Diabetes & Obesity Research Review™

Making Education Easy

Issue 118 – 2017

In this issue:

Abbreviations used in this issue

BMI = body mass index
CGM = continuous glucose monitoring
CV = cardiovascular
GLP = glucagon-like peptide
H/LDL = high/low-density lipoprotein
HbA_{1c} = glycosylated haemoglobin
HR = hazard ratio
OR = odds ratio
QOL = quality of life
RCT = randomised controlled trial
SGLT = sodium glucose cotransporter
SMBG = self-monitoring of blood glucose

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Welcome to issue 118 of Diabetes and Obesity Research Review.

A paper from JAMA reporting worse health outcomes in later life among US health professionals who gained weight earlier in their adulthood begins this issue. Other research from the US found that SMBG had no clinical impact on glycaemic control or health-related QOL at 1 year in insulin nonrecipients with type 2 diabetes, while another study showed that those treated with multiple daily insulin injections who used CGM on a daily or near-daily basis for 24 weeks did experience improvements in glycaemic control. NZ research concludes this issue, confirming that the association of prior gestational diabetes mellitus with undiagnosed diabetes exists in Māori women.

I hope you find these and the other papers selected for this issue helpful in your everyday practice. Please keep the comments and feedback coming.

Best regards,

Associate Professor Jeremy Krebs
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Associations of weight gain from early to middle adulthood with major health outcomes later in life

Authors: Zheng Y et al.

Summary: Associations between bodyweight gain from age 18–21 years to age 55 years and later life health outcomes were explored in cohorts of 29,837 women from the US Nurses' Health study and 25,303 men from the US Health Professionals' Follow-Up study; bodyweight gains for the respective cohorts were 12.6kg over 37 years and 9.7kg over 34 years. Compared with women and men who maintained a stable weight, those whose weight increased by 2.5–10kg had higher multivariable adjusted incidences (per 100,000 woman- and man-years, respectively) of: i) type 2 diabetes (207 vs. 110 and 258 vs. 147); ii) hypertension (3415 vs. 2754 and 2861 vs. 2366); iii) CV disease (309 vs. 248 and 383 vs. 340); and iv) obesity-related cancer (452 vs. 415 and 208 vs. 165). Compared with participants who maintained a stable weight, those who experienced moderate weight gain were significantly less likely to achieve the composite healthy ageing outcome, of freedom from of 11 chronic diseases and no major cognitive or physical impairment, in both the female (24% vs. 27%; adjusted OR 0.78 [95% CI 0.72, 0.84]) and male (37% vs. 39%; 0.88 [0.79, 0.97]) cohorts. Greater weight gain was associated with increased risks of major chronic diseases and a lower likelihood of healthy aging.

Comment: This is an interesting yet not surprising observation reported from the combined health professionals' cohort studies in the US. Those who gained more than 2.5kg through their adult life were more likely to develop chronic diseases known to be related to obesity than those who maintained their weight within a 5kg range over 30 or more years. Very few individuals were in this exclusive group and many gained more than 20kg, highlighting just how challenging it is to maintain a steady bodyweight through adult life, particularly in today's environment. There are of course many interacting and confounding variables in the observed association between weight gain and chronic disease; however, these findings can be used to encourage young adults to strive to maintain their bodyweight as they head towards the dreaded 'middle age'.

Reference: JAMA 2017;318(3):255–69
Abstract

Independent commentary by Associate Professor Jeremy Krebs, an endocrinologist with a particular interest in obesity and diabetes. He is an Associate Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established. As well as clinical and teaching activities, Assoc Prof Krebs maintains active research interests in the area of obesity and diabetes, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery.

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Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults

Authors: Trepanowski JF et al.

Summary: Obese adults were randomised to alternate-day fasting (25% of energy needs on fast days; 125% of energy needs on alternating 'feast days'; n=34), calorie restriction (75% of energy needs every day; n=35) or a control group with no intervention (n=31) for a 6-month weight-loss phase followed by a 6-month weight-maintenance phase; the dropout rates in the respective arms were 38%, 29% and 26%. Alternate-day fasting group participants ate more than prescribed on their fasting days and less than prescribed on their feast days, whereas calorie restriction group participants generally complied with their prescribed energy goals. Mean bodyweight losses (primary endpoint) in the alternate-day and calorie restriction groups were similar at month 6 (–6.8% and –6.8%, respectively) and month 12 (–6.0% and –5.3%, respectively) relative to the control group. No significant difference was seen between the intervention groups for blood pressure, heart rate, insulin resistance or triglyceride, fasting glucose, fasting insulin, C-reactive protein or homocysteine level at 6 or 12 months. Relative to the calorie restriction group, the alternate-day fasting group had a significant increase in mean HDL cholesterol level of 6.2 mg/dL at 6 months, but not at 12 months, and a significant increase in mean LDL cholesterol level of 11.5 mg/dL at 12 months.

Comment: Weight loss requires a reduction in energy intake to below energy expenditure over a prolonged period. How that is achieved is largely irrelevant – at least as far as the degree of weight loss is concerned. What is constantly challenging for individuals and healthcare professionals alike is how to achieve sustained restriction in energy intake in the real world. There are numerous diets from common-sense small daily reductions in a balanced diet, through to extreme manipulations of macronutrients. All can be effective if followed to the prescription, but lack of adherence for a whole range of reasons is the limiting factor. There is current interest in the idea of intermittent fasting – or restriction to very low energy intake on some days but not others. This study examines whether such an approach results in greater weight loss than a daily less intensive energy restriction. The interesting findings here are that either approach seems to result in similar weight loss, which means that individuals could choose which suited them better, or potentially swap between approaches over time. Secondly and not surprisingly, those on the alternate-day fasting diet tended to consume more than prescribed on those days but less than prescribed on the other days and had higher dropout rates overall. This may suggest that extreme approaches are less sustainable, although they may provide an alternative for short periods of time.

Reference: JAMA Intern Med 2017;177(7):930–8
Abstract

Glucose self-monitoring in non-insulin-treated patients with type 2 diabetes in primary care settings

Authors: Young LA et al., for the Monitor Trial Group

Summary: Primary-care patients aged >30 years with type 2 diabetes not treated with insulin and HbA_{1c} levels >6.5% but <9.5% (n=450) were randomised to once-daily SMBG with or without enhanced patient feedback, including automatic tailored messages delivered via their meter, or no SMBG in the pragmatic, open-label Monitor Trial; 418 participants completed their final assessment. HbA_{1c} levels did not differ significantly among the groups, with estimated adjusted mean differences of –0.09% and –0.05% for SMBG with and without messaging, respectively, versus no SMBG (p=0.74). There were also no significant differences among the groups for health-related QOL scores or key adverse events, including hypoglycaemia frequency, healthcare utilisation and insulin initiation.

Comment: The question of whether SMBG has a role in people with type 2 diabetes has been a controversial and emotive topic for many years. It is highly relevant and important in NZ where the cost of test strips for SMBG outstripped the cost of all glucose-lowering medications several years ago. This study addresses this issue again, in an RCT of once daily testing with or without tailored feedback compared with no testing. The bottom line was that SMBG made no difference to glycaemic control. I have always been a promoter of SMBG, but this type of evidence brings into question the place of testing in type 2 diabetes. There are of course complexities to this discussion, including whether people are on insulin secretagogues or insulin therapy, comorbidities, age, individualised target HbA_{1c} levels, willingness to test and more importantly interpret and act on the result. It is easy to slip into the belief that SMBG must be effective in empowering people and facilitating better control because it just makes sense, but does the evidence really support this?

Reference: JAMA Intern Med 2017;177(7):920–9
Abstract

Canagliflozin and cardiovascular and renal events in type 2 diabetes

Authors: Neal B et al., for the CANVAS Program Collaborative Group

Summary: The impact of canagliflozin treatment on CV, renal and safety outcomes was assessed using data integrated from two trials enrolling 10,142 patients with type 2 diabetes (mean duration, 13.5 years) who had a high risk of CV disease (65.6% had a history of CV disease). Mean follow-up was 188.2 weeks. Compared with placebo recipients, canagliflozin recipients had a lower rate of the composite of death from CV causes, nonfatal myocardial infarction or nonfatal stroke (primary outcome; 26.9 vs. 31.5 per 1000 patient-years; HR 0.86 [95% CI 0.75, 0.97]), and possible benefits with respect to the progression of albuminuria (HR 0.73 [95% CI 0.67, 0.79]) and the composite of a sustained 40% reduction in estimated glomerular filtration rate, need for renal replacement therapy or death from renal causes (0.60 [0.47, 0.77]). Adverse events were consistent with the known safety of canagliflozin, except for an increased risk of amputation (primarily at the level of the toe or metatarsal) compared with placebo (6.3 vs. 3.4 per 1000 patient-years; HR 1.97 [95% CI 1.41, 2.75]).

Comment: We have now seen several large CV outcome studies reported over the last 12 months for a range of agents in both the SGLT inhibitor and GLP-1 analogue classes of drug. There has been a clear pattern of benefit with reduced CV events for both classes. This paper reported the CANVAS programme utilising the SGLT-2 inhibitor canagliflozin, trials that many NZ centres including my own took part in. Canagliflozin joins others in the class in demonstrating CV benefit. It is difficult to know what the mechanism is and how important in clinical practice the observation of increased risk for amputation of toes will be. The absolute risk remains low, and may come down to patient selection. First we need one of these agents to be funded in NZ!

Reference: N Engl J Med 2017;377(7):644–57
Abstract

Liraglutide and renal outcomes in type 2 diabetes

Authors: Mann JFE et al., for the LEADER Steering Committee and Investigators

Summary: Prespecified secondary renal outcomes were reported for an RCT that had randomised patients with type 2 diabetes to receive liraglutide (n=4668) or placebo (n=4672). Median follow-up was 3.84 years. The risk of a renal outcome event (new-onset persistent macroalbuminuria, persistent doubling of serum creatinine level, end-stage renal disease or death due to renal disease) was significantly lower in the liraglutide arm than in the placebo arm (HR 0.78 [95% CI 0.67, 0.92]), driven primarily by fewer liraglutide recipients developing new-onset persistent macroalbuminuria (0.74 [0.60, 0.91]). The renal adverse event rates were similar in the respective liraglutide and placebo arms (15.1 and 16.5 per 1000 patient-years), including the acute kidney injury rate (7.1 and 6.2 per 1000 patient-years).

Comment: In addition to CV events, end-stage renal failure and dialysis are two of the feared long-term complications of diabetes. Therefore it is important that our treatments for diabetes are shown to actually reduce the risk of the development and/or progression of these. As discussed above, recent evidence has demonstrated reduced CV events with use of both SGLT-2 inhibitors and GLP-1 analogues, including liraglutide. Here, the effect of liraglutide on kidney disease from one of these large intervention studies is reported, demonstrating a reduction in the development of macroalbuminuria. The study may not have been long enough to examine whether this will translate into fewer patients requiring dialysis or lower rates of renal death, as it was primarily designed to look at CV outcomes. However, it is certainly encouraging that this class of agents is likely to have major benefits on hard outcomes. Once again we still have no funded access to GLP-1 agonists in NZ.

Reference: N Engl J Med 2017;377(9):839–48
Abstract

Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections

Authors: Beck RW et al., for the DIAMOND Study Group

Summary: Patients aged 35–79 years with type 2 diabetes (median duration, 17 years) receiving multiple daily injections of insulin and with HbA_{1c} levels of 7.5–9.9% were randomised to CGM (average usage, 6.7 days per week; n=79) or usual care (n=79). There was a significant difference between the CGM and control groups for reduction in mean HbA_{1c} level at 24 weeks (primary outcome; adjusted difference –0.3% [p=0.022]), but no significant difference for CGM-measured hypoglycaemia or QOL outcomes.

Comment: I included this paper as a contrast to the negative study of once-daily self-monitoring with capillary glucose level testing. This study examines whether monitoring using a subcutaneous CGM device compared with capillary testing in people with type 2 diabetes who are using insulin therapy improves glycaemic control. Unlike the other study, here there is a benefit, albeit small, in HbA_{1c} level after 6 months. This raises the question whether CGM should be funded for selected patient groups, such as those on basal bolus regimens, in preference to broader funding for capillary glucose level testing. The arrival of the newer flash technology devices certainly makes this more affordable, and I think this is a debate that we should be having.

Reference: Ann Intern Med 2017;167(6):365–74
Abstract

Association of pre-pregnancy body mass index with offspring metabolic profile

Authors: Santos Ferreira DL et al.

Summary: These researchers performed individual participant data meta-analyses on three European prospective birth cohorts to determine if relationships between mothers' BMIs and the systemic cardiometabolic profiles of their offspring are causal, occur via intrauterine mechanisms or due to shared familial factors. The offsprings' blood was collected at ages 16, 17 and 31 years, and paternal BMIs were used as negative controls. A 1-stage meta-analysis (5627–5377 mother-father-offspring trios) revealed strong associations between increasing maternal and paternal BMI and a range of adverse cardiometabolic markers in their offspring. These associations were slightly stronger with maternal BMI than paternal BMI, although there was no strong statistical evidence for heterogeneity. A 2-stage meta-analysis resulted in similar results in each cohort. The patterns of cross-sectional association with metabolic profile for the BMI of offspring were similar compared with the parental prepregnancy BMI associations, but the magnitudes were greater. Additional adjustments suggested that the parental associations were largely due to the association of parental BMI with offspring BMI.

Comment: In recent years there has been much attention focused on the intrauterine environment and the potential for metabolic programming of the foetus as a mechanism for the increasing obesity epidemic, particularly in childhood. Much of the evidence to support this theory has come from rodent models. Teasing out the relative effects of maternal and paternal genes and the external environment from intrauterine effects is challenging. This study used modern technology to characterise metabolic traits in the offspring of three different birth cohort studies, and maternal and paternal BMI before pregnancy. Whilst not excluding an effect of intrauterine factors, the dominant determinant of offspring BMI was maternal BMI. Whether this is predominantly genetic or due to shared external environment factors is less clear, and probably both are important and interacting. It is important to pick your parents wisely.

Reference: PLoS Med 2017;14(8):e1002376
Abstract

Nonnutritive sweeteners and cardiometabolic health

Authors: Azad MB et al.

Summary: This was a systematic review and meta-analysis of seven RCTs (n=1003; median follow-up 6 months) and 30 prospective cohort studies (n=405,907; median follow-up 10 years) evaluating non-nutritive sweeteners; most of the included RCTs were at high risk of bias and most cohort studies achieved only moderate quality scores. The RCT data revealed no significant effect of non-nutritive sweeteners on BMI (mean difference –0.37 kg/m^2 [95% CI –1.10, 0.36]) and no consistent effects on other measures of body composition or secondary outcomes. The cohort study data indicated that non-nutritive sweetener consumption was associated with a modest but significant increase in BMI, as well as increases in bodyweight and waist circumference and higher incidences of obesity, hypertension, metabolic syndrome, type 2 diabetes and CV events.

Comment: This may be another example of where something that seems intuitively right doesn't pan out to be correct when carefully studied. The substitution of noncalorific sweeteners for sugar in beverages and foods would appear on the surface to be almost certain to reduce energy intake, assist in weight loss and be beneficial in terms of glucose metabolism and risk of type 2 diabetes. So it comes as a surprise that this systematic review and meta-analysis of studies examining this issue does not conclude that there is any benefit on weight or metabolic risk factors. Indeed, prospective cohort studies suggest an adverse effect, but are limited by design and risk of confounding. This warrants deeper analysis and additional study. What mechanisms might underpin this observation? Is it behavioural conscious or unconscious overcompensation of calorie intake? Is it changes in food preferences for sweetness and energy density? Or are there changes in metabolic pathways promoted by these agents? Either way it appears that the message needs to be to avoid all sweetened beverages – sugar or otherwise.

Reference: CMAJ 2017;189(28):E929–39
Abstract

Prevalence of and risk factors for diabetic peripheral neuropathy in youth with type 1 and type 2 diabetes

Authors: Jaiswal M et al.

Summary: The prevalence of diabetic peripheral neuropathy (Michigan Neuropathy Screening Instrument score >2) and its risk factors were investigated in patients with type 1 (n=1734; mean age 18 years) or type 2 (n=258; mean age 22 years) diabetes of >5 years duration from the SEARCH for Diabetes in Youth study. The respective prevalences of diabetic peripheral neuropathy in the type 1 and type 2 diabetes groups were 7% and 22%. Risk factors for diabetic peripheral neuropathy in the patients with type 1 diabetes were older age, longer diabetes duration, smoking, increased diastolic blood pressure, obesity, increased LDL cholesterol and triglyceride levels and lower HDL cholesterol level, and in those with type 2 diabetes they were older age, male gender, longer diabetes duration, smoking and lower HDL cholesterol level. Individuals with diabetic peripheral neuropathy developed worse glycaemic control over time than those without diabetic peripheral neuropathy in patients with type 1 diabetes (OR 1.53 [95% CI 1.24, 1.88]) but not in those with type 2 diabetes (1.05 [0.7, 1.56]).

Comment: The management of diabetes in youth is so often consumed by a focus on adherence to testing and insulin administration in type 1 diabetes, and on apparently futile attempts to motivate lifestyle change in type 2 diabetes. The usually short duration of diabetes means that a focus on incident microvascular complications is less relevant – or is it? This study suggests that peripheral neuropathy may be a lot more common than we think – particularly for those with type 2 diabetes. Here, almost a quarter of those with type 2 diabetes had some evidence of peripheral neuropathy. This is alarming and again highlights the major challenge we face helping young people who develop type 2 diabetes.

Reference: Diabetes Care 2017;40(9):1226–32
Abstract

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Diabetes among Māori women with self-reported past gestational diabetes mellitus in a New Zealand Māori community

Authors: Simmons D et al.

Summary: The importance of gestational diabetes mellitus as a risk factor for the subsequent development of type 2 diabetes in Māori women (n=2786) was explored in this research. Prior gestational diabetes was self-reported by 1.8% of the 2786 women recruited for the study, who all underwent oral glucose tolerance tests. The prevalence of gestational diabetes significantly decreased with age (p=0.009). Compared with women aged <50 years without prior gestational diabetes, those with prior gestational diabetes had significantly higher BMI (35.6 vs. 32.4 kg/m^2 [p<0.01]), waist circumference (105.3 vs. 96.9cm [p<0.01]), fasting blood glucose level (5.5 vs. 5.1 mmol/L [p≤0.01]), 2-hour postprandial blood glucose level (6.6 vs. 5.6 mmol/L [p<0.01]) and HbA_{1c} level (6.0% vs. 5.8% [p<0.05]). Women with prior gestational diabetes had a significant 4-fold increased likelihood of having undiagnosed diabetes than those without prior gestational diabetes, with those aged <40 years having a particularly higher prevalence (20.0% vs. 1.5%).

Comment: Gestational diabetes has long been recognised as an important risk factor for the subsequent development of type 2 diabetes later in life. There is considerable variability in the magnitude of this risk between populations, and this is further complicated by the definition of gestational diabetes, and changes in this over time. It is therefore very helpful to have local NZ data in this area, and particularly for Māori who have higher rates of diabetes than European New Zealanders. In this cross-sectional study, self-reported previous gestational diabetes significantly increased the risk of undiagnosed diabetes in Māori women under the age of 40 years. This reinforces the message that the identification of women with gestational diabetes is an opportunity to intervene, both in the postpartum period and then subsequently to reduce this risk. Historically it has been difficult to get women to do a follow-up oral glucose tolerance test in the postpartum phase, but now that HbA_{1c} level has become the usual test for diabetes, this may be more convenient and achievable. A history of gestational diabetes should be a red flag to identify women for planned long-term follow-up and screening.

Reference: Aust N Z J Obstet Gynaecol; Published online May15, 2017
Abstract