audience. The effect was on glucose and neutral effects on CVD.

But this didn't turn out to be the case.

In fact, the results of the first CV-outcomes trials with the DPP-4 inhibitors saxagliptin (Onglyza, AstraZeneca) and alogliptin (Nesina, Takeda) — SAVOR-TIMI 53 and EXAMINE — "actually showed a significantly increased risk for hospitalization for heart failure with the respective drugs, a completely unexpected finding," he noted.

"We would never have found out this problem had we not done the trials," he asserted.

And a third outcomes trial with the DPP-4 inhibitor sitagliptin (Januvia, Merck), TECOS, while not showing any increase in heart-failure hospitalization, did not improve CV outcomes — it was neutral — and so "that was a third disappointment for DPP-4 inhibitors."

But patience paid off in the end, said Dr Nissen.

"We always had an ambitious agenda and we [eventually] got some really big bonuses. EMPA-REG is, in my opinion, a breakthrough study."

However, as people wait with bated breath here for the results of the second CV-outcomes trial with a SGLT2 inhibitor, CANVAS with canagliflozin, he reiterated that it's always important to wait for the results from each study.

For example, whereby LEADER with liraglutide showed cardiovascular benefit (as did SUSTAIN-6 with the investigational GLP-1 agonist semaglutide), another trial, ELIXA, with the GLP-1 agonist lixisenatide, was neutral.

"When you do large outcomes trials, you get surprises. The most important message I can give you [for each agent] is wait for the data."

American Diabetes Association 2017 Scientific Sessions. June 11, 2017; San Diego, California. Presentation 1-AC-SY13

From www.medscape.com

Nyhetsinfo 12 juni 2017
www red DiabetologNytt

ADA Report. Sexual Dysfunction in Diabetes: Underrecognized and Neglected

SAN DIEGO — Treatment options for sexual dysfunction in diabetic patients are surprisingly limited, and new therapeutic targets are needed for both sexes, according to new data presented here at the American Diabetes Association (ADA) 2017 Scientific Sessions.

To enable this, more information on who with diabetes is at highest risk of developing sexual dysfunction and the specific mechanisms underlying the dysfunction is needed, said Hunter Wessells, MD, of the department of urology, University of Washington School of Medicine, Seattle, during a symposium on urologic complications and sexual dysfunction in diabetes.

Clinicians should start asking about sexual function when diabetes patients are still in their 40s and intervene as soon as the first symptoms occur, said Dr Wessells.

This is because research indicates that sexual dysfunction can occur in those with diabetes years earlier than it affects those in the general population, he stressed.

Asked for comment, Aruna V Sarma, PhD, research assistant professor of urology, University of Michigan School of Public Health, Ann Arbor, said sexual dysfunction may not be as lethal as neuropathy or nephropathy, but "these are conditions that matter

to the participants, they are bothersome, and they impact quality of life.

”We have an opportunity to motivate individuals to improve their diabetes care, because an 18-year-old or 30-year-old type 1 diabetic may be more motivated to try to prevent erectile dysfunction that may occur in their 40s, rather than perhaps a more abstract notion of what may occur with neuropathy later in life. So there may be an opportunity here to try to improve sequelae that may occur in the future.”

Accelerated Aging: Sexual Dysfunction Manifests Early in Diabetes

For example, erectile dysfunction will affect 50% of men with diabetes by the time they are 50 years of age, with a mean age of onset of 45 years, Dr Wessells said.

”Is that abnormal? Absolutely.” Among men in the general population, the rate of erectile dysfunction does not reach 50% until they are in their 70s, so ”this represents a 20-year acceleration of the aging process” for diabetic men, he explained.

For women, data from the Diabetes Control and Complications Trial(DCCT) in type 1 diabetes suggest that two of the biggest risk factors for sexual dysfunction are being married and a history of depression or treatment with antidepressants.

”We think of diabetes as impacting blood vessels and nerves, but there are all these other aspects that need exploration so we can understand how we can better intervene to help these patients,” Dr Wessells explained.

Adding to the urgency of the problem is that as they live longer, men and women alike are seeking to prolong their sexual function as much as possible.

There is evidence that, for people with diabetes, the impact of sexual dysfunction on quality of life equals or exceeds that of neuropathy, nephropathy, or retinopathy.

A Multifactorial Problem

Treatments have been difficult to develop in part because of the multifactorial nature of sexual function, Dr Wessells said.

For men, most of the emphasis has been placed on erectile dysfunction, but problems may also take the form of diminished libido or ejaculatory or orgasmic dysfunction. Women similarly may experience low desire, impaired arousal, or difficulty with orgasm.

”We know almost nothing about how diabetes affects central nervous system control of sexual behavior or about its impact on other components of sexual tissue such as endothelial cells, smooth-muscle cells, and the autonomic nerves involved in arousal in both sexes,” he pointed out.

First-line treatment options for men include phosphodiesterase 5 inhibitors such as sildenafil (Viagra, Pfizer) and tadalafil (Cialis, Lilly).

These are effective ”but they are still not good enough, because these patients have more severe erectile dysfunction, so will they improve enough to be normal? That is the question.”

Second-line therapies include vacuum erection devices, injection of vasoactive substances into the penis, and penile implants.

For premenopausal women, flibanserin (Addyi, Sprout Pharmaceuticals), approved in the US in 2015, may restore some sexual desire, but its exact mechanism of action is unknown, and it is associated with side effects including hypotension and syncope, Dr Wessells warned.

Future Directions

An effective approach to the sexual complications of diabetes should start with risk stratification, because ”better knowledge of the risks may lead to earlier intervention,” Dr Wessells explained.

There is some evidence that better glycemic control in men is associated with a lower risk of developing erectile dysfunction, for example.

But the picture is more complicated than that, he added. Data from the DCCT for example, have shown that, while some men develop permanent erectile dysfunction, others may have it for a while, then go into remission, and continue this back-and-forth pattern until age catches up with them.

In addition, some men may smoke or have terrible glycemic control yet never develop erectile dysfunction, while a few who follow doctor’s orders to the letter nevertheless become impotent while still in their 40s.

”We have to learn what is protective in some men and see whether we can use that to help others.”

There is also evidence that intensive lifestyle interventions may improve sexual function in people with type 2 diabetes, Dr Wessells said.

Weight loss has been associated with an improvement of erectile dysfunction in men and a slight decrease in sexual dysfunction in women.

Neither Dr Wessells nor Dr Sarma disclosed any relevant financial relationships.

American Diabetes Association 2017 Scientific Sessions. June 9, 2017; San Diego, California. Presentation 1-AC-SY06

Nyhetsinfo 12 juni 2017
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ADA Report. Alirocumab PCSK9-I Underwhelming in ODYSSEY Trials in T2 Diabetes

SAN DIEGO — First data on use of a proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor specifically in patients with diabetes failed to excite here at the American Diabetes Association (ADA) 2017 Scientific Sessions .

Alirocumab (Praluent, Sanofi/Regeneron Pharmaceuticals) met its primary efficacy end points of reducing LDL cholesterol in the ODYSSEY DM-Insulin study and reducing non-HDL cholesterol in the ODYSSEY DM-Dyslipidemia study, both out to 24 weeks. The therapy was also safe, as assessed at 32 weeks.

But "I think the data to some extent are underwhelming," session chair Robert H Eckel, MD, University of Colorado, Anschutz Medical Campus, Aurora, told Medscape Medical News. "The results that were presented were kind of what was expected and the [short-term] safety issue was fulfilled."

Although long-term efficacy and safety is unclear, "it's presumed that efficacy would continue," he noted. "I think an outcome trial now in patients with diabetes, meeting the criteria of entrance here, would be important."

A cardiologist who blogs for theheart.org on Medscape, John Mandrola, MD, of Baptist Medical Associates, Louisville, Kentucky, agrees. The ODYSSEY results "simply show something we already know: that PCSK9 inhibitors improve lipid profiles."

"What would be better is to show a reduction of hard outcomes. But it took many thousands of patients in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial to show a small decrease in nonfatal events," Dr Mandrola pointed out.

FOURIER was a large outcomes trial conducted with a different PCSK9 inhibitor, evolocumab (Repatha, Amgen) in more than 27,000 participants with atherosclerotic disease already receiving statins, which was reported at the ACC meeting to great fanfare earlier this year.

But the absolute risk reduction was modest, at 1.5%, and the authors estimated that 74 patients would need to take evolocumab to prevent a cardiovascular event. Furthermore, evolocumab did not reduce cardiovascular death or death from any cause.

And most important, the cost of this class of drugs is currently approaching $15,000 a year and "we can't afford PCSK9 inhibitors at their current price," said Dr Mandrola at the time the FOURIER results were reported.

ODYSSEY DM-Insulin: Alirocumab Did Not Affect HbA1c

Results from 441 patients with type 2 diabetes who were part of the ODYSSEY DM-Insulin trial were presented by Lawrence Leiter MD, from St Michael's Hospital, Toronto, Ontario. The trial also included 76 participants with type 1 diabetes, but data for these patients were not presented.

At baseline, all the type 2 diabetes patients were on insulin and had LDL cholesterol ≥70 mg/dL on maximum tolerated statin therapy (some were unable to tolerate statins at all), and they also had established cardiovascular (CV) disease or at least one additional CV risk factor.

They were randomized 2:1 to 24 weeks of alirocumab 75 mg subcutaneously every 2 weeks or placebo. Alirocumab-treated patients who still had LDL cholesterol ≥70 mg/dL at week 8 were titrated up to double the dose at week 12. Most patients (80%) continued on their starting alirocumab dose.

At 24 weeks, compared with patients in the placebo group, those who received alirocumab had a greater percentage decrease in LDL cholesterol — the primary efficacy outcome — by 48.2%, vs a 0.8% reduction, for a mean difference between the two treatment arms of 49% (P < .0001).

Patients who received alirocumab also had an improved overall lipid profile, including significantly reduced non-HDL cholesterol, apolipoprotein B (apoB), and triglycerides.

Treatment emergent adverse events were similar in both groups and included nasopharyngitis, myalgia, arthralgia, and cough. There was no new safety signal with the concomitant use of alirocumab and insulin.

And "Importantly, alirocumab did not affect HbA1c,"Dr Leiter said.

ODYSSEY DM-Dyslipidemia

Meanwhile Robert Henry, MD, from the University of California, San Diego, presented results from the ODYSSEY DM-Dyslipidemia study in patients with type 2 diabetes and mixed dyslipidemia.

That trial randomized 413 patients with type 2 diabetes and mixed dyslipidemia at high cardiovascular risk who did not have not adequately controlled lipids with maximally tolerated statins.

Patients were randomized in a 2:1 ratio to receive alirocumab or usual care (which included statin, ezetimibe, fenofibrate, or other lipid-lowering therapy).

The primary end point was percentage change in non-HDL cholesterol [total cholesterol minus HDL cholesterol] from baseline to week 24.

At 24 weeks, non-HDL cholesterol was lowered more among patients in the alirocumab group than those in the usual-care group (37.3% lower vs 4.7% lower, for a mean difference of 32.5%; P < .0001).

Similarly, LDL cholesterol was lowered more in the alirocumab group (43.3% vs 0.3%, P < .0001).

The most frequent treatment emergent adverse events were urinary-tract infection, diarrhea, and nasopharyngitis.

As in the other trial, fasting plasma glucose and HbA1c levels remained stable in both treatment groups.

"These studies demonstrate no new safety signal" and "superiority in reducing non-HDL cholesterol vs usual care, as well as an improvement in levels of other lipids vs usual care," Dr Henry said.

Third-Party Payer Makes Final Decision

Expanding upon his thoughts, Dr Eckel said whether this class of PCSK9 inhibitor drugs — alirocumab or its "kissing cousin" evolocumab — are going to be effective in reducing cardiovascular risk over time remains to be seen.

And "the idea of additional modification of lipoprotein in diabetes is an unanswered question," he added.

Moreover, "I'm always concerned when you're modifying multiple lipoproteins at the same time....Is it really the additional LDL lowering, or is it in fact these other particles that are remnants and/or VLDL-cholesterol-carrying particles that are contributing to the benefit?"

PCSK9 inhibitors are currently approved for patients who have familial hypercholesterolemia (LDL cholesterol consistently above 190 mg/dL) or for those who have atherosclerotic cardiovascular disease (such as a previous heart attack or stroke) and LDL cholesterol that is insufficiently lowered by current therapy, he noted. The patient could be on a maximum statin dose or no statin at all if they are intolerant.

"But the final decision is made by the third-party payer, because these drugs cost [around] $14,000 to $15,000 dollars a year in US or in Europe 6000 US dollar per year," he reiterated.

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ADA Report. 2017 Diabetic Nurses are Diabetologists

Outstanding Educator in Diabetes Award recipient trumpets value of team-based care

The Diabetes Control and Complications Trial (DCCT) did more than confirm that intensive glucose control can reduce the complications and mortality associated with diabetes. It also established the role of a diabetes team in patient care.

"We didn't just learn that it takes a team to manage diabetes, we learned that the patient is the most important member of the team," said Davida F. Kruger, MSN, APRN-BC, BC-ADM, a nurse practitioner at the Henry Ford Health System. "Much of our current expertise in diabetes care, as well as our experts, came out of the DCCT."

Kruger is one of those experts. She received this year's ADA Outstanding Educator in Diabetes Award and presented her award lecture Saturday morning at the Scientific Sessions.

"By the time I had graduated from nursing school, my grandmother and her children had all been diagnosed with diabetes," she recalled. "It was no surprise that I wanted to work on diabetes."

Kruger's first nursing job was with the Detroit Visiting Nurses Association. Working in a hospital was not an option, she said.

"Even as late as 1976, nurses were expected to stand when a doctor entered the room. That wasn't going to happen," she joked.

The Detroit Visiting Nurses Association had a different outlook on patient care. Nurses didn't work alone with patients, they worked in teams with dieticians, social workers, therapists, and other specialists as needed.

Nurses were expected to coordinate the other nonphysician specialists and advocate for the patient. It was an experience that shaped Kruger's involvement in the DCCT and diabetes care.

"My mother did not receive any type of education or medical nutrition therapy for her T1DM" she explained. "The technology and knowledge of the time might not have extended her life, but it could have made a significant difference in her quality of life."

Kruger was recruited to the DCCT as one of 12 clinical coordinators. By the end of the trial, she was the National Chair of the Trial Coordinators Committee.

"That wasn't the most important change during the trials," she said. "When the trial began, the principal investigators [PIs] sat around a table and the clinical coordinators sat at the back of the room. The PIs spent so much time turning around asking us questions that we found ourselves at the table with them. The DCCT didn't just establish the clinical effects of intensive glucose control, it established the clinical utility of the team approach to diabetes, and the positive impact of diabetes education."

Diabetes education can have even greater impact when delivered by a nurse practitioner [NP], she added. NPs and physicians produce equivalent diagnostic results in diabetes, but nurse practitioners are far more likely to provide prevention counseling, health promotion, and more personalized therapies, Kruger said.

"There's a significant and growing gap between the need for diabetes care and the supply of adult and pediatric endocrinologists," she said.

"Nurse practitioners have now the knowledge and the expertise to fill that gap. Nurse practitioners are diabetologists."

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ADA Report. EMPA reduce nephropathy by 39% in T2DM

NEW ORLEANS — New data from the EMPA-REG OUTCOME trial with the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin (Jardiance, Boehringer Ingelheim) show that the drug significantly reduced the incidence of worsening nephropathy by 39% in the population of type 2 diabetes patients studied (ie, those who were at high cardiovascular risk).

The results were received to spontaneous applause here today at the American Diabetes Association (ADA) 2016 Scientific Sessions when presented by nephrologist Christoph Wanner, MD, of the Würzberg University Clinic, Germany; they were also simultaneously published in New England Journal of Medicine with Dr Wanner as lead author.

The assessment of renal outcomes in EMPA-REG was a prespecified outcome of the trial, Dr Wanner noted, and he added that the beneficial effects on the kidney observed in the trial "were there early and continued for the whole of the study." Moreover, these effects were observed with both doses of empagliflozin employed (10 mg and 25 mg once daily).

"Empagliflozin reduced clinically relevant renal events when added to standard of care in patients with type 2 diabetes and high cardiovascular risk," he announced, adding that this effect was primarily driven by a reduction in new-onset macroalbuminuria (hazard ratio [HR], 0.62 for those treated with empagliflozin compared with placebo; P < .001).

He pointed out that kidney disease is "a growing concern" in patients with type 2 diabetes, with 35% of patients eventually developing it, and noted that almost half (44%) of the renal-dialysis population at any current time is made up of those with diabetes, primarily type 2.

"In the placebo group you see the natural progression of kidney disease [as would be expected in type 2 diabetes] whereas the [estimated glomerular filtration rate] eGFR in the empagliflozin group remained stable," he observed.

Important Addition to Original Findings, but More Work Needed

Dr Wanner noted, however, that the EMPA-REG trial lasted only 3 years, "so we are certainly looking to the future for more on this."

And both he and discussant of the findings at ADA, endocrinologist and epidemiologist, William Herman, MD, MPH, of the University of Michigan, Ann Arbor, stressed that the results are applicable only "to the population studied in the EMPA-REG trial" (ie, older patients with type 2 diabetes at high cardiovascular risk).

Currently, about a third of the population of type 2 diabetes fall into that category, Dr Herman said.

Nevertheless, Dr Wanner observed in his presentation: "There have been no new diabetic kidney-disease–specific treatments in the past 15 years, until today."

And he hinted that the agent may well be used in those who don't yet have overt cardiovascular disease (CVD). "Nephrologists are waiting for this drug for patients with albuminuria," he told Medscape Medical News.

They and endocrinologists "maybe will not wait until the pa- ▶

tient has survived a myocardial infarction — there are some patients without cardiovascular disease but already with nephropathy, so I think we are all going to use this drug in the nephropathy patients with albuminuria."

But Dr Herman pointed out in his talk that "the absolute differences are relatively small" in EMPA-REG and the number needed to treat with empagliflozin to achieve the renal benefits was 200.

In addition, it's possible that the findings "had to do with medications not administered," he said. "So it may not be a benefit of empagliflozin but the fact that those in the empagliflozin group did not receive medications causing harm [as patients in the trial were also allowed certain other standard therapies for diabetes]."

Overall, as well as the demonstrated renal effects, empagliflozin is "moderately effective" at lowering HbA1c and results in a 2- to 3-kg reduction in body weight, with no issue with hypoglycemia, although it does increase the risk of genitourinary infections, Dr Herman surmised.

He concluded that empagliflozin is "a reasonable therapy, but we still don't know its exact role or exact mechanisms of action."

Chair of the session in which the EMPA-REG renal findings were presented at ADA, Matthew Riddle, MD, from Oregon Health & Science University, Portland, said the renal outcomes from EMPA-REF are "an important addition to the original findings," which nevertheless require further analysis.

Cost Is an Issue

Of key importance, said both Drs Herman and Riddle, is the fact that empagliflozin and other SGLT2 inhibitors — like the other newer agents for type 2 diabetes (dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagonlike peptide-1 [GLP-1] agonists, and insulin analogues) —are expensive, costing, in the US, in the region of $500 per month, as compared with a few dollars for metformin, the recommended first-line agent for type 2 diabetes and some other generically available drugs, such as sulfonylureas and pioglitazone.

Another trial with one of these newer agents, the GLP-1 agonist liraglutide (Victoza, Novo Nordisk), stole the headlines here yesterday with the results of the LEADER trial indicating that it significantly reduced the rates of major adverse cardiovascular events in a patient population similar to those in EMPA-REG, type 2 diabetes patients at elevated cardiovascular risk. This has prompted some experts to predict "a new era" in the management of type 2 diabetes.

Dr Riddle, however, believes this is a premature conclusion to draw: "I don't think the regulatory agencies' and the professional societies' recommendations are going to change immediately; we are going to have to digest these findings," he told Medscape Medical News.

Drilling down into renal outcomes

In the overall EMPA-REG trial, first reported last September to much acclaim, more than 6000 patients with type 2 diabetes at high risk of cardiovascular events were randomly assigned to one of two doses of empagliflozin or placebo on top of standard therapy. Empagliflozin reduced the risk of cardiovascular deaths by 38% relative to placebo.

In this new analysis of microvascular outcomes, incident or worsening nephropathy occurred in 525 of 4124 patients taking empagliflozin and 388 of 2061 in the placebo group (12.7% vs 18.8%; HR, 0.61; P < .001).

This renal end point consisted of a combination of progression to macroalbuminuria, a doubling of serum creatinine, the start of renal-replacement therapy, or renal death.

However, the benefit was primarily driven by the reduction in new-onset albuminuria, which occurred in 459 of 4091 patients taking empagliflozin compared with 330 of 2033 patients on placebo (11.2% vs 16.2%; HR, 0.62; P < .001).

Kidney dialysis was also reduced by more than half among those taking empagliflozin, although the absolute numbers affected were small (HR, 0.45; P = .0409).

In an editorial accompanying the renal findings in the published paper, Julie R Ingelfinger, MD, from Massachusetts General Hospital, Boston, Massachusetts, and Clifford J Rosen, MD, from the Center for Clinical and Translational Research, Maine Medical Center Research Institute, Scarborough, say: "This new report indicates that empagliflozin was associated with a slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care in [type 2 diabetes] patients at high cardiovascular risk."

And commenting on both EMPA-REG overall and LEADER, "We are left with differences that are encouraging yet are not a home run with regard to the management of diabetes," they point out.

Is empagliflozin a renal drug?

There was also some discussion at the ADA meeting about the mechanism of action of empagliflozin, both in lowering cardiovascular risk and now with regard to these renal benefits.

Most newer agent for diabetes will require dose adjustment in diabetic kidney disease because the majority are renally excreted; this includes DPP-4 inhibitors other than linagliptin, most GLP-1 ago-

nists with the exception of liraglutide, and the SGLT2 inhibitors.

The latter, including empagliflozin, have required dose adjustment in patients with diabetic kidney disease. The current licenses for most SGLT-2 inhibitors precludes their use in patients with renal failure (eGFR < 60 mL/min/1.73 m2 in some cases or < 45 mL/min/1.73 m2 in others).

Dr Wanner said that 25% of the patients in EMPA-REG had eGFR < 60 mL/min/1.73 m2, more than a third already had albuminuria, and almost a third already had prevalent kidney damage.

Yet, paradoxically, they seem to provide some renal protection. These newest findings from EMPA-REG bolster excitement about the potential for SGLT2 inhibitors to provide a renoprotective effect, despite being metabolized by the kidney.

”The effect of empagliflozin on renal outcomes was there early and continued for the whole of the study, with both doses showing an effect. Empagliflozin works at lower stages of kidney function too,” Dr Wanner stressed.

Silvio Inzucchi, MD, of Yale University, New Haven, Connecticut, the lead investigator of EMPA-REG, added also that, regarding the overall cardiovascular benefit of empagliflozin seen in the trial, ”there was no heterogeneity of effect based on eGFR; cardiovascular disease was reduced even in stage 3b renal-disease [eGFR 30–45 mL/min/1.73 m2] patients.”

Another SGLT2 inhibitor, canagliflozin (Invokana, Janssen) is being specifically tested in a diabetic kidney-disease population in the large multicenter randomized Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial.

This will enroll 3000 patients with stage 2 or 3 chronic kidney disease and macroalbuminuria already receiving standard of care. They will be randomized to canagliflozin 100 mg daily or placebo for 5 years, and results are not expected until 2019.

It is not known whether the latest caution from the Food and Drug Administration, strengthening the warning regarding acute kidney injury for canagliflozin and dapagliflozin, will affect this trial. This states that healthcare providers should consider factors that might predispose patients for example gastroenteritis to acute kidney injury prior to starting them on canagliflozin or dapagliflozin.

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ADA Report. New era of type 2 diabetes treatment after EMPA, LEADER etc

NEW ORLEANS — Details of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial of the glucose-lowering drug liraglutide (Victoza, Novo Nordisk), showing that it significantly reduced the rates of major adverse cardiovascular events in type 2 diabetes patients at elevated cardiovascular risk, were reported today.

The study is the second such mandated FDA cardiovascular safety study for a diabetes drug to show cardiovascular benefit, rather than just lack of harm, on top of standard therapy in type 2 diabetes patients at high cardiovascular risk after the EMPA-REG trial, and the first with an agent from the glucagonlike peptide 1 (GLP-1) receptor agonist class.

Results of a previous trial with another GLP-1 agonist, ELIXA, were neutral.

Experts here said that LEADER and EMPA-REG may now begin to change the landscape of diabetes therapy, giving doctors a somewhat clearer choice when deciding which drug to use second line after metformin in type 2 diabetes.

The results from the multicenter, international study were pre-

sented June 13, 2016 here at the American Diabetes Association (ADA) 2016 Scientific Sessions and were published online simultaneously in the New England Journal of Medicine, by Steven P Marso, MD, of University of Texas Southwestern Medical Center, Dallas, and colleagues.

LEADER began in 2010 and followed 9340 high-risk adults with type 2 diabetes for 3.5 to 5 years, who were randomly assigned to receive either a subcutaneous injection of liraglutide 1.8 mg once daily (or the maximum tolerated dose) or placebo along with standard treatment.

The primary end point was the first occurrence of the three-point major adverse cardiac event (MACE) components: cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke.

The degree of risk reduction for MACE was 13% (occurring in 608 of 4668 patients taking liraglutide) vs 14.9% (in 694 of 4672 taking placebo) (P = .01 for superiority), including a 22% lower rate of cardiovascular death (4.7 vs 6.0%, P = .007), Dr Marso reported in a press briefing held at the ADA meeting in advance of a special 2-hour symposium devoted to the findings.

The number of patients who would be needed to treat to prevent one event in 3 years was 66 for the MACE composite and 98 for death from any cause.

Liraglutide also reduced HbA1c, body weight, and hypoglycemia, and its safety profile was similar to what has been seen in previous trials, with gastrointestinal adverse events and increases in heart rate being the most common.

New Trials Inform Clinical Choice of Second Drug for Type 2 Diabetes

Coming on the heels of the cardiovascular benefit seen for the sodium glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin (Jardiance, Boehringer Ingelheim/Lilly) in the EMPA-REG trial, the LEADER findings have experts talking about a "new era" in the management of type 2 diabetes.

While most agree that metformin remains the first-line drug of choice, these new landmark study data are starting to better inform the clinical choice of second drug based on characteristics beyond their glucose-lowering capacity, speakers said during the press briefing.

"In type 2 diabetes, most of us agree that under most circumstances metformin is the drug of choice," briefing moderator Robert H Eckel, MD, of the University of Colorado, Denver, said, noting that additional potential cardiovascular and also anticancer benefits have been seen with that drug as well.

However, he said, "It's interesting, with LEADER the benefit for cardiovascular death is very similar to what statins do. I think with validation, it could potentially change practice. I'd like to see second and third trials for both [liraglutide and empagliflozin]. Keep in mind there are 25 or 30 trials for statins showing benefit," said Dr Eckel, who was not involved in LEADER or EMPA-REG.

Senior investigator of LEADER, John Buse, MD, of the University of North Carolina, Chapel Hill, added: "I think this changes the conversation with patients. Now, instead of just saying we're giving you this drug to manage your hyperglycemia in diabetes, [we can say] this drug also has the potential to modify your risk for cardiovascular disease and death.

"It was beyond our expectations that we would be able to demonstrate cardiovascular efficacy," he told the press briefing.

Asked to comment, Simon Heller, MD, professor of clinical diabetes, University of Sheffield, United Kingdom, told Medscape Medical News, "I think we are in a different era now. People die from hypoglycemia, whether by insulin or sulfonylureas. We shouldn't forget that.

"These drugs [liraglutide and empagliflozin] don't cause hypoglycemia and have other effects that may be beneficial. I agree absolutely we need to confirm with other studies, but I think we're definitely going to see a shift toward modern therapies."

Benefits Seen for Multiple Cardiovascular End Points

The LEADER trial included patients with type 2 diabetes who had HbA1c levels of 7.0% or higher. Entry criteria were either age 50 and above with established cardiovascular disease or chronic renal failure or age 60 and older with CVD risk factors.

Dr Robert H Eckel on podium; left to right, Drs Simon Heller, John Buse, Steven P Marso, and Bernard Zinman

Patients could be drug-naive or taking oral agents or basal insulin but not other GLP-1 agonists or DPP-4 inhibitors, pramlintide, or rapid-acting insulin. In both treatment and placebo groups, current standards of care were targeted for HbA1c, blood pressure, lipids, and antiplatelet therapy.

Subjects had a mean baseline age of 64 years, diabetes duration 13 years, and HbA1c 8.7%.

At 36 months' postrandomization, HbA1c levels were 0.40 percentage points lower in the liraglutide group, a significant difference (P < .001). Body weight also dropped significantly, by 2.3 kg (P < .001).

Overall, results for each of the components of the composite primary MACE outcome were in favor of liraglutide, with a 22% reduction in cardiovascular death (4.7% vs 6.0%, P = .007), which was significant, and a nonsignificant 12% reduction in nonfatal

MI (6.0% vs 6.8%, P = .11) and an 11% lower rate of nonfatal stroke (3.4% vs 3.8%, P = .30).

Also significant were a 15% reduction in all-cause death (8.2% vs 9.6%, P = .02) and an expanded composite CV outcome that included coronary revascularization, unstable angina, or hospitalization for heart failure (20.3% vs 22.7%, P = .005).

Hospitalization for heart failure itself was 13% less frequent in the liraglutide group (4.7% vs 5.3%, P = .14). Although not statistically significant in terms of benefit, the lack of any signal for concern with regard to heart failure is noteworthy, Dr Marso said. "There has been a lot of discussion in the incretin space about whether agents such as SGLT2 inhibitors, DPP-4 inhibitors, or GLP-1 receptor agonists are neutral, hazardous, or beneficial for heart failure."

He added: "What's striking is the consistency in the relative risk reduction in all of the major cardiovascular end points that we measured in LEADER."

The prespecified primary microvascular outcome in LEADER was a composite of nephropathy and retinopathy outcomes, and there was a benefit with liraglutide over placebo: time to first renal event was 22% longer with liraglutide, a significant difference. However, this latter effect drove the benefit, as there was no significant difference in retinopathy events between the two groups.

Safety profile shows no signals

Overall adverse events occurred in two-thirds of both treatment groups and were not significantly different (P = .12). Serious adverse events occurred in 50% of both groups and severe events in a third of both (P = .51).

Adjudicated cases of acute pancreatitis occurred in 0.4% of patients taking liraglutide compared with 0.5% on placebo (P = .44). There were two cases of chronic pancreatitis, both in the placebo group.

However, acute gallstone disease was more common with liraglutide, 3.1% vs 1.9% (P < .001).

Hypoglycemia was more common in the placebo group, both with overall confirmed cases of blood glucose levels below 56 mg/dL (43.7% with liraglutide vs 45.6% with placebo, P < .001) and in severe hypoglycemia requiring assistance (2.4% vs 3.3%, P = .016). The likely reason for this, Dr Eckel noted, is that the placebo patients may have been treated more intensively with insulin in attempt to achieve HbA1c targets.

Neoplasms were not different between the groups except for a 46% reduction in prostate cancer (0.9% vs 1.6%) and a lower rate of leukemias (0.1% vs 0.3%) in the liraglutide group.

There was a numeric increase in the number of pancreatic-cancer cases with liraglutide (13 vs five) for a higher rate of pancreatic cancer in the liraglutide group (0.3% vs 0.1%), but four more cases were identified on imaging in the placebo group that did not have pathology to establish the diagnosis, so the two groups were not significantly different, Dr Buse noted.

Everything Changing Modestly, but in the Right Direction

Dr Eckel said that the results of LEADER follow in the same vein as those of EMPA-REG.

"In EMPA-REG, many things related to CVD risk were modified in a modest but favorable way. LEADER gives a hint of the same kind of modification Everything is kind of changing modestly in the right direction."

But the LEADER investigators note some differences in how the drugs may be working.

"The pattern of cardiovascular benefits that were associated with liraglutide in our trial appears to differ from that with the SGLT-2 inhibitor empagliflozin in the previously reported EMPA-REG OUTCOME trial."

The time to benefit emerged earlier in EMPA-REG than in LEADER, they note, and the variability of the direction and magnitude of the effects on the components of the composite primary outcome in that trial "contrasts with the consistency of effect in the present trial."

The observed benefits in EMPA-REG "may be more closely linked to hemodynamic changes, whereas in the present trial, the observed benefits are perhaps related to the modified progression of atherosclerotic vascular disease," they conclude.

Dr Marso reports grants and personal fees from Novo Nordisk during the conduct of the study and personal fees from Abbott Vascular and AstraZeneca outside the submitted work. Disclosures for the coauthors are listed on the journal website .

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ADA Report. Sulfonylureas in T2DM, low cost but risks for hypoglycemia and weight increase. New better drugs coming in

SAN DIEGO — A talk on whether sulfonylureas still have a role in the contemporary treatment of type 2 diabetes garnered much interest here at the American Diabetes Association (ADA) 2017 Scientific Sessions.

Speaking to a large audience in a packed room, Kamlesh Khunti, MD, from the University of Leicester, United Kingdom, presented a fast-paced overview of the history of the use of sulfonylureas, randomized controlled trials vs observational data, mechanism of action, novel insights, and practical considerations.

While there is universal agreement that metformin should be the treatment of first choice in type 2 diabetes, there is still much debate about which and how many of the many classes of drugs should be used second line, when metformin alone isn't sufficient to control blood glucose. And if SU should be on the list

"I don't think you can throw away sulfonylureas (SU) completely; there are a lot of data showing that they can be beneficial for many countries, the low price, and a lot of it comes down to affordability," Dr Khunti told Medscape Medical Newsfollowing his talk. There is extensive experience in using them, and the risks and benefits are reasonably well-understood, he stressed.

While the larger database studies may show that sulfonylureas are not as good as other type 2 diabetes drugs, in the randomized controlled trials, the data on efficacy, safety, and durability "are pretty reasonable. There is still a place for sulfonylureas and in the UK, we still use them," he added.

On the other hand, "If affordability is not a problem, we don't have a question," he noted, implying that if cost were not a factor, he would choose a second-line agent other than a sulfonylurea.

Session chair Neda Rasouli, MD, University of Colorado, Aurora, told Medscape Medical News that with many newer class of medication to treat type 2 diabetes coming to the market, "some leaders in the diabetes field are saying that maybe there is no room for sulfonylureas."

But "it's hard to let them go because of the low cost," she acknowledged, adding, "Everybody wants to make sure that they are using a medication that is safe, and that's why I think there is great interest."

However, "if cost were not a factor, probably people wouldn't use sulfonylureas," she also acknowledged.

CAROLINA and GRADE Will Help Inform Choice

The extensive review presented by Dr Khunti at the ADA meeting showed that there are concerns about side effects such as hypoglycemia and weight gain with sulfonylureas, but the data were inconclusive about potential cardiovascular harm, Dr Rasouli noted.

Dr Khunti said: "We really need to [see] the head-to-head comparisons that we are all eagerly waiting for."

These include data from the cardiovascular-outcome study of the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin (Tradjenta, Lilly/Boehringer Ingelheim) vs the sulfonylurea glimepiride in patients with type 2 diabetes (CAROLINA).

And findings from the Comparative Effectiveness Study of Major Glycemia-lowering Medications for Treatment of Type 2 Diabetes(GRADE) study. GRADE is comparing four commonly used diabetes medications — the sulfonylurea glimepiride, the DPP-4 inhibitor sitagliptin (Januvia, Merck), the glucagon peptide-1 (GLP-1) receptor agonist liraglutide (Victoza, Novo Nordisk), and insulin glargine — head to head, when added to metformin. Patients will be followed for 4 to 5 years, and "that study will help us to decide what the best medication is after metformin," Dr Khunti noted.

Both studies are expected to complete their data collection for primary outcomes in February 2019 and August 2020, respectively, and the results will help guide clinical practice, Dr Rasouli agreed.

However, GRADE does not include sodium-glucose cotransporter 2 (SGLT2) inhibitors, and one of these agents, empagliflozin (Jardiance, Boehringer Ingelheim) was the first type 2 diabetes medication to show cardiovascular protection in the landmark EMPA-REG OUTCOME study reported in September 2015.

Two glucagon peptide-1 (GLP-1) agonists have since also shown this, liraglutide in LEADER and the investigational agent semaglutide (Novo Nordisk) in SUSTAIN-6.

"It will be interesting to see if other SGLT2 inhibitors and GLP-1 receptor agonists are cardioprotective," Dr Rasouli commented to Medscape Medical News. "Then you might consider them as a second agent, but if [trials] don't confirm it, then we go back to the costs of the medication."

She also noted that "right now, in the ADA guideline, basal insulin can be used after metformin,

but there is clinical inertia, and not everybody is comfortable with starting an injectable therapy as a second agent, and ity is also the risks of hypoglycemia."

Can't ignore cost when considering diabetes therapies

Stressing the importance of cost, Dr Khunti said: "Worldwide, 415 million people have diabetes, and 80% live in low–middle-income countries." And price is an important consideration even for developed countries, he emphasized. Diabetes UK has said that the costs of treating diabetes threaten to bankrupt the National Health Service, for example.

There "is a massive difference" in cost for an annual supply of antidiabetic agents, which, in the United States, ranges from $96 US for glipizide and $192 for glyburide — both sulfonylureas — to $1243 for generic metformin to around $5000 for DPP-4 inhibitors and around $5400 for SGLT2 inhibitors, he noted.

A recent study reported that sulfonylureas are still used by too many patients, 31% of patients with diabetes in the United States, and rates of use are even higher in Europe — 41% to 45% of patients in the United Kingdom and 47% of patients in the Netherlands use a sulfonylurea, he added.

There may however be differences between countries in the type of sulfonylurea that is used, Dr Khunti explained.

"In the UK, gliclazide is the [sulfonylurea] that is used the most," he said, noting that it does seem to have a better profile than other sulfonylureas in the ADVANCE trial.

And "over time we have improved and use a lower dose" of gliclazide, he said.

Gliclazide is not available in the United States, Dr Rasouli noted, but glimepiride and glipizide are available.

Get Patients on Whatever Therapy They Can Afford

Summarizing, Dr Khunti said: "What I've shown you is there are controversial issues in terms of whether we use sulfonylureas or not, and a lot of it comes down to affordability."

"We have great drugs, but we are not using them in a timely manner, and we are waiting far too long to intensify therapy in patients."

"We should be getting these patients on whatever therapy we can afford, bringing HbA1c down to control from diagnosis, keeping the HbA1c down for as long as possible, as safely as possible, with whatever therapy is available and affordable to the patient." That is more likely to generate better outcomes for the patients in the longer term, he explained.

"There's good efficacy and durability. There's a bit lower risk of hypoglycemia with the second-generation sulfonylureas. We've established long-term benefit with decreased risk of micro- and to a certain extent macrovascular complications from randomized controlled trials." And sulfonylureas are affordable for the 80% of diabetes patients worldwide who reside in low- to middle-income countries, he reiterated.

From www.medscape.com

Nyhetsinfo 11 juni 2017
www red DiabetologNytt

SGLT2 Inhibitors Double the Risk for Diabetic Ketoacidosis. N Engl J Med

The risk of developing diabetic ketoacidosis (DKA) among type 2 diabetes patients initiating a sodium–glucose cotransporter 2 (SGLT2) inhibitor medication is about double that seen among patients starting a dipeptidyl peptidase-4 (DPP-4) inhibitor, but the overall risk is still low, new research suggests.

Findings from the largest study conducted to date to investigate the issue were published as a research letter in the June 8 issue of the New England Journal of Medicine by Michael Fralick, MD, and colleagues at the Brigham and Women's Hospital, Boston, Massachusetts.

"We found a doubling in the risk of DKA, which sounds frightening, but the absolute risk is quite small....I still think this is a very good class of medications and for certain patients will continue to be. Now we just have a little more information to add to the discussion when the risks and benefits are being considered," Dr Fralick told Medscape Medical News.

He estimates that between 5 and 8 patients per 1000 initiating SGLT2 inhibitors will develop DKA.

And he advises that patients be monitored for signs of DKA or full information to thew patients of the symtoms of DKA to seek help if DKA appears after starting on SGLT2 inhibitors, noting, "This is something that can happen relatively quickly, so that's why I think it's important right after patients are started on these drugs that they're closely monitored and the clinician considers ordering bloodwork."

But overall, Dr Fralick, a general internist, supports use of the SGLT2 inhibitor class for selected patients with type 2 diabetes, ▶

given the recent results from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study showing reduction in cardiovascular deaths, as well as renal protection, with empagliflozin (Jardiance, Boehringer Ingelheim/Lilly).

”I completely agree that these medications have significant benefits,” he commented.

All eyes will be on the results from another cardiovascular-outcomes trial with a different SGLT2 inhibitor, canagliflozin (Invokana, Johnson & Johnson) to be reported on Monday at the American Diabetes Association (ADA) 2017 Scientific Sessions.

Results from the Canagliflozin Cardiovascular Assessment Study(CANVAS) program will reveal whether the cardiovascular protection observed with empagliflozin in EMPA-REG OUTCOME is a class effect or not.

And the findings will further inform on some of the side effects so far associated with this drug class, including DKA, as well as fracture risk and a doubling of amputations of the lower limb, already identified with canagliflozin compared with placebo in CANVAS, which resulted in the Food and Drug Administration adding a boxed warning to this effect to the product label.

Largest study of its kind

For the current study, Dr Fralick and colleagues used a claims database of commercially insured US patients (Truven MarketScan) and identified 50,220 type 2 diabetes patients who had received a new prescription for an SGLT2 inhibitor and 90,132 initiating a DPP-4 inhibitor (chosen as the comparator class because it is used similarly to SGLT2 inhibitors, as second-line after metformin for type 2 diabetes, but has no known link to DKA).

The primary outcome was hospitalization for DKA — the unadjusted rate within 180 days of SGLT2 inhibitor initiation was 4.9 per 1000 person-years, compared with 2.3/1000 person-years following DPP-4–inhibitor initiation (hazard ratio, 2.1).

After propensity score matching with 38,045 patients in each arm to account for confounders such as age, comorbidities, use of other medications, and healthcare utilization, the hazard ratio for hospitalization for DKA with SGLT2 inhibitors vs DPP-4 inhibitors was still significant at 180 days (4.9 vs 2.2/1000 person-years; HR, 2.2), as well as at 30 days (7.5 vs 3.3/1000 person-years; HR, 2.3) and 60 days (5.6 vs 2.3; HR, 2.5).

The DKA risk at 180 days was also significantly higher with SGLT2 inhibitors among patients not taking insulin (2.5 vs 1.0; HR, 2.5).

”Still so much work to be done”

Once the investigators had the data, they strove to get them published as quickly as possible — hence in a research letter rather than a full paper, Dr Fralick told Medscape Medical News, adding, ”There’s still so much work to be done to identify specific risk factors.”

Meanwhile, the group is using the same database to examine the risk of amputations with canagliflozin; results are expected in a few weeks.

The study was supported by the division of pharmacoepidemiology and pharmacoeconomics, department of medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston. Dr Fralick reports grants from the University of Toronto Clinician Scientist Program and Clinician Investigator program and grants from the Detweiller Traveling Fellowship funded by the Royal College of Physicians and Surgeons of Canada, outside the submitted work. Disclosures for the coauthors are listed on the journal website.

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Inhibitors of sodium–glucose cotransporter 2 (SGLT2) decrease plasma glucose by blocking the reabsorption of glucose at the proximal tubule.1,2 Case reports have suggested that SGLT2 inhibitors may be associated with an increased risk of diabetic ketoacidosis, which led to a warning from the Food and Drug Administration (FDA) in May 2015.3,4 The objective of our study was to assess the risk of diabetic ketoacidosis after the initiation of an SGLT2 inhibitor.

Using a large claims database of commercially insured patients in the United States (Truven MarketScan), we identified a cohort of adult patients (≥18 years of age) who had newly started treatment with either an SGLT2 inhibitor or a dipeptidyl peptidase-4 (DPP4) inhibitor between April 1, 2013, and December 31, 2014 (before the FDA warning). DPP4 inhibitors were chosen as the comparator medication because they are similarly used as a second-line treatment for diabetes but have no known association with diabetic ketoacidosis. We excluded patients with human immunodeficiency virus infection, end-stage renal disease, cancer, type 1 diabetes, or past diabetic ketoacidosis. Our primary outcome was hospitalization for diabetic ketoacidosis (using the primary position code of the International Classification of Diseases, Ninth Revision)

within 180 days after the initiation of an SGLT2 inhibitor or a DPP4 inhibitor. We censored data for patients at the time that they discontinued the initial medication, had the outcome, lost insurance coverage, or died.

We used 1:1 propensity-score matching to balance 46 characteristics of the patients and Cox regression to estimate hazard ratios and 95% confidence intervals for diabetic ketoacidosis within 180 days after treatment initiation. Predefined sensitivity analyses included shorter durations of follow-up (30 days and 60 days). All statistical analyses were performed with the use of the validated Aetion platform and R software, version 3.1.2.5

We identified 50,220 patients who had received a new prescription for an SGLT2 inhibitor and 90,132 who had received a new prescription for a DPP4 inhibitor. Patients who were receiving SGLT2 inhibitors were younger and had fewer coexisting illnesses than those receiving DPP4 inhibitors but were more likely to receive insulin. After propensity-score matching was performed, these differences were well balanced (Table 1TABLE 1Characteristics of the Patients at Baseline.). Before propensity-score matching, the unadjusted rate of diabetic ketoacidosis within 180 days after the initiation of an SGLT2 inhibitor was about twice the rate after the initiation of a DPP4 inhibitor (4.9 events per 1000 person-years vs. 2.3 events per 1000 person-years) (hazard ratio, 2.1; 95% confidence interval [CI], 1.5 to 2.9). After propensity-score matching, the hazard ratio was 2.2 (95% CI, 1.4 to 3.6) (Table 2TABLE 2Primary and Other Outcomes.). The results were robust across sensitivity analyses.

In conclusion, shortly after initiation, SGLT2 inhibitors were associated with approximately twice the risk of diabetic ketoacidosis as were DPP4 inhibitors, although cases of diabetic ketoacidosis leading to hospitalization were infrequent. The increased risk of diabetic ketoacidosis with SGLT2 inhibitors is among the factors to be considered at the time of prescribing and throughout therapy if patients present with symptoms suggestive of diabetic ketoacidosis.

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www red DiabetologNytt

ADA Report. Researchers call for standardizing CGM

Continuous glucose monitoring (CGM) outcomes provide meaningful metrics for clinical trials and diabetes care, but the benefits can't be demonstrated without a standard set of definitions, according to a panel of experts who spoke at a Friday symposium.

The researchers outlined three published and three forthcoming CGM metric statements, and called for combining those into one international consensus during the session Reaching an International Consensus on Standardizing Continuous Glucose Monitoring (CGM) Outcomes—Aligning Clinicians, Researchers, Patients, and Regulators. A unified set of definitions would aid in the development of new drugs and devices, the researchers said.

Key metrics derived from CGM data include time in range of glucose levels, time above range, time below range, and glucose variability, which may impact both hyperglycemia and hypoglycemia and may have other detrimental effects.

Richard M. Bergenstal, MD

"CGM has the potential to be a critical tool in clinical trials to evaluate and compare new medications and new technologies to see which is more effective at obtaining more control and minimizing hypoglycemia and variability," said Richard M. Bergenstal, MD, Executive Director of the International Diabetes Center at Park Nicollet. "But with no standard definition, every trial might use a different definition of what's high and what's low, so we can't easily compare the data. We need to get everyone to agree."

The researchers reviewed three published CGM consensus statements:

- The International Hypoglycaemia Study:
- A Joint Position Statement of ADA and EASD;
- Outcome Measures for Artificial Pancreas Clinical Trials: A Consensus Report; and results from the Helmsley/IDC Standardized Glucose Reporting Expert Working Group.

They also highlighted the findings of three soon-to-be published CGM consensus statements: Improving the Clinical Value and Utility of CGM Systems:

- Issues and Recommendations,
- ADA-EASD Diabetes Technology Working Group; Priority Outcome Measures for Type 1 Diabetes:
- Consensus Statement of JDRF, Helmsley Charitable Trust,
- AACE, Endocrine Society, PES, AADE, T1D Exchange and ADA; and the International Consensus Statement on CGM Outcomes: ATTD.

A key point repeated often during the symposium is the fact that there's only a slight difference in the suggested values for many CGM ▶

metrics. For example, in the six CGM consensus statements noted in the session, hypoglycemia was defined as: 70 mg/dL,

Simon Heller, FRCP, MD, Professor of Clinical Diabetes at the University of Sheffield, England, argued that there needs to be three standard glucose levels to manage hypoglycemia.

"If you're going to have glucose levels that are relevant to hypoglycemia, you can't have one or two. We have argued for three," he said. "You don't want a patient to go down as low as 54 mg/dL. By that time, they're already in trouble. People need to be aware that hypoglycemia has consequences that aren't captured by current classifications and in research studies and in clinical trials."

Thomas Danne, MD, PhD

Thomas Danne, MD, PhD, Director of the Department of General Pediatrics and Endocrinology/ Diabetology at Kinderkrankenhaus auf der Bult in Hannover, Germany, outlined the levels he, and other experts in the room, believed should be the "standard" metrics.

Dr. Danne said time out of range has two components: moderate and serious hypoglycemia. For reasons of conformity, the terms 'alert hypoglycemia' and 'serious hypoglycemia' are recommended to be used analogously for CGM and self-monitoring blood glucose (SMBG) threshold ranges, he said. Levels

Dr. Danne added that a key measure of glycemic variability is the coefficient of variation (CV), which is independent of mean glucose concentration. Stable glucose levels are defined as a CV 50 percent, and intermediate stability as CV between 33 and 50 percent, he said.

"A composite goal of flash glucose monitoring or CGM, reported in a standardized way and in conjunction with an A1C value, could establish with more confidence whether or not a particular insulin formulation, new technology for insulin delivery, or an innovative patient-centered approach to care was an important factor in helping individuals with diabetes reach optimal glycemic control," Dr. Danne said.

Aaron J. Kowalski, PhD, Chief Mission Officer for the JDRF, said the diabetes community needs to recognize that although important, A1C has limitations. Dr. Kowalski has been working with the T1D Outcomes Program, a community to develop better ways to define clinically meaningful type 1 diabetes outcomes beyond A1C.

Dr. Bergenstal agreed with Dr. Kowalski's assessment of A1C.

Simon Heller, FRCP, MD

"A1C doesn't tell you where you were high or where you were low, or how you should adjust your medication," Dr. Bergenstal said. "If you're doing it for research, it tells you your risk for complications, but it doesn't tell you if you have more or less hypoglycemia. CGM adds important information to the A1C. Instead of getting in a fight with the A1C, CGM adds value and gives you the whole picture, or tells you the patient's story."

Unlike blood glucose meters, CGM devices have the ability to measure 96 to 288 blood sugars every day and allow patients to monitor their glucose "continuously" to help avoid reaching hypoglycemia, Dr. Danne said.

Other CGM hurdles include technology software and data visualization. Companies that make CGM devices have proprietary software that makes it difficult to compare data across systems or companies, Dr. Heller said.

From a clinician's perspective, it's difficult to look at data from different devices that use different target ranges and standards for hyperglycemia and hypoglycemia, agreed Anne Peters, MD, Director of the University of Southern California Clinical Diabetes Program.

Anne Peters, MD

"It increases the complexity of analysis and can lead to errors in interpretation and dose adjustments," Dr. Peters said. "A common set of standards would lead to an easier way to interpret research trial results, as well as data viewed in a clinical setting."

Drs. Peters and Heller urged industry and developers to create one default reporting system or way to visualize CGM profiles and patterns.

If the diabetes community—clinicians, researchers, patients, developers, and regulators—can agree oxn a consensus for CGM metrics and visualization, it will help everyone with the end goal: Helping people with diabetes self-manage their condition more effectively, Dr. Heller said.

"We're beginning to have technologies that can [help with that goal], but the trouble is they're expensive," he said.

"Governments and health insurance companies are unwilling to pay this money because they don't see the potential benefit. We've got to do something about that. Technology and people's abilities to use them effectively have to be a major focus for assisting people to live with this incredibly burdensome condition. If people can get it right, people with diabetes can live with both improved quality of life and a normal life expectancy."

Nyhetsinfo

At the Meeting the audience was told that there is an internationeal harmony in nomenclature of CGM, it should include both GM with and without alarms, dexcom and Medtronic enlite as well as Abbott´s Libre

Nyhetsinfo 10 juni 2017
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Reducing SBP targets below current guidelines cuts risk reducing SBP to 120 to 124 mm Hg linked to reduced risk of cardiovascular disease, all-cause mortality. J42 trials. 144220 patients. JAMA Cardiology

For adults with hypertension treated with antihypertensive medication, reducing systolic blood pressure (SBP) levels to 120 to 124 mm Hg is associated with reduced risk of cardiovascular disease and all-cause mortality, according to a review published online May 31 in JAMA Cardiology.

Joshua D. Bundy, M.P.H., from the Tulane University School of Public Health and Tropical Medicine in New Orleans, and colleagues examined the correlation of mean achieved SBP levels with the risk of cardiovascular disease and all-cause mortality in adults with hypertension. Data were included from 42 trials, with 144,220 patients.

The researchers observed linear associations between mean achieved SBP and risk of cardiovascular disease and mortality; the lowest risk was seen at 120 to 124 mm Hg. For randomized groups with a mean achieved SBP of 120 to 124 mm Hg, the hazard ratios for major cardiovascular disease were 0.71 compared with SBP of 130 to 134 mm Hg, 0.58 compared with SBP of 140 to 144 mm Hg, 0.46 compared with SBP of 150 to 154 mm Hg, and 0.36 compared with SBP of 160 mm Hg or more. The corresponding hazard ratios for all-cause mortality were 0.73, 0.59, 0.51, and 0.47, respectively.

"These findings support more intensive control of SBP among adults with hypertension," the authors write.

From http://www.physiciansbriefing.com

Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and MortalityA Systematic Review and Network Meta-analysis

Joshua D. Bundy, MPH1; Changwei Li, MD, PhD1; Patrick Stuchlik, MS1; et alXiaoqing Bu, MD1,2; Tanika N. Kelly, PhD1; Katherine T. Mills, PhD1; Hua He, PhD1; Jing Chen, MD1,3; Paul K. Whelton, MD1,3; Jiang He, MD, PhD1,3. Author Affiliations Article Information. JAMA Cardiol. Published online May 31, 2017. doi:10.1001/jamacardio.2017.1421

Key Points

Question What is the optimal target for reduction of systolic blood pressure among patients with hypertension?

Findings In this systematic review and network meta-analysis of 42 trials, including 144 220 patients, linear associations were seen between mean achieved systolic blood pressure and risk of cardiovascular disease and mortality, with the lowest risk at a systolic blood pressure of 120 to 124 mm Hg.

Meaning

Reducing systolic blood pressure below currently recommended targets with commonly used antihypertensive medications may significantly reduce the risk of cardiovascular disease and all-cause mortality.

Abstract

Importance

Clinical trials have documented that lowering blood pressure reduces cardiovascular disease and premature deaths. However, the optimal target for reduction of systolic blood pressure (SBP) is uncertain.

Objective

To assess the association of mean achieved SBP levels with the risk of cardiovascular disease and all-cause mortality in adults with hypertension treated with antihypertensive therapy.

Data Sources

MEDLINE and EMBASE were searched from inception to December 15, 2015, supplemented by manual searches of the bibliographies of retrieved articles.

Study Selection

Studies included were clinical trials with random allocation to an antihypertensive medication, control, or treatment target. Studies had to have reported a difference in mean achieved SBP of 5 mm Hg or more between comparison groups.

Data Extraction and Synthesis

Data were extracted from each study independently and in duplicate by at least 2 investigators according to a standardized protocol. Network meta-analysis was used to obtain pooled randomized results comparing the association of each 5–mm Hg SBP category with clinical outcomes after adjusting for baseline risk.

Main Outcomes and Measures Cardiovascular disease and all-cause mortality.

Results Forty-two trials, including 144 220 patients, met the eligibility criteria. In general, there were linear associations between mean achieved SBP and ▶

risk of cardiovascular disease and mortality, with the lowest risk at 120 to 124 mm Hg. Randomized groups with a mean achieved SBP of 120 to 124 mm Hg had a hazard ratio (HR) for major cardiovascular disease of 0.71 (95% CI, 0.60-0.83) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.58 (95% CI, 0.48-0.72) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.46 (95% CI, 0.34-0.63) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.36 (95% CI, 0.26-0.51) compared with those with a mean achieved SBP of 160 mm Hg or more. Likewise, randomized groups with a mean achieved SBP of 120 to 124 mm Hg had an HR for all-cause mortality of 0.73 (95% CI, 0.58-0.93) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.59 (95% CI, 0.45-0.77) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.51 (95% CI, 0.36-0.71) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.47 (95% CI, 0.32-0.67) compared with those with a mean achieved SBP of 160 mm Hg or more.

Conclusions and Relevance

This study suggests that reducing SBP to levels below currently recommended targets significantly reduces the risk of cardiovascular disease and all-cause mortality. These findings support more intensive control of SBP among adults with hypertension.

The Article

Introduction

Hypertension is the leading global preventable risk factor for cardiovascular disease (CVD) and premature death.1,2 Observational epidemiologic studies have shown a strong, independent, and log-linear association between usual systolic blood pressure (SBP) and mortality from CVD and all causes, with no evidence of a threshold down to at least 115 mm Hg.3 Randomized clinical trials have documented that lowering blood pressure (BP) with commonly used regimens reduces the risk of CVD and all-cause mortality.4,5 However, post hoc analyses based on achieved BP in some clinical trials, in which the results were not analyzed according to the randomized treatment assignment, identified a J-shaped association between achieved BP and risk of CVD and all-cause mortality, especially between achieved BP and coronary heart disease (CHD).6,7

The uncertainty of optimal goals for treatment for patients with hypertension has resulted in inconsistent recommendations for BP targets in clinical practice guidelines.4,8,9 For example, compared with the 2003 Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,4 the 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults8 raised the recommended SBP treatment goal from less than 130 mm Hg to less than 140 mm Hg for patients with type 2 diabetes or chronic kidney disease and from less than 140 mm Hg to less than 150 mm Hg for individuals 60 years of age or older. Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) reported that intensive treatment (targeting an SBP of <120 mm Hg), as compared with standard treatment (targeting an SBP of <140 mm Hg), significantly reduced CVD and all-cause mortality among adults with hypertension who were at high risk for CVD, but without diabetes or stroke.10 The data from SPRINT support a more intensive SBP treatment goal, although concerns remain regarding its generalizability to populations at large with hypertension.

Finding the optimal SBP target could have far-reaching implications for the reduction of CVD and premature death in general populations. By using a network meta-analysis to combine available data from randomized clinical trials, we compared the association of different levels of SBP reduction with the risk of major CVD, stroke, CHD, CVD mortality, and all-cause mortality.

Methods

Data Sources and Searches

We searched MEDLINE and EMBASE using the following search terms as medical subject headings and key words: (antihypertensive agents OR blood pressure lowering OR antihypertensive treatment) AND (cardiovascular disease OR coronary disease OR myocardial infarctionOR stroke OR heart failure OR mortality). The searches were conducted without language or date restriction, from inception to December 15, 2015. We limited searches to randomized clinical trials in human adults. Additional trials were identified by hand-searching bibliographies from included studies, reviews, and meta-analyses.

Study Selection

Titles and abstracts of retrieved articles were independently screened by at least 2 of us (J.D.B., C.L., P.S., and X.B.). Articles deemed potentially eligible by either reviewer were retrieved for full-text review. Disagreements on full-text review were resolved by discussion and consensus.

Studies were included if they met the following criteria: (1) participants were randomly allocated to an antihypertensive medication, control, or treatment target; (2) the allocation to antihypertensive treatment was independent

of other treatment regimens; (3) the sample size was 100 patients or more in each treatment group; (4) trial duration was 6 months or more; (5) one or more events for an outcome of interest were reported in each treatment group; (6) mean achieved SBP level was reported for each treatment group, and the difference in mean achieved SBP between the comparison groups was 5 mm Hg or more; and (7) outcomes included major CVD, stroke, CHD, CVD mortality, or all-cause mortality. Clinical trials with mean achieved SBP of 160 mm Hg or more in both comparison groups were excluded because they do not contribute information to the optimal target for SBP treatment. For studies with multiple publications, data from the article with the longest trial follow-up time were included.

Data Extraction and Quality Assessment

Data abstraction was conducted by 2 of us (J.D.B., C.L., P.S., and X.B.) who independently used a predefined, standardized protocol and data collection instrument. Information was recorded on sample size, demographic characteristics, and medical history of the trial participants; BP measurement methods; mean achieved BP during treatment; follow-up time; outcome ascertainment methods; and number of events for each outcome. The predefined outcomes were major CVD events (including CHD, stroke, heart failure, and CVD deaths), stroke, CHD, CVD mortality, and all-cause mortality.

Risk of bias was assessed by 2 of us (J.D.B., C.L., P.S., and X.B.) using the Cochrane Collaboration's risk of bias tool, based on 7 domains11: random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete data, selective reporting, intention-to-treat analysis, and other sources of bias. Disagreement was resolved by consensus.

Data Synthesis and Analysis

Network meta-analysis allows pooling of results derived from direct and indirect evidence across multiple different treatments while preserving the benefits of randomized comparisons within each trial.12 We constructed network diagrams for each outcome and the overall network to visualize direct and indirect comparisons between SBP treatment levels. Treatment nodes were defined by categorizing SBP into the following 10 separate treatment levels: less than 120, 120 to 124, 125 to 129, 130 to 134, 135 to 139, 140 to 144, 145 to 149, 150 to 154, 155 to 159, and 160 mm Hg or more. We used a Bayesian hierarchical random-effects model with a binomial likelihood and complementary log-log link function to model the probability of events.13 Hazard ratios (HRs) for each possible comparison were calculated using Markov Chain Monte Carlo simulation.

For an individual trial, each randomization group was assigned to 1 category of achieved SBP according to the group's mean SBP level during the trial, irrespective of medications used or initial treatment target. Thus, each trial contributed to 2 distinct achieved SBP categories based on randomization groups. Hazard ratios comparing the lower vs higher achieved SBP categories from each trial using intention-to-treat analysis results within specific SBP comparison groups (eg, 120-124 vs 130-134 mm Hg) were pooled. Therefore, randomized comparisons within each trial were preserved. The pooled HR for a given comparison is composed of direct evidence obtained from trials comparing the 2 SBP randomization groups and indirect evidence obtained from the association of all randomized SBP comparisons in the network. In addition, we conducted the following 2 sensitivity analyses: the first excluding SPRINT10 to assess its influence on the results, given its large sample size and treatment effects, and the second excluding trials with 4 or more categories deemed at "high" or "unclear" risk of bias.

To account for trial heterogeneity in the intervention duration and baseline risk of CVD or mortality, we adjusted for trial length and event rate (or mortality) of the reference groups for each trial in the model.14 The median of the posterior distribution was selected as the point estimate, bounded by the 2.5th and 97.5th percentiles to form a 95% CI. Heterogeneity was assessed by monitoring the posterior between-trial SD. We used inconsistency models, design-by-treatment interaction models, and the node-splitting method to evaluate the differences between direct and indirect comparisons.15,16

Finally, publication bias was assessed using funnel plots and the Egger test for direct comparisons with 4 or more studies. All analyses were conducted using WinBUGS, version 1.4.3 (Medical Research Council Biostatistics Unit), R, version 3.2.1 (R Project for Statistical Computing), and Stata, version 12.1 (StataCorp LP). A detailed description of the methods is available in the eAppendix in the Supplement.

Results

Searches of MEDLINE and EMBASE yielded 2721 records, and manual searches of bibliographies of reviews, meta-analyses, and other trial publications identified an additional 26 articles (Figure 1). After removal of duplicates, 2371 titles and abstracts were screened for eligibility, and 449 article texts were reviewed in full.

A total of 42 trials were included in the analyses, with a combined ▶

sample size of 144 220 individuals (eTable 1 in the Supplement). The mean achieved SBP levels ranged from 114 to 171 mm Hg among treatment groups. The trials were conducted in diverse study populations with various comorbidities, and 30 trials included participants with type 2 diabetes. Trial duration ranged from 6 months to more than 8 years, with a mean follow-up of 3.7 years across all trials. Most trials used standardized BP measurement methods (eTable 2 in the Supplement) and had a low risk of bias (eTable 3 in the Supplement).

The network of included trials was well connected, with many direct comparisons across the categories of mean achieved SBP levels (Figure 2; eFigure 1 in the Supplement). The group with an SPB of 130 to 134 mm Hg defined the center of the network, with 21 trials directly comparing a mean achieved SBP of 130 to 134 mm Hg with 7 other mean achieved SBP groups. A total of 31 trials contributed to network comparisons for major CVD, 27 trials for stroke, 27 trials for CHD, 41 trials for all-cause mortality, and 33 trials for CVD mortality. Descriptions of outcomes are available in eTable 4 in the Supplement.

In general, there were linear associations between mean achieved SBP levels and the risk of major CVD, stroke, CHD, all-cause mortality, and CVD mortality (Figure 3 and Figure 4; eFigure 2 and eTables 5-7 in the Supplement). The lowest risks for major CVD, CHD, all-cause mortality, and CVD mortality were at a mean achieved SBP of 120 to 124 mm Hg, whereas the lowest risk for stroke was at a mean achieved SBP of less than 120 mm Hg.

Randomized groups with a mean achieved SBP of 120 to 124 mm Hg had an HR for major CVD of 0.71 (95% CI, 0.60-0.83) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.58 (95% CI, 0.48-0.72) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.46 (95% CI, 0.34-0.63) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.36 (95% CI, 0.26-0.51) compared with those with a mean achieved SBP of 160 mm Hg or more (Figure 3; eTable 5 in the Supplement). Randomized groups with a mean achieved SBP of 120 to 124 mm Hg had an HR for stroke of 0.69 (95% CI, 0.40-1.07) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.51 (95% CI, 0.26-0.87) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.36 (95% CI, 0.17-0.68) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.27 (95% CI, 0.12-0.51) compared with those with a mean achieved SBP of 160 mm Hg or more (eFigure 2 and eTable 5 in the Supplement). A similar but weaker association between mean achieved SBP and CHD was observed (eFigure 2 and eTable 6 in the Supplement).

Randomized groups with a mean achieved SBP of 120 to 124 mm Hg had an HR for all-cause mortality of 0.73 (95% CI, 0.58-0.93) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.59 (95% CI, 0.45-0.77) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.51 (95% CI, 0.36-0.71) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.47 (95% CI, 0.32-0.67) compared with those with a mean achieved SBP of 160 mm Hg or more (Figure 4; eTable 7 in the Supplement). Randomized groups with a mean achieved SBP of 120 to 124 mm Hg had an HR for CVD mortality of 0.67 (95% CI, 0.40-1.22) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.55 (95% CI, 0.30-1.07) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.43 (0.22-0.93) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.34 (0.17-0.76) compared with those with a mean achieved SBP of 160 mm Hg or more (eFigure 2 and eTable 7 in the Supplement).

In a sensitivity analysis excluding SPRINT, HRs and 95% CIs were consistent with results from the main analyses for major CVD, CHD, and all-cause mortality, indicating the lowest risk at an SBP of 120 to 124 mm Hg for these outcomes (eTables 8-10 in the Supplement). However, in the sensitivity analysis, the lowest-risk group for stroke was the group with an SBP of 120 to 124 mm Hg, and the lowest-risk group for CVD mortality was the group with an SBP of less than 120 mm Hg. In the main analyses, the lowest-risk group for stroke was the group with an SBP of less than 120 mm Hg, and the lowest-risk group for CVD mortality was the group with an SBP of 120 to 124 mm Hg. A second sensitivity analysis excluding trials with 4 or more categories deemed at "high" or "unclear" risk of bias did not substantively change the results compared with the main analyses (eTables 11-13 in the Supplement).

Model fit for all outcomes was adequate according to the Bayesian deviance information criterion, and the baseline risk covariate did not significantly alter the models (eTables 14-18 in the Supplement). Heterogeneity was present for each outcome, with random-effects models fitting better than fixed-effects models according to the Bayesian deviance information criterion. The magnitude of heterogeneity was low to moderate,

with a between-trial SD of 0.081 for major CVD and an SD ranging from 0.103 to 0.248 for the other outcomes (eTables 14-18 in the Supplement).

There was no network-wide evidence of inconsistency between direct and indirect comparisons in any of the outcomes based on inconsistency models and design-by-treatment interaction analyses (eTables 19-23 in the Supplement). However, inconsistency was present in a few individual comparisons based on node-splitting analyses (major CVD, 125-129 vs 130-134 mm Hg; CHD, 125-129 vs 130-134 mm Hg; and CVD mortality, 120-124 vs 130-134 mm Hg, and 120-124 vs 135-139 mm Hg). There was no evidence of publication bias.

Discussion

This network meta-analysis of randomized clinical trials documented significant and linear associations between mean achieved SBP and the risk of CVD and all-cause mortality. The lowest risks for CVD and all-cause mortality were among randomized groups with a mean achieved SBP of 120 to 124 mm Hg. These findings support recently published results from SPRINT10 and suggest a benefit of reducing SBP below the currently recommended target among adults with hypertension.8

The SPRINT trial randomly assigned 9361 persons 50 years of age or older with an SBP of 130 to 180 mm Hg who had an increased risk of CVD, but without diabetes or stroke, to receive intensive treatment or standard treatment of SBP.10 Blood pressure was measured in accordance with a prespecified, standardized protocol. The mean achieved SBP was 121.5 mm Hg in the intensive-treatment group and 134.6 mm Hg in the standard-treatment group during the intervention. During a median follow-up of 3.26 years, a significant 25% reduction in the primary composite outcome of CVD events (HR, 0.75; 95% CI, 0.64-0.89; P < .001) and a 27% reduction in all-cause mortality (HR, 0.73; 95% CI, 0.60-0.90; P = .003) were reported.

In our network meta-analysis, compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, CVD was reduced by 29% (HR, 0.71; 95% CI, 0.60-0.83), and all-cause mortality was reduced by 27% (HR, 0.73; 95% CI, 0.58-0.93), among randomized groups with a mean achieved SBP of 120 to 124 mm Hg. This agreement persisted even after excluding SPRINT in a sensitivity analysis. The findings from SPRINT10 and our network meta-analysis suggest that a more intensive treatment target than currently recommended (eg, SBP of 120-124 mm Hg) provides additional benefits for prevention of CVD complications and all-cause mortality.

Our study contributes additional information on SBP management strategies beyond SPRINT.17 First, our study included 42 clinical trials conducted for 144 220 patients with various comorbidities (including diabetes and stroke), age ranges, and mean BP levels at baseline. Therefore, these results are generalizable to populations at large with hypertension. Second, our study compared multiple levels of achieved SBP on the risk of CVD and all-cause mortality and found positive and linear associations between achieved SBP and clinical outcomes. Our findings do not support the existence of a J-shaped association between achieved SBP and the risk of CVD and all-cause mortality. Furthermore, our study indicates that there is a linear association between the magnitudes of SBP reduction and the risk of CVD and all-cause mortality. For example, by lowering SBP by 10 mm Hg to achieve the treatment goal of 120 to 124 mm Hg, the risk of CVD was reduced by 29% (95% CI, 17%-40%), by lowering SBP by 20 mm Hg, the risk of CVD was reduced by 42% (95% CI, 28%-52%), by lowering SBP by 30 mm Hg, the risk of CVD was reduced by 54% (95% CI, 37%-66%), and by lowering SBP by 40 mm Hg or more, the risk of CVD was reduced by 64% (95% CI, 49%-74%). These data support a more intensive SBP management approach to achieve a lower SBP goal.

Several meta-analyses have examined the association with CVD and mortality of more intensive vs less intensive treatment of BP.18,19 Recently, Xie and colleagues18 reported an updated meta-analysis of 19 clinical trials, including 44 989 participants, on the association of intensive BP reduction with CVD outcomes. The mean achieved SBP was 133 mm Hg (range, 118-144 mm Hg) in the more intensive treatment group and 140 mm Hg (range, 124-154 mm Hg) in the less intensive treatment group. Intensive BP-lowering treatment was associated with a reduction of 14% (95% CI, 4%-22%) for major CVD, 13% (95% CI, 0%-24%) for myocardial infarction, and 22% (95% CI, 10%-32%) for stroke. However, more intensive treatment had no significant association with CVD mortality (9%; 95% CI, –11% to 26%) or all-cause mortality (9%; 95% CI, –3% to 19%). Another recent meta-analysis conducted by Ettehad and colleagues19 suggested that every 10–mm Hg reduction in SBP, including to levels less than 130 mm Hg, significantly reduced the risk of major CVD and CHD. Our network meta-analysis results complement and expand on the findings from these traditional meta-analyses. Our analyses, based on many achieved SBP categories while maintaining ran-

domized treatment assignments, show a beneficial linear association between more intensively reduced mean achieved SBPs and clinical outcomes, and identify the lowest risk at a mean SBP of 120 to 124 mm Hg.

The association of intensive treatment in subgroups of patients with certain comorbidities, especially type 2 diabetes, have been of particular interest.18,20- 23 The Action to Control Cardiovascular Risk in Diabetes trial examined the association of an intensive SBP target (<120 mm Hg) compared with a standard SBP target (<140 mm Hg) for patients with diabetes, finding a nonsignificant benefit on reducing risk for CVD events, which could be a consequence of reduced statistical power or use of a factorial design.20,21 A 2012 meta-analysis conducted by McBrien and colleagues22 reported a small reduction in the risk of stroke associated with more intensive BP reduction in adults with type 2 diabetes but found inconclusive results for mortality and CHD. Another recent meta-analysis by Brunström and Carlberg23 reported increased risk of CVD mortality among patients with diabetes who had a baseline SBP of less than 140 mm Hg and reduced their level of SBP via treatment, suggesting a J-shaped association. We were able to include many trials of patients with diabetes and other comorbidities. Our findings do not support the existence of a J-shaped association among populations at large with hypertension.

Strengths and Limitations

There are several strengths in this network meta-analysis compared with the previous meta-analyses that used traditional analysis methods. Network meta-analysis methods offer a unique advantage compared with traditional meta-regression techniques by allowing the simultaneous comparison of multiple achieved SBP levels on clinical outcomes while preserving trial-level treatment randomization and its associated protection against bias. Our study allowed for comparisons of a wider range of mean achieved SBP levels than has been possible in traditional meta-analyses, with a spread from less than 120 mm Hg to more than 160 mm Hg, and identified the lowest risks for CVD and all-cause mortality at a mean achieved SBP of 120 to 124 mm Hg. Another strength of our network meta-analysis is that it uses all available information (direct and indirect comparisons) to compare the association of each mean achieved SBP level with clinical outcomes. Therefore, it was possible to base the comparisons between various SBP levels on a much larger number of clinical trials compared with similar meta-analyses limited to trials examining more intensive compared with less intensive therapy; our study included 42 trials compared with the traditional analysis from Xie et al18 that included 19 trials. Our data indicate that there was no significant difference between direct and indirect comparisons at the network level. In addition, we used a systematic and comprehensive search strategy to identify a wide coverage of available antihypertensive clinical trials. Most of the included trials had low risk of bias; a sensitivity analysis indicated that trials with unclear risk of bias did not substantially influence our results. Finally, our analyses included a large number of trials conducted in diverse patient populations and were adjusted for differences in intervention duration and baseline risk among trials, which increases the generalizability of our findings.

Our findings should be interpreted in light of several limitations, most of which have been common to all meta-analyses conducted in this topic area. First, we had limited sample size in some mean achieved SBP comparisons. For example, only 3 trials achieved mean SBP levels below 120 mm Hg, with a combined sample size of 7333. Thus, most of the evidence in our analyses is based on trials treating participants to achieve SBP levels above 120 mm Hg. Second, few trials reported heart failure outcomes, which resulted in an insufficiently connected network to analyze this outcome. Similarly, we were unable to assess the association of intensive SBP reduction with kidney disease outcomes, dementia, or adverse events such as hypotension or falling, which have been concerns with intensive treatment of BP.18 Furthermore, we were unable to conduct subgroup analyses by age, race/ethnicity, history of CVD, stroke, chronic kidney disease, or diabetes owing to insufficient data. Finally, we defined treatment nodes according to the mean achieved SBP in each randomization group, which does not consider the distribution of individual SBP levels within groups. Thus, mean achieved SBP groups may represent a range of SBPs. In addition, analysis of mean achieved SBP does not guide treatment decisions regarding diastolic BP.

There are several implications for clinicians based on findings from SPRINT,10 other meta-analyses, and our network meta-analysis. First, data suggest that treatment to achieve an SBP below currently recommended guidelines reduces the risk for major CVD and all-cause mortality in adults with hypertension. However, there may be a tradeoff between these benefits and potential adverse effects of intensive SBP reduction, including hypotension, electrolyte abnormalities, and kidney injury.10,18 Thus, clinicians should continue to monitor acute adverse effects in individual patients and

make treatment decisions based on accurate BP measurements, according to standardized protocols similar to those used in clinical trials. Second, although our analysis suggests that intensive SBP reduction reduces risk for major CVD and all-cause mortality in populations at large with hypertension, including in those with diabetes, the outcomes of intensive SBP reduction for patients with diabetes warrant further exploration. Clinicians should be particularly vigilant when treating patients with comorbidities, including diabetes. Finally, the most effective strategies for implementing more intensive SBP reduction in general clinical practice remain to be established. Future research should consider the best practices for treating patients to reduce SBP levels below current guidelines in the routine clinical management of hypertension.

Conclusions

Our study indicates that treating patients to reduce SBP below currently recommended targets may significantly reduce risk of CVD and all-cause mortality. These findings support more intensive SBP control among adults with hypertension and suggest the need for revising the current clinical guidelines for management of hypertension.

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Nyhetsinfo 6 juni 2017
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Se också sid 161.

Nyupptäckt sjukdomsmekanism för typ 2-diabetes. Betaceller blir omogna. Djurstudie. Anders Rosengren, Göteborg. Nature Communcations

Publicering i Nature Communications i dag klockan 11:00. Artikeln nu synlig hos tidskriften efter viss fördröjning.

Nyupptäckt sjukdomsmekanism för typ 2-diabetes

Nu presenteras en nyupptäckt mekanism bakom den minskade insulinproduktionen vid diabetes typ 2. I en artikel i Nature Communications beskriver forskare vid Sahlgrenska akademin hur insulinproducerande celler backar i sin utveckling, blir omogna, och inte fungerar som de ska. Ett fynd som öppnar för nya kliniska behandlingar.

– Om man kan påverka på cellnivå, och återställa kroppens egen sekundsnabba reglering, får man en bättre fininställning av blodsockret än vad insulinsprutor kan ge, säger Anders Rosengren, docent i metabol fysiologi, och verksam vid Institutionen för neurovetenskap och fysiologi och Wallenbergcentrum för molekylär och translationell medicin vid Göteborgs universitet.

Det har länge varit känt att de insulinproducerande cellerna sviktar vid typ 2-diabetes. Kroppen får inte tillräckligt med insulin och blodsockret stiger.

En teori har gjort gällande att de insulinproducerande cellerna blir färre, en annan att deras funktion försämras.

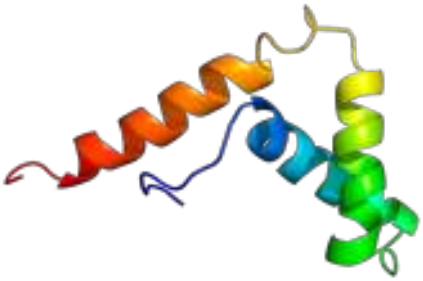
Den nya förklaringen, som förenar de omdebatterade teorierna, går ut på att de insulinproducerande cellerna går tillbaka i utveckling och blir omogna. På så sätt minskar antalet funktionsdugliga celler.

Genen som driver

Med hjälp av 124 vävnadsprover, varav 41 från personer med diabetes typ 2, ringade forskarna in vilka genförändringar i cellerna som påverkade sjukdomsförloppet mest. En analys som Anders Rosengren beskriver med en bild från flygets värld.

– Alla flygplatser är förbundna i ett stort nätverk, men en störning på Frankfurts flygplats är mycket allvarligare än en störning i Göteborg. Vi letade upp hubbarna, nyckelgenerna, och de stora förbindelselänkarna. Av nästan 3 000 gener som var förändrade vid diabetes var 168 så kallade Frankfurtgener, och det var dem vi fokuserade på, säger han.

Den fortsatta analysen visade att genen SOX5, tidigare okänd i diabetessammanhang, påverkar sjukdomen.



– Om man artificiellt undertrycker och stänger av SOX5 så försämras funktionen hos de 168 generna och cellerna backar i mognadsgrad. Om man sedan tillför SOX5 skruvas de 168 generna upp och insulinförsättningen kan normaliseras, förklarar Anders Rosengren.

– Det var väldigt spännande att se. Det var nästan som en volymkontroll där mognadsgraden kunde dras upp och ner i de insulinproducerande cellerna.

Befintliga läkemedel

Läkemedel som återställer mognaden hos insulinproducerande celler är inte långt borta, menar Anders Rosengren. Troligen finns de redan i form av mediciner som används vid andra sjukdomar.

Samtidigt betonar han vikten av hälsosamma levnadsvanor vid diabetes typ 2. Den aktuella forskningen visar att SOX5 minskar om man äter onyttigt och rör sig för lite.

– Det är viktigt att inte dra alla över en kam. Vissa klarar sig länge trots ohälsosamma levnadsvanor, för andra tippar det över tidigare. Men oavsett genetiska förutsättningar har man en möjlighet att göra något år sin sjukdom, säger Anders Rosengren.

Länk till artikeln: https://www.nature.com/articles/ncomms15652
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ABSTRACT

Sox5 regulates beta-cell phenotype and is reduced in type 2 diabetes
A. S. Axelsson, T. Mahdi[...]A. H. Rosengren

Nature Communications 8, Article number: 15652 (2017)doi:10.1038/ncomms15652Download

Type 2 diabetes (T2D) is characterized by insulin resistance and impaired insulin secretion, but the mechanisms underlying insulin secretion failure are not completely understood.

Here, we show that a set of co-expressed genes, which is enriched for genes with islet-selective open chromatin, is associated with T2D. These genes are perturbed in T2D and have a similar expression pattern to that of dedifferentiated islets.

We identify Sox5 as a regulator of the module. Sox5 knockdown induces gene expression changes similar to those observed in

T2D and diabetic animals and has profound effects on insulin secretion, including reduced depolarization-evoked Ca2+-influx and β-cell exocytosis. SOX5 overexpression reverses the expression perturbations observed in a mouse model of T2D, increases the expression of key β-cell genes and improves glucose-stimulated insulin secretion in human islets from donors with T2D.

We suggest that human islets in T2D display changes reminiscent of dedifferentiation and highlight SOX5 as a regulator of β-cell phenotype and function.

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LCHF to T1DM Children. Risks For Life. Pediatric Diabetics. Carmel Smart

Low carbohydrate diets for the management of type 1 diabetes have been popularised by social media.

The promotion of a low carbohydrate diet in lay media is in contrast to published pediatric diabetes guidelines that endorse a balanced diet from a variety of foods for optimal growth and development in children with type 1 diabetes. This can be a source of conflict in clinical practice.

We describe a series of 6 cases where adoption of a low carbohydrate diet in children impacted growth and cardiovascular risk factors with potential long-term sequelae.

These cases support current clinical guidelines for children with diabetes that promote a diet where total energy intake is derived from balanced macronutrient sources.

CASE REPORT

Endocrine and metabolic consequences due to restrictive carbohydrate diets in children with type 1 diabetes: An illustrative case series

From Pediatric Diabetes. 2017;1–9. wileyonlinelibrary.com/journal/pedi 1

1 | INTRODUCTION

Nutritional management is a core aspect of diabetes care. Interna-tional clinical guidelines on the management of type 1 diabetes univer-sally describe the requirement for a healthy diet based on a variety of nutritious foods. The International Society for Paediatric and Adoles-cent Diabetes (ISPAD)1 and National Institute for Health and Care Excellence (NICE)2 Paediatric guidelines recommend that ~50%-55%, <35%, and 15%-20% of energy should be derived from carbohydrate, fat, and protein, respectively.1 with an individualized assessment required. At the same time, alternative diets such as low carbohydrate 30%-40% energy from carbohydrate) and very low carbohydrate diets (21-70 g/d)3 are promoted for the management of type 1 and type 2 diabetes in various media forums in order to optimise glycaemic control. While there is some evidence that low carbohydrate diet can be effective for weight loss in obese adults,4 and improve glycemia in adults with type 2 diabetes,5 there is no supportive scientific literature in children with type 1 diabetes, and there are concerns that any cardi-ovascular benefits of weight loss using a low carbohydrate diet in adults may be countered by an unfavourable lipid profile.4

A nutrient-rich diet that meets individual energy, vitamin, and mineral requirements is important for normal growth and development in children. Adherence to a low carbohydrate diet in a bid to reduce glycemic excur-sions and insulin requirements has the potential to result in a low total caloric intake, mineral deficiencies and lead to suboptimal growth. While clinical guidelines note the potential for poor growth in children adopting a low carbohydrate diet,1 there are no published data to support this. Fur-thermore, substitution of carbohydrate with other energy sources such as saturated fat, can lead to an increased risk of developing cardiovascular disease.6,7To address this gap in the literature, pediatric endocrinologists, and dietitians across Australia and New Zealand were invited to describe type 1 diabetes cases where adherence to a restricted carbohydrate diet was believed to result in endocrine and metabolic consequences. Publica-tion of each case was approved by the local ethics committee from the contributing centre. Nutrient Reference Values for Australia and New Zealand8 were used to determine recommended intakes for each individual. Anthropometry utilised the CDC reference growth charts in all cases.9

2 | CASES

2.1 | Case 1

Patient A was diagnosed with type 1 diabetes aged 12 years 1 month. On initial presentation A had hyperglycemia and mild dehydration, with no history of polyuria, polydipsia, or reported weight loss. During diagnosis, his HbA1c was 10.3% (89 mmol/mol) and thyroid function tests were normal. Type 1 diabetes was subsequently confirmed with positive diabe-tes autoantibodies. Patient A commenced multiple daily injection ▶

therapy with meal-time insulin to carbohydrate ratios. Patient A lived with both parents and was involved in numerous sporting activities.

After diagnosis for 3 months his HbA1c had fallen to 6.1% (43 mmol/mol). Eight months after diagnosis, aged 12 years 9 months, his HbA1c was 5.8% (40 mmol/mol) with his height 149 cm (–0.67 SDS) and weight 34.9 kg (–1.21 SDS). At this time his parents expressed concern about patient A's blood glucose levels increasing above the normal range particularly following his afternoon recess at school. Patient A was advised to eat more at lunchtime in accordance with appetite and to cover this with additional insulin, as the family were reluctant to give an additional insulin injection at recess.

After 3 months, at 13 years of age, patient A and his parents imple-mented a lower carbohydrate diet in an effort to control his blood glucose excursions. A 3-day food record showed an average daily intake of ~90 g of carbohydrate. His energy intake was an estimated 8200 kj/d with 20% energy from carbohydrate, 30% from protein, and 50% from fat. Calcium intake was less than 30% recommended dietary intake (RDI). At the same time patient A joined a cycling team and began training sessions for 1 to 2 hours on 4 occasions per week. Between 13 and 15 years, patient A attended clinic less regularly than recommended. During this time his weight fell from –1.22 to –1.88 SDS (Figure 1). Investigations for coeliac and thyroid disease were normal.

At 15 years 3 months, patient A requested a dietary review as he was hungry and becoming very fatigued during and after cycling. His fam-ily were also concerned about glucose excursions noted after high fat, high protein meals. A 24 hour dietary recall showed an average intake of 60 g of carbohydrate per day with <70% RDI of calcium and thiamin. He reported that he was finding the dietary restrictions difficult, and asked his family during the interview "Can I please have milk after training?" His usual post-exercise intake consisted of eggs, sausages, bacon, and salad. Annual blood tests revealed an elevated fasting cholesterol level of 5.5 mmol/L.

From this time onwards patient A increased his carbohydrate intake to 150 g/d with carbohydrate pre- and post-training sessions.

At 16 years his calcium intake met 80% RDI, weight had recovered to –1.31 SDS and his HbA1c was 6.3% (45 mmol/mol).

2.2 | Case 2

Patient B was diagnosed with type 1 diabetes at age 8 years 7 months after a classical 3 week pro-drome of polyuria and polydipsia, and confirmatory diabetes autoantibodies. Born to Egyptian parents, her mother had a history of gestational diabetes, her father had type 2 diabetes (on insulin) and a paternal grandmother had type 2 diabe-tes. The mid-parental height, defined as the genetic height potential based on the parental height, was reported as 162.5 cm (–0.13 SDS).

Patient B transitioned to insulin pump therapy at the age of 9 years. She was academically high achieving and required a high level of counselling support to manage diabetes related and social anxieties.

From age 10 years, patient B expressed concern about her body weight and a strong desire to lose weight. By age 12 years, patient B con-tinued to identify her main concern as being her weight and had a firm goal to reach a desired weight of 50 kg and be more athletic. At this time, she was 59.2 kg (1.99 SDS) and had a body mass index (BMI) of 23.7 kg/ m2 (1.31 SDS) (Figure 2). Menarche had occurred at age 11 years 10 months.

At the age of 12, patient B and her parents reported extensive lifestyle changes made within the family unit following her father's own attempts to manage his type 2 diabetes and weight loss follow-ing bariatric surgery. He encouraged patient B to join him in following a low carbohydrate diet. Her parents reported that she was exercising more regularly and insulin pump downloads revealed an average daily carbohydrate intake of ~50 g/d. HbA1c at this time was 7.0% (53 mmol/mol). Her dairy intake was noted to be minimal and calcium intake less than 50% of daily requirements. Concurrently, patient B reported

poor concentration levels but was willing to pursue the low carbohydrate eating plan as she had started to achieve some weight loss (BMI 1.26 SDS) and her parents continued to encourage and pro-vide this diet in the family home. At age 12 years 7 months, elevated fasting total cholesterol of 5.7 mmol/L and low vitamin D were noted. Systolic blood pressure was at the 95th percentile for age.

At age 13 years, carbohydrate intake was restricted further, to an average intake of 22 g carbohydrate per day. Patient B reported low energy levels and lack of enjoyment when playing sport. Fear of hypoglycemia was expressed, impacting upon her sleep, engagement in sport and normal daily activities, fear of entering carbohydrate into the insulin pump, frequently decreasing the recommended bolus dose for meals and disconnection of the insulin pump from 1 to 3 AM. There was an increase in her HbA1c from 6.0% (42 mmol/mol) to 8.1% (65 mmol/mol).

Patient B then developed secondary amenorrhoea. She under-went numerous investigations, including magnetic resonance imaging (MRI) of the brain and pituitary, laboratory tests for pubertal hor-mones, coeliac and thyroid serology, folate and iron studies, all of which were normal. Her BMI continued to decrease over this time (Figure 2), despite frequent dietetic interventions that aimed to sup-port the family in achieving a balanced, nutritious diet. Concerns regarding the development of disordered eating were raised when she was 13 years of age, primarily due to self-reported fear of includ-ing additional carbohydrate in her diet because it may lead to weight gain. This was coupled with obsessively weighing herself every day. Extensive psychological counselling continued to help patient B man-age these persistent feelings of high anxiety.

From age 14 years onwards, her diet started to become less restrictive, as she herself identified that "it was not the right diet for me" and concern over the disruption to her menstrual cycle was high.

She increased her carbohydrate intake to 120 to 140 g\d, her men-strual cycle resumed and energy levels improved enough to engage in regular physical activities. At this time, her BMI was 24.3 kg/m2 (0.84 SDS).

2.3 | Case 3

Patient C was diagnosed with type 1 diabetes aged 6 years 3 months.

He presented with hyperglycaemia, polyuria, polydipsia, ketosis, and bed wetting. His weight on diagnosis was 20.9 kg (−0.22 SDS) and height was 124.8 cm (1.32 SDS). Positive autoantibodies for type 1 diabetes were confirmed. He started multiple daily injection ther-apy using insulin-to-carbohydrate ratios for meals and long acting insulin before bed. A 24-hour diet recall based on pre-diagnosis intake showed a wide variety of foods which met Nutrient Reference Value requirements1 for age. His mother showed a good dietary knowledge; however, his father was unable to attend education ses-sions despite efforts made by the diabetes team.

Two weeks following diagnosis patient C was commenced by his family on a low carbohydrate, high-fat diet in an attempt to avoid mealtime insulin injections. Carbohydrate intake was limited to 75 g daily, with tinned fish, and green salad replacing his usual sandwich at school. The mid-morning fruit break was restricted to low carbohy-drate fruit only. At this time, it was noted that patient C had only gained 500 g in weight since diagnosis (see Figure 3) so a carbohy-drate intake of at least 40 g was recommended at school in accord-ance with requirements and food preferences prior to diagnosis.

At his second review appointment 2 months after diagnosis, patient C had lost further 0.6 kg (weight 20.3 kg, −0.55 SDS) and was still eating only salad at school with lean meat or fish despite the previous recommendation. The lunch-time injection and often the dinner injection were omitted. A diet history showed his carbohy-drate intake was reduced further to 60 g/d, providing an estimated 20% of his daily energy intake. His diet met ~70% of his expected energy needs, with calcium intake providing only 200 mg/d, 28% of his requirement for age. The multi-disciplinary team recommended that a minimum of 30 g carbohydrate were included at both lunch and dinner to meet nutritional needs and also assist with patient C's self-reported hunger.

On review 3 months later, patient C had lost further weight (400 g). Thyroid function tests were normal and a coeliac screen negative. He was continuing to follow a low carbohydrate meal plan with ~50 g carbohydrate/d, with less than 7 g carbohydrate at lunch and dinner. Insulin injections were not being given at school. His HbA1c at this time was 7.9% (63 mmol/mol). Patient C's mother expressed the opinion that a very low carbohydrate diet would achieve the best results for her son's overall health and diabetes. This was related to information provided by social media. A hospital admission for re-stabilisation of his diabetes was recommended but refused by his mother.

At the time of his next appointment, the diabetes team were con-tacted by staff at patient C's school. They reported patient C was hun-gry and asking for food from other children and staff. His teachers noted he had only salad and tins of fish, with protein balls ▶

in his lunch-box. During a visit to the school by the Diabetes team, there was a dis-cussion of the importance of a healthy diet at school inclusive of fruit, wholegrains and dairy foods and patient C's mother seemed prepared to begin to include carbohydrate foods at school. However, later it emerged that patient C's mother was angry with the advice given and expressed the desire to have a different multi-disciplinary team.

Nevertheless, at his subsequent appointment a diet history showed a much less restrictive dietary intake of 150 g carbohydrate with 45 to 60 g eaten at school. Patient C had gained 1.8 kg in weight (22.3 kg, −0.35 SDS). His carbohydrate intake was an esti-mated 35% of his current energy intake with an excessive fat intake >40% energy. Laboratory results revealed an elevated fasting choles-terol 6.3 mmol/L (reference range <5.5 mmol/L); LDL cholesterol

3.04 mmol/L (reference range <2 mmol/L) and triglycerides 1.66 mmol/L (reference range <1.59 mmol/L). Lower fat alternatives to achieve <10% energy from saturated fat and fish oil supplementa-tion were recommended.

In subsequent visits, with a more liberalized carbohydrate intake patient C's growth improved with weight 24 kg (−0.1 SDS) and height 131.8 cm (1.32 SDS) centile (Figure 3). Food seeking behaviour ceased at the school.

2.4 | Case 4

Patient D was diagnosed with type 1 diabetes aged 4 years. She pre-sented with classical symptoms of polyuria, polydipsia, and a 1-2 kg weight loss over a 4-week period. She was not in diabetic ketoacido-sis. Her HbA1c at diagnosis was >14% (>130 mmol/mol). Her father also had type 1 diabetes, but died 9 months after patient D was diag-nosed. Her grandparents were the primary caregivers thereafter.

Four weeks after diagnosis her height was 93.5 cm (−2.0 SDS) and weight 13.5 kg (−1.49 SDS). The mid-parental height was 154 cm (−1.6 SDS). Within 4 months of diagnosis a reduced carbohy-drate diet had been implemented (less than 40% energy from carbo-hydrate), and there was weight loss to 12.85 kg. For the next 8 years while followed at the clinic, her growth continued to be poor (Figure 4). Patient D continued a diet low in carbohydrate with a pro-portionally high amount of energy derived from fat. For example, based on a 3-day food record at the age of 11 years, she was reach-ing 76% of expected energy requirement, with 39% coming from car-bohydrate, 42% from fat (48% saturated), and 19% from protein. This food record reached 47% of the calcium, 70% of the phosphorous, and 74% of the magnesium recommended daily intake, respectively. She had elevated fasting total cholesterol of 5.2 mmol/L while adher-ing to this diet.

Patient D was last seen aged 11.3 years; height 123.9 cm (−3.28 SDS), weight 27 kg (−1.77 SDS). At this point her HbA1c was 8.6%

(71 mmol/mol), on 0.7 U/kg/d of insulin, using a twice daily injection insulin regimen. Subsequently, the family refused to attend clinic due to conflict between the clinical team and her grandparents regarding the diet implemented in the household. She was lost to follow up despite efforts from social services. Her final adult height is not available.

Patient D had a mean HbA1c over her entire paediatric follow up of 8.1% (65 mmol/mol) (range: 6.4-10.4%, 46-90 mmol/mol). She had no admissions for diabetic ketoacidosis, and while she experienced frequent mild and moderate hypoglycaemia, there were no documen-ted severe hypoglycaemic events resulting in coma or seizure. Her poor growth was extensively investigated; she had normal thyroid function, coeliac screen, growth hormone testing, and normal female karyotype. Her bone age was delayed by 2 years. She was screened for an eating disorder and this was discounted.

2.5 | Case 5

Patient E was diagnosed with type 1 diabetes aged 2 years, after a classical history of polyuria and polydipsia. He did not present with diabetic ketoacidosis. His HbA1c at diagnosis was 12.6% (114 mmol/ mol). He was the first born child of his parents, and there was no family history of type 1 diabetes. Two weeks after diagnosis his height was 84 cm (−1.36 SDS) and his weight was 14.2 kg (1.31 SDS). The mid parental height was recorded 182 cm (1.15 SDS).

After 18 months of diagnosis, at the age of 3.5 years, a low car-bohydrate diet was introduced by the parents. Two months after commencing this diet, HbA1c had improved from 6.1% (43 mmol/mol) to 5.3% (34 mmol/mol) with no severe hypoglycaemia. Patient E was not growing well, with height now 92.4 cm (−2.16 SDS) and weight 15.3 kg (−0.54 SDS) (Figure 5). A strict low carbohydrate and high fat diet continued to be adhered to, and 6 months later patient E had not gained significant weight (15.5 kg, −0.86 SD). Dietetic eval-uation from a 3-day food record revealed that total energy intake reached 86% of estimated energy requirements. Energy derived from carbohydrate was 6%, protein 27%, fat 67% (saturated fat 36%). He had 406% of recommended daily sodium intake. Calcium was 50% of recommended daily intake.

The poor weight gain and short stature were investigated. Thy-roid function and coeliac screen were normal. IGF1 was very low (<25

mcg/L). Other laboratory investigations showed an elevated total cholesterol of 4.7 mmol/L, with normal triglycerides and normal HDL (1.9 mmol/L). Serum magnesium, vitamin B1, and folate were normal.

He proceeded to growth hormone testing, initially with an argi-nine stimulation test which failed. Peak growth hormone was

4.3 mU/L (normal >19 mU/L). At this stage after negotiation with the family, more carbohydrate was introduced into the diet.

Two months later, average daily carbohydrate intake was 45 g/d, total insulin dose was 0.31 U/kg/d (on insulin pump therapy), and the HbA1c was 4.9% (30 mmol/mol). The patient showed significant hypoglycemia with 2 weeks of continuous glucose sensor data showing 20% of sensor glucose values less than 3.9 mmol/L and 3% of time spent with a sensor glucose below 2.9 mmol/L. A total of 47% of hypoglycemic events occurred between 11 PM and 5 AM. There were no episodes of hypoglycemic seizures. Poor height velocity was continuing with height now 95.9 cm (–2.36 SDS), and weight 16.6 kg (–0.55 SDS). Further laboratory investigations demonstrated an improvement in IGF-1 (28 mcg/L). Pituitary growth hormone secre-tion was tested again with an overnight growth hormone profile, which showed only 1 overnight peak of 20 mU/L. Other pituitary hormones, and a brain MRI, were normal.

2.6 | Case 6

Patient F was diagnosed with type 1 diabetes at the age of 22 months after presenting with a 1 month history of polyuria, polydipsia, and a 2.0 kg weight loss. Four months after diagnosis she was 95.1 cm tall (–0.18 SDS) and weighed 14.7 kg (0.07 SDS). The mid-parental height was recorded as 170 cm (1.1 SDS). Patient F transitioned to insulin pump therapy at age 3.5 years and at this time, her parents decided to commence Patient F on a low carbohydrate diet in order to achieve less excursions in the blood glucose readings. They cited pop-ular literature and used other internet-based blog sites to support this change, including low carbohydrate recipes. However, they were only able to maintain their daughter on a restricted carbohydrate intake of 40 g/d for 1 month as they could not find an adequate variety of low carbohydrate foods that their child would accept. At aged 6 years 9 months of age, patient F was placed on a low carbohydrate diet again by her parents. The carbohydrate content of her diet was reduced to ~40 g/d for 3 months by following a plan that provided 12 g of carbohydrate for each main meal and 6 g of carbohydrate for 1 midmeal, with other carbohydrate free foods also offered. The goal in doing this was to help improve glycaemia stabil-ity, as although she continued to have an average HbA1C of 7.6% (60 mmol/mol) [range 7.3%-7.8% (56-62 mmol/mol)] her parents hoped to alleviate the spikes in her blood glucose levels. At this point patient F weighed 21 kg (–0.31 SDS) and measured 120 cm (–0.31 SDS).

Adherence to the low carbohydrate diet was challenging. Her mother described the daily challenge of finding an adequate variety of acceptable foods for her daughter to eat as annoying and relent-less, made more difficult by the fact that her daughter's school was egg and nut-free. Patient F quickly tired of the limited number and repetitive offering of low carbohydrate foods and would often demand more food at bedtime or wake during the night, complaining of hunger. She did continue dance and swimming classes despite her reports that she was hungry all the time.

After 3 months, patient F's parents decided to cease the diet again due to their concerns that she looked unwell and tired most of the time, describing her as "deflated" and lacking in energy. She was reportedly very irritable, was always hungry and never satiated by the foods that were offered. She had lost weight, now weighing 20 kg (–0.89 SDS) but her linear growth was tracking (121.5 cm [–0.08 SDS]) (Figure 6). Laboratory investigations showed normal thy-roid function and a negative coeliac screen.

Patient F returned to a normal family diet that contained on average 130-140 g of carbohydrate per day. The family continue to offer predominantly foods of a low glycemic index. After 3 months she regained 3.7 kg to return to her pre-low carbohydrate diet weight percentile. This trend was sustained at her subsequent follow-up visit 6 months after returning to normal carbohydrate intake (Figure 6).

3 | DISCUSSION

This case series illustrates that carbohydrate restriction in growing children can lead to anthropometrical deficits and a higher cardiovas-cular risk metabolic profile. Further, fatigue and low enjoy-

ment of sports was reported.

To our knowledge, this is the first time that cases have been collated which illustrate the published guidelines that warn to this effect.1,10 The likely mechanism is that carbohydrate restriction, without compensatory energy intake through other macronutrients (fat and protein), leads to a deficit in total energy intake. This occurs more easily in children than adults as children have additional energy needs for growth. A similar observation for growth has been observed when a very low carbohydrate (ketogenic) diet has been applied to children with intractable epilepsy.11,12 Fur-thermore, when dietary fat becomes the principle source of energy, this can result in a high proportion of saturated fat intake, and lead to a lipid profile that raises cardiovascular disease risk13 as seen in cases 1, 2, 4, and 5. High fat diets have also been shown to blunt pituitary growth hormone release,14 which may explain the poor growth hor-mone response shown in case 5.

A number of studies have examined the association of carbohy-drate intake with glycemic control in people with type 1 diabetes.13,15–17 Delahanty et al15 explored the dietary intakes of 532 intensively treated participants in the Diabetes Control and Complications Trial and reported that diets lower in carbohydrate and higher in fat were associated with worse glycemic outcomes. This finding has been supported by studies in children and adolescents using intensive insulin therapy that found higher total fat16 and lower carbohydrate17 intakes were associated with higher hemoglobin A1c levels. These studies concluded that improving dietary quality by increasing consumption of fruit and wholegrain bread and cereals may enhance metabolic profiles in young people with type 1 diabetes.

The effects of restrictive diets in type 1 diabetes are not confined to the physical domain. Common themes in these illustrative cases are anxiety, fatigue, subjection to unnecessary medical investi-gations and in some cases, clinical conflict, and loss to follow up which can have long-term implications. The families who adopt low carbohydrate diets, as in this case series, are often well educated, yet rely on personal blogs from social media as evidence that such a diet is in the best interest of their child. Furthermore, while under-reporting of food intake should be considered in any assessment of the nutritional intake of children and adolescents with diabetes,18 families who follow restricted carbohydrate diets often fastidiously monitor carbohydrate intake. Health professionals face a predicament between trying to maintain a positive patient relationship, while trying to convince the family that the diet may be detrimental to their child's health.

It is well documented that children and adolescents with type 1 diabetes are at a greater risk for psychological disorders, including a 2-fold risk of experiencing a psychiatric disorder and 2.4 times more likely to develop an eating disorder.19 Adoption of restricted eating behaviour can further contribute to the social isolation that patients with type 1 diabetes already experience, and feasibly add to psycho-social burden. Further, the diet may become an additional source of conflict within the family as the child approaches adolescence.

The decision made by families to adopt a restrictive diet is likely to be multi-factorial. Increasing use of newer technologies such as continuous glucose monitoring has enabled parents of children with type 1 diabetes to observe excursions resulting from food contribut-ing to anxiety. Behaviours such as giving insulin during or after the meal20 or inaccurate insulin to carbohydrate ratios21 will cause marked deviations in blood glucose levels following carbohydrate containing meals. Low carbohydrate diets are also fashionable for weight control and are promoted as healthy in lay media. These issues should be carefully addressed by the clinical team. Contributing to this is the variety of media, including popular television, books, magazines articles, and personal internet blogs, that have popularised restrictive diets in type 1 and type 2 diabetes. Such media exploit the intuition that if carbohydrate is the cause of glycemic excursion, then the reduction of carbohydrate intake provides a solution for families dealing with the frustration of daily glycemic variability. Further, the notion that 'less insulin is better' is a commonly expressed theme by families and necessary for the multi-disciplinary team to respectfully discuss.

Health care professionals working in a multi-disciplinary team may use a variety of strategies to encourage maintenance of a bal-anced diet when families express the desire to adopt a low carbohy-drate diet to control glycemic excursions. For example, postprandial glycemic excursions due to delayed administration of insulin boluses should be checked for, and reassurance given that postprandial glyce-mic targets can be met without carbohydrate restriction when insulin to carbohydrate ratios are optimized. Further, substitution of lower glycemic index (GI) for higher GI carbohydrates,22 and enhancing die-tary quality by decreasing foods high in saturated fat and increasing fibre intake,16,17 can assist in improving glycemic control. Encouraging meal-time routines, whilst minimising snacking episodes, is also important.23 Utilizing continuous glucose monitoring

can be an effec-tive tool to reinforce that pre-prandial insulin dosing and improved dietary quality can achieve better glycemic control, as well as facilitat-ing insulin dose optimization.

Currently, there is a lack of balanced lay information warning against the dangers of restricted carbohydrate diets in growing chil-dren with type 1 diabetes. Published diabetes guidelines, and the societies that commission and endorse them are not visible in the popular media with respect to their dietary recommendations, nor do they react to popular media that promotes potentially dangerous advice. Hence, it is vital that the diabetes team educate families about behaviours to lower postprandial glucose excursions within the context of a balanced diet and the potentially adverse consequences of low carbohydrate diets in childhood.

In conclusion, diets that restrict carbohydrates in children with type 1 diabetes can lead to growth failure, low energy intakes, and a higher risk lipid profile. They are also likely to contribute to psychological co-morbidity and social isolation. Health care professionals caring for children with type 1 diabetes need to carefully monitor families who adopt restrictive nutritional plans to improve glycemic control, and should counsel about the possible physical and psycho-social implications that this may incur.

The purpose of this manuscript is not to comment on the adoption of low carbohydrate diets in adults with type 1 diabetes, where optimal growth and development is no longer an issue. Clinical guidelines should continue to caution against such diets in children with type 1 diabetes.

Conflict of interest

The authors have no relevant conflicts of interest to disclose.

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www red DiabetologNytt

Metformin joins forces with gut microbes to improve blood sugars, new study finds from Gothenburg. Nature Medicine

Researchers at the University of Gothenburg and the Institute of Biomedical Investigation of Girona have found that gut microbial shifts under metformin treatment contribute to improved blood sugar control.

They believe that the drug effects on blood glucose may result from normalising the dysbiosis or imbalance of the gut flora that has been previously linked with type 2 diabetes.

Earlier research has found that metformin is distinctly different from other types of diabetes medication in that it caused profound changes in the gut microbiome of users.

In the new findings, published in the journal Nature Medicine, the authors suggest that these differences may influence both metformin's efficacy and side effects.

Although there was a lag or delay of about two months in how long it took for communities of gut microbes to normalise, the paper showed that the microbiome of participants evidently adapted to the treatment.

Specifically, there appears to be common metformin treatment signatures in the gut microbiome, with an increase in abundance of beneficial gut microbe species and a decrease in less favourable ones.

Metformin acts like a growth factor for raising the bacteria count of species that have been shown to lower blood sugar levels, decrease visceral and total body fat, dampen inflammation and gut permeability as well as improve insulin resistance.

Furthermore, when researchers transplanted (through fecal transfers) the gut microbes of metformin-treated participants to germ-free mice, the animals's glucose tolerance readily improved.

One proposed mechanism for the effects has to do with the way the newly formed communities of microbes process certain nutrients, like flavonoids. These compounds have been associated with a reduced risk of type 2 diabetes.

Overall, the results suggest that metformin response is intrinsically linked with the gut, but there are many more questions that remain about the nature of this relationship and the correct way to look at it.

For example, researchers are also considering the possibility that these effects may be mediated through changes in functions of genes in the gut microbiome, which constitute our second genome.

Nyhetsinfo 5 juni 2017
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Recension av ”Det finns inga häxor – en bok om kunskap” av Arne Jarrick

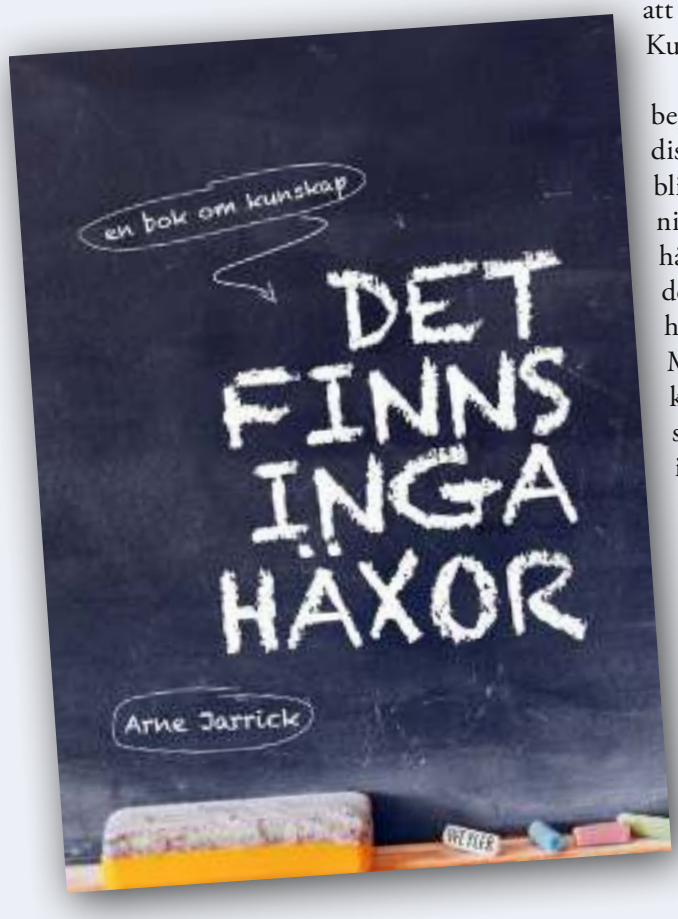
Utgiven 2017 och kostar inbunden 269 kr i bokhandeln, 195 kr via nätet.

Foto © Marcus Marcetic

Arne Jarrick, professor i historia vid Stockholms Universitet och ledamot av Kungliga Vetenskapsakademin, har flera omskrivna böcker bakom sig, så som *”Kärlekens makt och tårar”, ”Hamlets fråga – en svensk självmordshistoria”* liksom *”Behovet att behövas”.*

Jarrick oroas över vikande intresse för kunskap och över fallande respekt för skillnaden mellan sant och falskt. Donald Trump, som med sitt uttalade förakt för sanning ändå gick till seger i USA:s presidentval, förefaller vara den berömda droppen som fick Jarrick att skriva boken.

Den är på strax under 190 sidor, uppdelad i sex kapitel: Driften att veta, Mitt kunskapsuppdrag till mig själv, Ett kunskapssamhälle – vad är det? Lever vi i ett kunskapssam-hälle? Vad är kunskap och betydelsen av lusten att förvärva den samt Kunskapspolitik.



Han tar bl.a. upp begreppet kognitiv dissonans; när man blir varse uppfattningar eller sakförhållanden som strider mot det man håller för sant. Människor har olika sätt att förhålla sig till detta. Oron inne i våra huvuden har sin grund i två omständigheter; en kognitiv och en social. Det kognitiva är vad vi faktiskt tror och det sociala vår benägen-het att tro på samma sätt som de andra medlemmarna av vår grupp tror – eller verkar tro! Sir Karl Poppers (1902 – 1994) förhållningssätt är ett föredöme för vår författare. Denne vetenskapsteoretiker betonade vikten att motstå impulsen att få rätt och i stället tvinga sig att försöka få fel, d.v.s. söka bevis för att den egna hypotesen är fel.

Att vi lever i ett kunskapssamhälle är väl svårt att säga nej till, kunskaperna ökar. Det finns risker med detta, enligt Jarrick; världen blir så komplex att några drar sig undan information – och besluten lämnas till experterna, men hos var och en av dessa saknas kunskapsbredd och överblick.

Arne Jarrick kan sin kunskapshistoria och det skrivna liknar en böljande monolog, där han har en rik källa att ösa ur. Han rör sig fritt mellan 1500-talet och nutid, mellan objektiva fakta och personliga erfarenheter. Han önskar få läsaren att reflektera.

Författaren säger att han är oroad – men att detta inte är lika med hopplöshet. I slutet av boken ger han några förslag på hur man kan ▶

minska kunskapsmotståndet. Flera av för-slagen handlar om insatser i tidig skolålder så våra skolpolitiker borde ta del av dem. Men… är dessa mottagliga? I boken finns ett exempel på faktaresistans; i tio år ledde Jarrick panelsamtal där forskare skulle presentera för politiker relevanta vetenskapliga rön inom områden där politiska beslut skulle tas. Vid en efterföljande enkät visade det sig att ingen enda politiker hade ändrat uppfattning om någonting, den nya kunskapen till trots…

Jag kan därför inte motstå att rekommendera också en annan, helt annorlunda bok. Hade Jarrick använt sig av den metod som beskrivs i den hade dialogsamtalen kanske lett till andra resultat?

Edward de Bono: Six Thinking Hats – run better meetings, make faster decisions.

Penguin Life. Reviderad och omarbetad version från 1999. Häftad 114 kr.

Boken har funnits på svenska, men är slut på förlaget. De 177 sidorna är mycket lättillgängliga.

Edward de Bono är brittisk läkare och författare som framförallt har fokuserat på kreativitet, ofta med barn. Han ligger bakom begreppet lateralt tänkande, till skillnad från vertikalt tänkande.

Författaren utgår från tänkandet som en viktig mänsklig förmåga. Ett problem är att vi försöker greppa för mycket på en gång och blandar därmed känslor, fakta, önskningar, logik och kreativitet när vi diskuterar.

De sex ”tänkarhattarna” är mera tänkta som symboler än som konkreta hattar (utom möjligen när barn arbetar enligt metoden, vilket går utmärkt). Syftet är att endast använda ett tänkesätt åt gången.

Varje hatts färg representerar en viss inriktning i tänkandet.

Vit färg; Neutral, faktabaserad och rationell. Vilken information har vi redan? Hur väl underbyggd är den? Vilken ytterligare kunskap/information behövs?

Röd hatt; tänk eld, passion, känsla. Att lita på sin intuition har i forskning visat sig vara avgörande för att ta bra beslut. Känslan behöver inte motiveras.

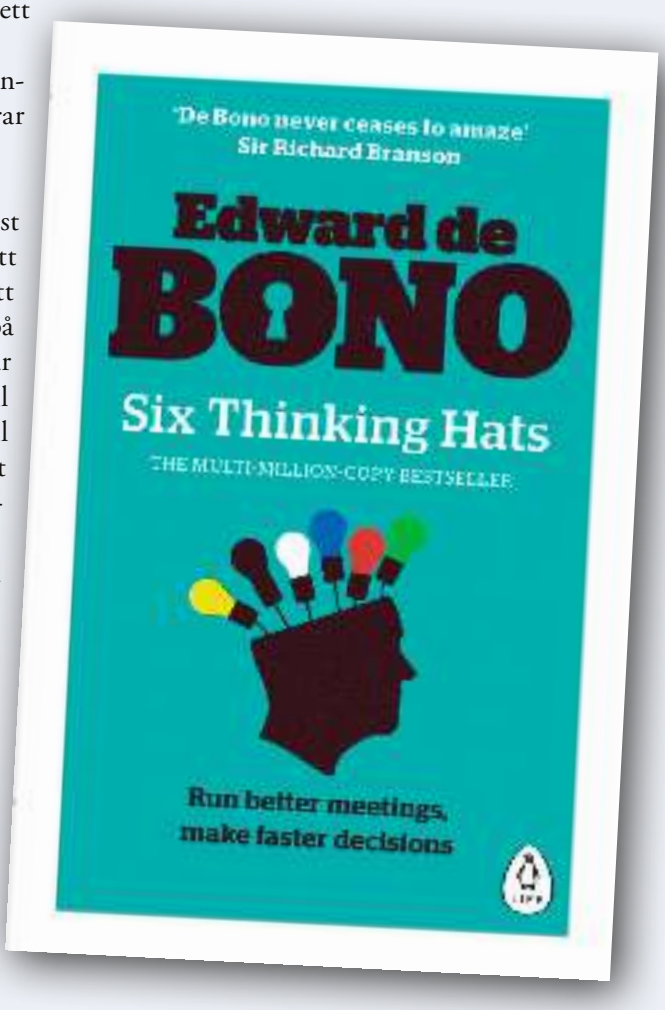
Svart hatt; Svarta tanka, pessimisten. Det kritiska tänkandet med varningar och risk-bedömningar. Var finns hindren, svagheterna?

Gul hatt; solsken och optimism. Att se möjligheter och fördelar med förslagen.

Grön hatt; grön växtlighet, kreativitet. Att tänka utanför ramarna, kläcka nya idéer med brainstorming.

Blå hatt; himlen, överblick, ser helheten, analyserar, söker samband och mönster. Under blå hatt sätts dagordningen, bestäms vilken ordning hattarna skall användas. Intar ett metaperspektiv; tänker om tänkandet. Summerar diskussionen.

Metoden är främst tänkt som ett verktyg för att höja kvaliteten på diskussionen när en grupp skall komma fram till en lösning på ett specifikt problem (som definieras av den blå hatten). Oftast är det att föredra att alla delger sina tankar inom varje inriktning. Erfarenhetsmässigt har det visat sig att mötestiden fram till beslut förkortats avsevärt med metoden och att genomförbarheten och nöjdheten med besluten har varit god.



Längtar du efter att någonsin få se en TV-debatt där någon av debattörerna ändrar sin ståndpunkt?

Har Du deltagit i möten där du frustrerad konstaterat att var och en kör i sina gamla hjulspår; den negative är som vanligt emot alla förslag, den känslosamme verkar i vanlig ordning helt tappat förmågan till logik etc. – du kan nästan gissa i förväg vad respektive person kommer att säga?

Då är det här boken för Dig!

Läs och låt dig inspireras – och nästa möte blir ett äventyr!

Marie Insulander
Leg. psykolog, specialist i klinisk psykologi
Leg. psykoterapeut, handledare

Vårmöte svensk förening för diabetologi
tillsammans med endokrinföreningen

VÄLKOMMEN TILL GÖTEBORG OCH ENDODIABETES 7-9 MARS 2018

Quality Hotel 11, Göteborg

Mötet arrangeras tillsammans med Svenska Endokrinologföreningen och många gemensamma intresseområden kommer att diskuteras

Programmet kommer att ligga på
https://www.endodiabetes.se

ORGANISATIONSKOMMITTÉ FÖR MÖTET
Katarina Eeg-Olofsson katarina.eeg-olofsson@vgregion.se
Oskar Ragnarsson oskar.ragnarsson@medic.gu.se
Jörgen Isgaard jorgen.isgaard@medic.gu.se
Johan Svensson johan.svensson@medic.gu.se
Ragnhildur Bergthorsdottir Ragnhildur.Bergthorsdottir@medic.gu.se
Björn Eliasson bjorn.eliasson@medic.gu.se

PREL PROGRAM OMFATTAR:
- Transition från barn och ungdomar med endokrina diagnoser till vuxenvården
- Bästa kosten och behandlingsriktlinjer för kost
- Transgender
- Kognition vid endokrina sjukdomar
- PCSK9 - mekanismer och effekter av dess hämning
- Hypoparathyroidism
- Aggressiva hypofystumörer
- Kardiovaskulär sjukdom vid diabetes: omfattning, behandlingsstudier och riktlinjer
- Postrar och fria föredrag

Mötet vänder sig till specialister i allmänmedicin, diabetologi/endokrinologi, internmedicin och närliggande specialiteter liksom programpunkter för diabetes- och endosköterskor liksom hela diabetesteamet

Hjärtligt välkommen!

SVENSK FÖRENING FÖR DIABETOLOGI
SWEDISH SOCIETY FOR DIABETOLOGY

SVENSKA ENDOKRINOLOGFÖRENINGEN

Berzelius symposium no 96

23–25 MAY 2018 IN MALMÖ, SWEDEN

Diabetes and the cardiovascular risk challenge – mechanisms, epidemiology and treatment aspects

Organising Committee:

Peter M Nilsson, Professor, MD, PhD, Lund University (chair)
Margrét Leosdottir, MD, PhD, Lund University
Lars Rydén, Senior Professor, MD, PhD, Karolinska Institute (co-chair)
Linda Mellbin, MD PhD, Karolinska Institute
Carl Johan Östgren, Professor, MD, PhD, Linköping University
Stig Attvall, Associate Professor, MD, PhD, Sahlgrenska Academy

More information and registration:

http://www.sls.se

Svenska Läkaresällskapet

LUND UNIVERSITY

Karolinska Institutet

WELCOME TO THE SYMPOSIUM ON

Diabetes and the cardiovascular risk challenge – mechanisms, epidemiology and treatment aspects

The Berzelius symposia are the most prestigious scientific meetings organised by the Swedish Society for Medicine (SSM), this time in collaboration with Lunds Universitet (LU) and Karolinska Institutet (KI). The symposium will focus on mechanisms and clinical aspects of the relationship between diabetes and cardiovascular disease in the light of new studies and trial data that expand our understanding of this relationship and new treatment possibilities. An abstract book and proceedings will be published.

The conference is open to all clinicians and basic science representatives from the Nordic area, international guests and lecturers, as well as representatives from pharma and device manufacturers.

We hope that you will join us for the Berzelius symposium on 23–24th May 2018 and look forward to your active participation. There will be a number of oral presentations but also a possibility to submit abstracts for poster presentation.

Welcome to Malmö in May 2018!

Organising Committee:
Peter M Nilsson, Professor, MD, PhD, Lund University (chair)
Margrét Leosdottir, MD, PhD, Lund University
Lars Rydén, Senior Professor, MD, PhD, Karolinska Institute (co-chair)
Linda Mellbin, MD PhD, Karolinska Institute
Carl Johan Östgren, Professor, MD, PhD, Linköping University
Stig Attvall, Associate Professor, MD, PhD, Sahlgrenska Academy

Contact information:
Peter M Nilsson (chair), peter.nilsson@med.lu.se, phone +46-40-33 24 15
Lars Rydén (co-chair), lars.ryden@ki.se, phone +46-70-7292171
Camilla Key, Symposium secretariat, camilla.key@med.lu.se, phone +46-40-33 23 01
Annie Melin, Symposium secretariat, annie.melin@sls.se, phone: +46-8-440 88 78

PRELIMINARY PROGRAM

WEDNESDAY MAY 23RD, 2018

11.00–13.00 Registration at Jubileumsaulan, Malmö
13.00 Opening of symposium
Stefan Lindgren, President, the Swedish Society of Medicine Jan Nilsson, President, HLF Foundation Mona Landin-Olsson, President SFD, Lund Peter M Nilsson, Chair, Organizing committee, Malmö

Session 1 Definition of diabetes and origins of cardiovascular complications

Chair: Lena Jonasson, Linköping
13.10–13.30 Diabetes – a disease with many faces. Leif Groop, Malmö
13.30–13.50 Lifestyle interventions in the context of precision medicine. Paul Franks, Malmö
13.50–14.10 The red blood cell in diabetes. John Pernow, Stockholm
14.10–14.30 The gene-diet-microbiota-metabolism link. Marju Orho-Melander, Malmö
14.30–15.00 **Coffee, Posters**

Session 2 Epidemiology and trends

Chair: Annika Rosengren, Göteborg
15.00–15.20 Life course perspectives. The Finnish experience. Johan Eriksson, Helsinki, Finland
15.20–15.40 Early life programming of cardiometabolic disease – Global perspectives. Chittaranjan Yajnik, Pune, India
15.40–16.00 Global trends in diabetes and prediabetes – A threatening scenario. William Knowler, Phoenix, USA
16.00–16.20 Global trends in cardiovascular disease – increased disease burden, but not everywhere. Helena Nordenstedt, Stockholm

Session 3 State-of-the-Art 1

Chair: Leif Groop, Malmö
16.20–16.50 Personalized medicine to treat patients with diabetes. Andrew Hattersley, Exeter, UK
16.50–17.00 **Best poster abstract 1.**
19.00 Welcome Reception at Malmö Town Hall (“Rådhus”)hosted by the Malmö City Council.

THURSDAY MAY 24RD, 2018

Session 4 Diabetes – the clinical spectrum

Chair: Anna Norhammar, Stockholm

08.30–08.50 Micro- and macrovascular complications. John Petrie, Glasgow

08.50–09.10 Importance of postprandial hyperglycaemia. Antonio Ceriello, Milano

09.10–09.30 Risk factors, omics and the heart in diabetes. Martin Magnusson, Malmö

09.30–09.50 Lipid disorders in diabetes. Olle Melander, Malmö

09.50–10.20 **Coffee, Posters**

Session 5 State-of-the-Art 2

Chair: Marju Orho-Melander, Malmö

10.20–10.50 Lifestyle as the first step for prevention and treatment of diabetes. Mai-Lis Hellenius, Stockholm

Session 6 Primary prevention of CVD complications in diabetes

Chair: Peter Rossing, Copenhagen

10.50–11.10 Glycaemic control. Katarina Eeg-Olofsson, Göteborg

11.10–11.30 Lipid control. Mats Eriksson, Stockholm

11.30–11.50 Blood pressure control. Karin Manhem, Göteborg

11.50–12.10 Cardio-renal protection. Per-Henrik Groop, Helsinki, Finland

12.10–13.00 **Lunch, Posters**

Session 7 Secondary prevention of CVD complications in diabetes

Chair: Linda Mellbin, Stockholm

13.00–13.20 The importance of a target driven multifactorial approach. Lars Rydén, Stockholm

13.20–13.40 New lipid-lowering treatment and goals. Olov Wiklund, Göteborg

13.40–14.00 Arterial stiffness – A new treatment target? Peter M Nilsson, Malmö

Pro-Pro debate

14.00–14.40 Second-line treatment for type 2 diabetes – incretin active drugs or SGLT2 inhibitors as first choice?! Pro incretin drugs: Jens Juul Holst, Copenhagen Pro SGLT2 drugs: Jan Eriksson, Uppsala

14.40–15.10 **Coffee, Posters**

Session 8 The role of guidelines for prevention of cardiovascular complications

Chair: Lars Rydén, Stockholm

15.10–15.30 European perspective. Francesco Cosentino, Stockholm

15.30–15.50 Transatlantic perspective. William M Herman, USA

15.50–16.10 Swedish perspective. Carl Johan Östgren, Linköping

Session 9 State-of-the Art 3

Chair: Martin Ridderstråle, Malmö

16.10–16.40 Integration of basic and clinical science for prevention of diabetes complications – focus on the incretin system. Eberhard Standl, Germany

16.40–17.00 **Best poster abstract 2 and 3**

19.00 Symposium Dinner in Malmö (pre-registration is necessary).

FRIDAY MAY 25TH, 2018

Session 10 Quality Assessment and Developments, Registers

Chair: Emil Hagström, Uppsala

08.30–08.50 The National Diabetes Register, Sweden. Soffia Gudbjörnsdottir, Göteborg

08.50–09.10 SWEDEHEART, Sweden. Tomas Jernberg, Stockholm

09.10–09.30 SEPHIA Register, Sweden. Margrét Leosdottir, Malmö

09.30–09.50 EUROASPIRE . Viveca Gyberg, Stockholm

09.50–10.20 **Coffee, Posters**

Session 11 The role of Patients, Relatives and the Health Care Organisation

Chair: Mona Landin-Olsson, Lund

10.20–10.40 Swedish Diabetes Association. Fredrik Löndahl, Helsingborg

10.40–11.00 Patient centered health care. Åsa Hörnsten, Umeå

11.00–11.20 Primary Health Care. Carl Johan Östgren, Linköping

11.20–11.40 The Steno Diabetes Centre Concept. Allan Flyvbjerg, Copenhagen, Denmark Panel debate: Quality of diabetes care – New challenges for 2020! Chair: Anders Frid, Malmö

11.40–12.30 Panelists: Karin Wikblad, Fredrik Löndahl, Carl Johan Östgren, Allan Flyvbjerg, Soffia Gudbjörnsdottir, Viveca Gyberg, Stig Attvall

12.30–12.40 Closing remarks. Lars Rydén and Peter M Nilsson

POSTERS

You are most welcome to submit a poster abstract to the meeting! Please register for the meeting before you send in the abstract! Max length 44 lines with Times New Roman 12 p. A limited number of abstracts will be selected for an oral presentation in the poster sessions. Please send your abstract to annie.melin@sls.se, no later than 15 April, 2018. Poster boards at the meeting: approx size of 90 cm wide x 120 cm. If you already have a poster in larger size, two boards can be used.

WHEN & WHERE, PAYMENT?

Venue

23–25 May 2018 at the Jubileumsaulan, Medicinskt forskningscentrum, SUS Malmö at Jan Waldenströms gata 1 in Malmö, Sweden. Registration 10 April 2018, is deadline for registration.

When & Where, Payment?

Registration for the meeting will start on Wednesday 23rd May 2018 at 11.00.

Registration fees

SEK 2 500 (members of the SSM)
SEK 3 000 (non-member)
SEK 1 000, students
After 10 April, 2018: Late registration: SEK 4500
Symposium dinner on Thursday May 24th: SEK 500

The registration fee includes:

- Lunch, coffee (Aug 31st and Sept 1st) and the welcome reception on Wednesday May 23rd (pre-reservation is necessary). The symposium dinner on Thursday May 24th costs SEK 500/person.

Payment

The registration fee must be paid before 10 April, 2018, at the latest. Registration after this date may be possible, but at extra cost, as outlined above. Please pay via PayPal or we can send you an invoice for the fee (please state the correct invoice address, reference/kostnadsställe).

Cancellation

Cancellation of your participation has to be made in writing and sent to annie.melin@sls.se before 10 April, 2018. For cancellations received before 10 April, 2018, a cancellation fee of SEK 500 will be charged. After this date, no refund will be possible.

Transfer of registration

In the event that you are unable to attend the meeting and would like to transfer your registration to a colleague, this can be done at no charge, but please contact the congress secretariat no later than one week before the congress (before 16 May 2018).

Accommodation

Please book your room through this on-line service: http://bookskane.malmotown.com/en/accommodation
Your hotel costs are to be settled directly with the hotel. All major credit cards are accepted.

To and from the airport

International flights: Copenhagen (Kastrup) Airport is located 10 km west of Malmö. There are trains regularly from the airport and the trip to Malmö takes 20 minutes by train. Step off the train at the second stop from Copenhagen Airport ”Triangeln”, and take the escalators located at the end of the platform that your train arrived at, and you will be 200 m from the entrance to Jubileumsaulan.
Domestic flights: Malmö Airport is located nearly 30 km east of Malmö and the Airport bus takes just over a half an hour to get to the heart of Malmö. http://www.malmotown.com/en/travel/

Jubileumsaulan – the conference hall

Malmö University Hospital Emergency centre

More information and registration
http://www.sls.se/diabetes

Res med SFD på Diabetes Konferens 2018

- Enkelt Smidigt Tryggt

ATTD i Wien den 13–17 februari 2018

Res med oss till ATTD i Wien!
Vi erbjuder:

- Bokning av hotell med bra läge och standard
- Bokning av reguljärflyg och tåg
- Bästa möjliga pris – valuta för pengarna!
- Kongressregistrering – slipp alla krångliga registreringssidor!
- Möjlighet att förlänga din vistelse i samband med kongressen
- Vi hjälper dig med bokning av medföljande resenär t ex. sambo/make/maka
- Alla kostnader samlade på en och samma faktura eller uppdelade – en del till arbetsgivaren och en del privat om så önskas.
- Vi erbjuder avbeställningsförsäkring samt reseförsäkring genom Europeiska ERV eller Gouda
- Vi skräddarsyr din resa utefter just Dina behov
- Vid frågor eller bokning är kontaktperson Camilla Stattin. Kontakt sker i första hand per mejl camilla.stattin@linnetravel.se

Exempel på flygtider med Austrian Airlines - Arlanda:

13 feb	OS314	Stockholm – Wien	16.50-19.05
17 feb	OS313	Wien – Stockholm	12.50-15.15

*Prisexempel från **2.846:-** inkl. skatter, bränsletillägg & bagage*

Hotell:
Hotel Stefanie
www.schick-hotels.com/en/hotel-stefanie/index.html
3 stationer med U-bahn till Austria Center Vienna

Pris **1.330:-**/rum/natt inkl. frukost – Kan avbokas utan kostnad fram till den 09/2, därefter debiteras 100%

Vi håller inga rum i dagsläget. OBS! det är hög beläggning på hotellen under kongressen så vi råder Dig att vara ute i god tid!

Kongressregistrering:

Early Brird fram till den 19/12	495 €
Regular fee fram till den 31/1	590 €
Onsite from den 01/2	675 €
Arvode kongressregistrering	350:-

Linné Travel Service AB
Box 19097
104 32 Stockholm
Tel: 08-459 16 60
Fax: 08-662 08 85
www.linnetravel.se

ADA i Orlando den 21–26 juni 2018

Res med oss till ADA i Orlando!
Vi erbjuder:

- Bokning av hotell med bra läge och standard
- Bokning av reguljärflyg och tåg
- Bästa möjliga pris – valuta för pengarna!
- Kongressregistrering – slipp alla krångliga registreringssidor!
- Möjlighet att förlänga din vistelse i samband med kongressen
- Vi hjälper dig med bokning av medföljande resenär t ex. sambo/make/maka
- Alla kostnader samlade på en och samma faktura eller uppdelade – en del till arbetsgivaren och en del privat om så önskas.
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Exempel på flygtider Lufthansa - Arlanda:

21 juni	LH801	Stockholm - Frankfurt	09.55-12.05
21 juni	LH464	Frankfurt – Orlando	13.50-17.50
26 juni	LH465	Orlando - Frankfurt	20.05-10.55
27 juni	LH6226	Frankfurt - Stockholm	12.50-14.50

Prisexempel från **7.750:-** *inkl. skatter, bränsletillägg & bagage - Mat ingår*

Hotell:
DoubleTree by Hilton Orlando at SeaWorld
http://www.hiltonhotels.com/sv_SE/forenta-staterna/doubletree-by-hilton-hotel-orlando-at-seaworld/
Det tar ca 17 minuter att promenera till Orange County Convention Center.

Pris **2.950:-**/ enkelrumt/natt inkl. frukost - kan avbokas utan kostnad fram till den 10/5 därefter debiteras 100% av kostnaden

Vi håller inga rum i dagsläget. OBS! det är hög beläggning på hotellen under kongressen så vi råder Dig att vara ute i god tid!

Kongressregistrering:
Det finns inga uppgifter om kongressregistrering i dagsläget.

Arvode kongressregistrering 350:-

Linné Travel Service AB
Box 19097
104 32 Stockholm
Tel: 08-459 16 60
Fax: 08-662 08 85
www.linnetravel.se

EASD i Berlin den 01–05 september 2018

Res med oss till EASD i Berlin!
Vi erbjuder:

- Bokning av hotell med bra läge och standard
- Bokning av reguljärflyg och tåg
- Bästa möjliga pris – valuta för pengarna!
- Kongressregistrering – slipp alla krångliga registreringssidor!
- Möjlighet att förlänga din vistelse i samband med kongressen
- Vi hjälper dig med bokning av medföljande resenär t ex. sambo/make/maka
- Alla kostnader samlade på en och samma faktura eller uppdelade – en del till arbetsgivaren och en del privat om så önskas.
- Vi erbjuder avbeställningsförsäkring samt reseförsäkring genom Europeiska ERV eller Gouda
- Vi skräddarsyr din resa utefter just Dina behov
- Vid frågor eller bokning är kontaktperson Camilla Stattin. Kontakt sker i första hand per mejl camilla.stattin@linnetravel.se

Exempel på flygtider - Arlanda::

13 feb	OS314	Stockholm – Wien	16.50-19.05
17 feb	OS313	Wien – Stockholm	12.50-15.15

*Prisexempel från **2.095:-** inkl. skatter, bränsletillägg*

Hotell:
Louisa´s Place
www.louisas-place.de/
Det tar ca 18 minuter att resa med kommunaltrafik till Messe Berlin

Pris **2.170:-**/svit deluxe/natt inkl. frukost
Kan avbokas utan kostnad fram till den 27/9 därefter debiteras 100% av kostnaden.

Vi håller inga rum i dagsläget. OBS! det är hög beläggning på hotellen under kongressen så vi råder Dig att vara ute i god tid!

Kongressregistrering:
Det finns inga uppgifter om kongressregistrering i dagsläget.

Arvode kongressregistrering 350:-

Linné Travel Service AB
Box 19097
104 32 Stockholm
Tel: 08-459 16 60
Fax: 08-662 08 85
www.linnetravel.se

ISPAD i Hyderabad den 10–15 oktober 2018

Res med oss till ISPAD i Hyderabad!
Vi erbjuder:

- Bokning av hotell med bra läge och standard
- Bokning av reguljärflyg och tåg
- Bästa möjliga pris – valuta för pengarna!
- Kongressregistrering – slipp alla krångliga registreringssidor!
- Möjlighet att förlänga din vistelse i samband med kongressen
- Vi hjälper dig med bokning av medföljande resenär t ex. sambo/make/maka
- Alla kostnader samlade på en och samma faktura eller uppdelade – en del till arbetsgivaren och en del privat om så önskas.
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Exempel på flygtider Quatar - Arlanda:

10 okt	QR170	Stockholm – Doha	09.30-16.35
10 okt	QR500	Doha – Hyderabad	19.45-02.20
15 okt	QR501	Hyderabad - Doha	03.30-05.25
15 okt	QR167	Doha - Stockholm	20.20-22.35

*Prisexempel från **8.519:-** inkl. skatter och bränsletillägg*

Hotell:
The Westin Hyderabad Mindspacel
http://www.westinhyderabadmindspace.com/
Det tar ca 15 minuter med taxi eller 30 minuter till Hyderabad International Convention Centre (HICC)

Pris **1.710:-**/ enkelrumt/natt inkl. frukost
Kan avbokas utan kostnad fram till den 8/10 därefter debiteras 100% av kostnaden.

Vi håller inga rum i dagsläget. OBS! det är hög beläggning på hotellen under kongressen så vi råder Dig att vara ute i god tid!

Kongressregistrering:
Det finns inga uppgifter om kongressregistrering i dagsläget.
Arvode kongressregistrering 350:-

OBS! Pass och visum till Indien
För att få visum till Indien gäller: Passet måste vara giltigt i minst sex månader från ankomstdatum i Indien. Passet måste även ha minst 2 tomma sidor för myndigheternas stämplar. Du ansöker själv via denna länk: https://indianvisaonline.gov.in/evisa/tvoa.html

Linné Travel Service AB
Box 19097, 104 32 Stockholm
Tel: 08-459 16 60, Fax: 08-662 08 85
www.linnetravel.se

Kongress- och möteskalender

2017

18-21/10 ISPAD Innsbruck, Austria. www.ispad.org

12-13/10 SFDs höstmöte tillsammans med Svensk Förening för Psykiatri. Malmö. www.jamlikvard.org För info: hostmotet@meaconsulting.se

2018

7-9/3 SFDs vårmöte tillsammans med Svensk Förening för Endokrinologi. Göteborg.

14-17/2 ATTD, Wien, www.attd.kenes.com/2018/keep-me-update

22-26/6 ADA, Orlando, www.diabetes.org

2-5/10 EASD, Berlin, www.easd.com

10-15/10 ISPAD, Hyderabad, Indien www.ispad.org

2019

13-15/3 SFD vårmöte tillsammans med Barndiabetes, Stockholm