Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 145 – 2021

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Abbreviations used in this issue
CGM = continuous glucose monitoring
CV = cardiovascular
HbA_{1c} = glycosylated haemoglobin
HR = hazard ratio
RCT = randomised controlled trial
SMBG = self-monitoring of blood glucose

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Welcome to issue 145 of Diabetes and Obesity Research Review.

This issue begins with research that helps to clarify the relationship between vascular complications of early-onset type 2 diabetes and dementia. There is also a paper investigating the association between bariatric surgery and all-cause mortality in severely obese type 2 diabetics. An RCT of intragastric injection of botulinum toxin A administered endoscopically to obese patients has reported significant reductions in bodyweight as a result. This issue concludes with a paper from France reporting notable declines in hospitalisations for acute diabetes complications among patients with type 1 or type 2 diabetes after they switch from SMBG to CGM with the FreeStyle Libre system.
We hope you enjoy the papers selected for this issue. We always appreciate your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Association between age at diabetes onset and subsequent risk of dementia

Authors: Amidei CB et al.

Summary: These researchers used data from the UK population-based Whitehall II cohort (n=10,095) to investigate whether a younger age at onset of diabetes strengthens the association with incident dementia. There were 1710 cases of diabetes and 639 cases of dementia recorded over median follow-up of 31.7 years. Compared with nondiabetics aged 70 years, diabetes onset ≤5, 6–10 and ≥10 years earlier was associated with increasing rates of dementia (10.0, 13.0 and 18.3, respectively, vs. 8.9 per 1000 person-years; adjusted HRs 1.11 [95% CI 0.70, 1.76], 1.49 [0.95, 2.32] and 2.12 [1.50, 3.00]; p<0.001 for trend). At age 70 years, each previous 5 years of age at type 2 diabetes onset was associated with an increased likelihood of dementia (adjusted HR 1.24 [95% CI 1.06, 1.46]).

Comment: We are well versed in associations between diabetes, glycaemic control and the common microvascular complications, as well as the increased risk of macrovascular disease. However, as this paper illustrates, people with diabetes are also at increased risk of other long-term complications such as dementia, which of course can be secondary to vascular changes. One of the more important observations from this analysis of the very long-term outcomes of the population cohort Whitehall study from the UK is that age at onset of diabetes is strongly related to risk of dementia. This is a surrogate of duration of exposure to hyperglycaemia. This is important because we are seeing an increasing trend of diabetes being diagnosed at younger ages, thus heralding a likely increase in incidence of early dementia in the coming years.

Reference: JAMA 2021;325:1640–9
Abstract

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Risk of progression to diabetes among older adults with prediabetes

Authors: Rooney MR et al.

Summary: These researchers compared different prediabetes definitions, and characterised the prediabetes and diabetes risks for 3412 older adults (mean age 75.6 years) from the Atherosclerosis Risk in Communities Study without diabetes at baseline who were followed semi-annually; 2496 of the patients attended their follow-up visit or died. During 6.5 years of follow-up, 156 incident diabetes cases (118 diagnosed) and 434 deaths were recorded. HbA_{1c} levels of 5.7–6.4% were recorded for 44% of the patients and 59% had an impaired fasting glucose level (100–125 mg/dL), with 73% being in either of these groups and 29% in both. Among patients with a baseline HbA_{1c} level of 5.7–6.4%, 9% progressed to diabetes, 13% regressed to normoglycaemia and 19% died; the corresponding proportions in patients with an impaired fasting glucose level at baseline were 8%, 44% and 16%. Among patients with a baseline HbA_{1c} level of <5.7%, 17% progressed to an HbA_{1c} level of 5.7–6.4% and 3% developed diabetes, and among those with a baseline fasting glucose level of <100 mg/dL, 8% progressed to an impaired fasting glucose level and 3% developed diabetes.

Comment: Prediabetes is a topic I am very interested in. There continues to be a lot of uncertainty about what it really means. This translates into uncertainty and inconsistency in how health professionals deal with prediabetes, both in terms of screening and management. Historical data suggested that people with prediabetes, defined by an oral glucose tolerance test, progressed to diabetes at a rate of about 10% per annum and had a 70% lifetime risk of progression. However, as with this paper, we are seeing an increasing body of literature that reports much lower rates of progression when prediabetes is defined by HbA_{1c} level or fasting glucose level criteria. This highlights the underlying physiological differences determining each of these metrics. Getting greater clarity on this issue is very important so that we can confidently plan policy and practice.

Reference: JAMA Intern Med 2021;181:511–9
Abstract

Association between bariatric surgery and major adverse diabetes outcomes in patients with diabetes and obesity

Authors: Doumouras AG et al.

Summary: The association between bariatric surgery and mortality in severely obese (BMI ≥35 kg/m²) individuals with type 2 diabetes was explored in a retrospective, population-based matched cohort study; 3455 patients who underwent bariatric surgery were matched with 3455 nonsurgical controls. Compared with controls, a significantly smaller proportion of patients who underwent surgery died during median follow-up of 4.6 years (2.4% vs. 5.2%; HR 0.53 [95% CI 0.41, 0.69]), with reduced risks of CV-related mortality (HR 0.32 [0.15, 0.66]), a composite cardiac event endpoint (0.68 [0.55, 0.85]) and nonfatal renal events (0.58 [0.35, 0.95]). Among groups with the greatest absolute benefit from bariatric surgery, males, patients with diabetes for ≥15 years and those aged ≥55 years had absolute risk reductions of 3.7% (95% CI 1.7%, 5.7%), 4.3% (0.8%, 7.8%) and 4.7% (3.0%, 6.4%), respectively.

Comment: As stated by the authors, we have several high quality RCTs comparing bariatric surgery with standard care for the management of obesity. These are all relatively small and generally too short to determine the ultimate outcome of premature mortality. This current study, which is a retrospective case-matched cohort study, adds to the previous literature from the landmark Swedish Obesity Study. It is important because it includes people who underwent a sleeve gastrectomy, not included in the Swedish Obesity Study. It confirms the finding that bariatric surgery does reduce all-cause mortality and particularly CV-related mortality in those with type 2 diabetes. These data reinforce the message that for individuals with type 2 diabetes who are obese, bariatric surgery is a very valid and appropriate option for long-term management.

Reference: JAMA Netw Open 2021;4:e216820
Abstract

Cooking oil/fat consumption and deaths from cardiometabolic diseases and other causes

Authors: Zhang Y et al.

Summary: This prospective study evaluated associations between cooking oils/fat consumption (assessed using a validated food frequency questionnaire) and mortality in 521,120 participants aged 50–71 years from the NIH-AARP Diet and Health study. There were 129,328 deaths reported during median follow-up of 16 years. Intakes of butter and margarine were associated with higher total mortality while intakes of canola oil and olive oil were associated with lower total mortality. Adjusted HRs for cardiometabolic mortality (deaths from CV-related disease and diabetes) for each 1-tablespoon per day incremental increase in intake were 1.08 (95% CI 1.05, 1.10) for butter, 1.06 (1.05, 1.08) for margarine, 0.99 (0.95, 1.03) for corn oil, 0.98 (0.94, 1.02) for canola oil and 0.96 (0.92, 0.99) for olive oil. Butter consumption was also positively associated with cancer mortality.

Comment: I include this paper just to reinforce the message again. Incorporating mono- and polyunsaturated fats and reducing consumption of saturated fat is an important nutritional and health goal. Other literature has demonstrated benefits of mono- and polyunsaturated fats previously. This study reaffirms this, although we do need to be careful since it is retrospective and observational, and therefore may be confounded by any number of other healthy dietary and lifestyle choices that the participants were also making. Nonetheless, whilst butter may butter better, olive oil keeps you alive longer!

Reference: BMC Med 2021;19:92
Abstract

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Associations between dietary patterns and the incidence of total and fatal cardiovascular disease and all-cause mortality in 116,806 individuals from the UK Biobank

Authors: Gao M et al.

Summary: This analysis of UK Biobank data investigated associations of various dietary patterns with CV disease and all-cause mortality in 116,806 participants using a 24-hour online dietary assessment on ≥2 occasions. There were 4245 cases of CV disease, 838 of fatal CV disease and 3629 of all-cause mortality during a mean of 4.9 years of follow-up. Two dietary patterns were found to be associated with increased risk of CV disease and all-cause mortality. The first was characterised by high intakes of chocolate and confectionery, butter and low-fibre bread, and low intakes of fresh fruit and vegetables; this diet had a positive linear association with total CV disease and all-cause mortality. The second dietary pattern was characterised by higher intakes of sugar-sweetened beverages, fruit juice and table sugar/preserves; this pattern had a nonlinear association with total CV disease risk and all-cause mortality.

Comment: Foods are generally not consumed in isolation. Most people settle into a particular dietary pattern of eating, whether intentionally or not. We are increasingly learning about the importance of dietary patterns and their effect on health and risk or protection from chronic diseases such as diabetes and CV disease and also cancers. This study utilising data from the UK biobank highlights two specific patterns which are associated with increased CV disease and mortality. Perhaps not surprisingly, they centre around increased consumption of sugar in various forms and lower consumption of fibre, fruit and vegetables. This reinforces knowledge we already have. What we need is effective ways to help people modify their habitual dietary pattern to move away from these components.

Reference: BMC Med 2021;19:83
Abstract

Endoscopic intragastric injection of botulinum toxin A in obese patients on bariatric surgery waiting lists

Authors: Torralvo FJS et al.

Summary: Fifty-two obese patients scheduled for bariatric surgery were randomised to intragastric botulinum toxin A or saline via endoscopy in the IntraTox study. Compared with saline, botulinum toxin A was associated with significantly greater reductions in bodyweight from baseline at weeks 2, 4, 8, 16 and 24 (1.9 vs. 0.6kg, 2.0 vs. 0.4kg, 2.8 vs. 0.4kg, 3.5 vs. 0.2kg and 4.5 vs. 0.6kg, respectively [p values 0.016, 0.031, 0.014, 0.021 and 0.023]), as well as a significantly higher quality of life score (GIQLI questionnaire) relative to baseline (104.4 vs. 97.7 points [p=0.024]). There was no significant between-group difference for perception of satiety or for biomarkers of satiety or appetite.

Comment: I can see the marketing strategy now – 'Get rid of wrinkles and your fat at the same time'. Is there nothing that Botox® (botulinum toxin A) isn't good for? This is an interesting study comparing the effect of intragastric injection of Botox with a control of saline on weight loss. Botox was effective in promoting greater weight loss out to 24 weeks. It is of course an invasive procedure, not without risks and it is hard to see it being cost effective. Furthermore, it is unknown how effective it would be in the long-term. However, it is an interesting and novel mechanism to promote weight loss. It may gain some utility where an initial weight loss is required to enable subsequent surgery or to kickstart other weight loss efforts.

Reference: Clin Nutr 2021;40:1834–42
Abstract

Sustained type 1 diabetes self-management: specifying the behaviours involved and their influences

Authors: Hamilton K et al., on behalf of the DAFNEplus study group

Summary: These researchers sought to identify behaviours involved in sustained type 1 diabetes self-management, their influences and relationships with each other using a mixed-methods study that followed the first two steps of the Behaviour Change Wheel framework: behaviours involved in self-management of type 1 diabetes were identified by expert stakeholder consultation; and modifiable barriers and enablers to sustained self-management were identified and synthesised by systematic review, healthcare provider-generated 'red flags' and participant-generated 'frequently asked questions' – these were characterised according to the COM-B (Capability-Opportunity-Motivation-Behaviour) model. There were 150 distinct behaviours identified, which were organised into the following three self-regulatory behavioural cycles that reflected different temporal and situational aspects of diabetes self-management: 'routine' (e.g. checking blood glucose level), 'reactive' (e.g. treating hypoglycaemia) and 'reflective' (e.g. reviewing blood glucose level data to identify patterns). There were also 34 barriers and five enablers identified, with ten relating to 'capability', 20 to 'opportunity' and nine to 'motivation'.

Comment: There is no way around it. Type 1 diabetes is a bugger of a disease. It is relentless, invasive and pervasive. It is a wonder that anyone with type 1 diabetes ever maintains excellent glycaemic control and remains sane at the same time. Whilst the principles of managing diabetes are pretty simple, the execution of these on a moment-to-moment basis, day in and day out, is a major challenge. As this study highlights, there are numerous barriers and enablers to successful management, and they centre around three main behavioural themes. I always say to people diabetes loves routine, sad as that may be. Secondly, how people react to a change in their situation is critical; and finally, and perhaps most importantly, whether people have the time and bandwidth to reflect or review their situation, information and then modify their management based on that. Chapeau anyone with an HbA_{1c} level of <60 mmol/mol I say.

Reference: Diabet Med 2021;38:e14430
Abstract

Topical oxygen therapy for diabetes-related foot ulcers

Authors: Thanigaimani S et al.

Summary: This was a systematic review with meta-analysis of six RCTs (n=530; two, one and three had high, moderate and low risk of bias, respectively) reporting on topical oxygen therapy for diabetes-related foot ulcers. Compared with controls, topical oxygen therapy was associated with an increased likelihood of ulcer healing (risk ratio 1.94 [95% CI 1.19, 3.17]) with a number needed to treat of 5.33; this finding was robust in sensitivity analyses and was consistent when the analysis was restricted to trials judged to be at low risk of bias (2.37 [1.52, 3.68]); however there remained the possibility of publication bias. A meta-analysis was not possible for amputation as an outcome due to limited data.

Comment: Diabetic foot ulcers can lead to amputation and all of the morbidity associated with that. A lack of podiatry services in diabetes has been identified as a priority in a recent report on the state of diabetes in NZ. This was brought home to me just this week in clinic when I saw a patient who despite his best efforts had fallen between the cracks in the system and was facing the possibility of losing his job as a result of poorly healing ulcers in a Charcot's foot. This paper caught my eye because I had little knowledge of topical oxygen therapy. It seems to come in various guises, but as this paper reports, is associated with improved ulcer healing. I need to learn more about this and particularly consider how such treatments can be incorporated into a multidisciplinary team structure.

Reference: Diabet Med; Published online April 19, 2021
Abstract

Cost considerations for adoption of diabetes technology are pervasive

Authors: Addala A et al.

Summary: This qualitative study of patients with type 1 diabetes and their families reported on decision-making processes around the costs and usage of diabetes technologies. Relevant themes/nodes were identified from transcripts of four stakeholder groups, with the Social Ecological Model applied for interpreting five thematic levels of cost. Policy, organisational, insurance, interpersonal and individual were the five thematic levels of cost identified. Equitable access to diabetes technology was an important policy-level theme. There were a number of subthemes within the insurance-level theme that predominantly carried a negative valence. The participants also highlighted the psychosocial burden of cost, specifically identifying diabetes costs to their families, the guilt associated with diabetes-related costs and frustrations with respect to the time and involvement necessary to ensure insurance coverage.

Comment: This is such a topical issue for us in NZ. The arrival of flash glucose monitoring has made CGM a reality for more people in NZ, but it is still expensive and still beyond the reach of many. Furthermore, the rapid evolution of pump-based algorithms to automatically manage glucose fluxes, prevent hypoglycaemia and now reduce hyperglycaemic excursions takes us closer to a true artificial pancreas. None of this technology is cheap, and it doesn't always help everyone with type 1 diabetes. Unfortunately, clinical trials that report the mean group effects on HbA_{1c} level often lose the rich data of individual experiences, which may be positive or negative. This makes it difficult to persuade funding bodies. Furthermore, there are so many additional costs and benefits of these technologies that need to be taken into account, as highlighted by this paper. Let's hope that some of PHARMAC's new chest of gold can fund some glucose sensors for those with type 1 diabetes.

Reference: Diabet Med; Published online April 1, 2021
Abstract

Important drop rate of acute diabetes complications in people with type 1 or type 2 diabetes after initiation of flash glucose monitoring in France

Authors: Roussel R et al.

Summary: The RELIEF study included 74,011 patients with type 1 or type 2 diabetes who had started using the FreeStyle Libre CGM system, subclassified according to SMBG strip acquisition prior to CGM. After starting the CGM system, there were decreases in hospitalisations for acute diabetes complications among the patients with type 1 and type 2 diabetes (–49.0% and –39.4%, respectively), with respective decreases of –56.2% and –52.1 % for diabetic ketoacidosis admissions, –39.6% and –31.9% for diabetes-related coma admissions and –10.8% and –26.5% for hypoglycaemia or hyperglycaemia admissions. Prior to CGM initiation, hospitalisations mainly occurred in patients who were noncompliant with SMBG and for those with highest acquisition of SMBG; after initiation of the CGM system, these fell by 54.0% and 51.2%, respectively. Twelve-month persistence with the CGM system was 98.1%.

Comment: Further to the review of the previous paper, here is an example of a study that does show a tangible and cost-saving benefit of availability of CGM in France. Notably this benefit was seen in both type 1 and type 2 diabetes. The introduction of FreeStyle Libre flash glucose monitoring reduced admissions to hospital for extended glucose-related events in people who struggled to monitor themselves with capillary glucose monitoring, when given the opportunity to use flash monitoring after 12 months. As previously alluded to, this is not the answer for everyone with diabetes, but we will all have seen the major transformation it allows for some people.

Reference: Diabetes Care; Published online April 20, 2021
Abstract

Independent commentary by Professor Jeremy Krebs MBChB, FRACP, MD

Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He trained in Endocrinology at Wellington Hospital in New Zealand and then did his doctorate with the Medical Research Council - Human Nutrition Research unit in Cambridge England. His thesis was on the impact of dietary factors on obesity and insulin resistance. Professor Krebs returned to New Zealand in 2002 to take up a consultant Endocrinology post at Wellington Hospital, where he was Clinical Leader of Endocrinology and Diabetes. He heads the research group and is Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established. **FOR FULL BIO CLICK HERE.**