Diabetes & Obesity Research Review™

Making Education Easy

Issue 124 – 2018

In this issue:

Abbreviations used in this issue

BMI = body mass index
BP = blood pressure
CV = cardiovascular
HbA_{1c} = glycosylated haemoglobin
HF = heart failure
HR = hazard ratio
MI = myocardial infarction
OR = odds ratio
RCT = randomised controlled trial
SGLT = sodium glucose cotransporter

Welcome to issue 124 of Diabetes and Obesity Research Review.

This issue begins with research reporting that women with gestational diabetes according to contemporary criteria are at increased risk of glucose metabolism disorders during long-term follow-up. This is followed by an RCT reporting the benefits of a postnatal lifestyle intervention for women who have experienced gestational diabetes. Research from the US published in N Engl J Med found that while bodyweight gain related to quitting smoking increased the short-term risk of type 2 diabetes, it did not mitigate the benefits of smoking cessation on reducing CV-related or all-cause mortality. This issue concludes with a prespecified exploratory analysis of RCTs from the CANVAS programme suggesting a renoprotective effect of canagliflozin in patients with type 2 diabetes.

I hope this issue helps to keep you up to date. You are welcome to send any comments or feedback you have to the email address below.

Best regards,

Associate Professor Jeremy Krebs
jeremykrebs@researchreview.co.nz

Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity

Authors: Lowe WL et al., for the HAPO Follow-up Study Cooperative Research Group

Summary: The impact of gestational diabetes on maternal glucose metabolism and childhood adiposity 10–14 years postpartum was explored in a cohort of 4697 women and 4832 children followed for a median of 11.4 years. The International Association of Diabetes and Pregnancy Study Groups criteria for gestational diabetes were met by 14.3% and 14.1% of mothers overall and those with participating children, respectively. Compared with mothers without gestational diabetes, those with gestational diabetes had a higher rate of glucose metabolism disorders (52.2% vs. 20.1%; OR 3.44 [95% CI 2.85, 4.14]), and greater proportions of their children were overweight or obese (maternal BMI adjusted OR 1.21 [1.00, 1.46]) or obese only (1.58 [1.24, 2.01]).

Comment: It is generally accepted that gestational diabetes is an established risk factor for subsequent development of type 2 diabetes in the women. Furthermore, children of mothers with gestational diabetes also have an increased risk of overweight and obesity. There is controversy regarding whether this risk is related to maternal obesity alone or whether there are important intra-uterine environmental or epigenetic factors that contribute. Recent changes to the criteria for the definition of gestational diabetes to lower the glucose thresholds for diagnosis have been driven by evidence that pregnancy outcomes are affected down to the new diagnostic threshold. This study is therefore timely to update our knowledge of the long-term outcomes for mothers and children of pregnancies affected by gestational diabetes based on these new lower glucose level criteria. For me the most striking figure is that 52.2% of women had either prediabetes or diabetes by an average of 11 years follow-up. This surely makes this group of women a prime target for preventative interventions postpartum.

Reference: JAMA 2018;320:1005–16
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. **FOR FULL BIO CLICK HERE.**

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form.

One form per review read would be required. Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE.**

Postnatal lifestyle intervention for overweight women with previous gestational diabetes

Authors: Holmes VA et al., PAIGE Study Group

Summary: Postnatal overweight women with previous gestational diabetes were randomised to usual care with (n=29) or without (n=31) an intervention consisting of a 1-hour educational programme, a 3-month referral to a commercial weight management organisation, a pedometer and structured telephone and text support. Compared with controls, the intervention was associated with greater mean bodyweight loss at 6 months (primary outcome; 3.9 vs. 0.7kg [p=0.02]) and a significantly greater reduction in bodily pain (p=0.007), with no between-group difference in blood glucose levels.

Comment: Following on from the previous study identifying the need for targeting women with gestational diabetes with interventions to help reduce the risk of subsequent type 2 diabetes, here is a small lifestyle intervention study aiming to do just that. Although it is only short term, the results were encouraging, showing that with a simple intervention that utilises a commercial weight loss programme, women were able to lose weight compared with the control arm. The study is too short to determine whether this translates into a long-term reduction in diabetes incidence, but does show that in the postpartum period lifestyle interventions are possible. The authors make the important points that further work needs to help understand the optimal timing for such interventions and whether more inclusive family approaches might further enhance the effect. It is often assumed that women will not be open to such interventions in the immediate postpartum period, but this study shows that is not necessarily the case. Timing can be everything.

Reference: J Clin Endocrinol Metab 2018;103:2478–87
Abstract

Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset

Authors: Rawshani A et al.

Summary: This study investigated how age at type 1 diabetes onset related to excess mortality and CV risk in a cohort of 27,195 Swedish registry patients and 135,178 matched controls from the country's general population. Over median follow-up of 10 years, there were 959 deaths in the diabetic group and 1501 among the controls. Patients who developed type 1 diabetes at ages 0–10 years had increased likelihoods of the following outcomes relative to controls that were up to 5-fold greater than those who developed diabetes at ages 26–30 years: death from any cause (adjusted HRs 4.11 [95% CI 3.24, 5.22] vs. 2.83 [2.38, 3.37]); death from CV causes (7.38 [3.65, 14.94] vs. 3.64 [2.34, 5.66]); death from non-CV causes (3.96 [3.06, 5.11] vs. 2.78 [2.29, 3.38]); CV disease (11.44 [7.95, 16.44] vs. 3.85 [3.05, 4.87]); coronary heart disease (30.50 [19.98, 46.57] vs. 6.08 [4.71, 7.84]); acute MI (30.95 [17.59, 54.45] vs. 5.77 [4.08, 8.16]); stroke (6.45 [4.04, 10.31] vs. 3.22 [2.35, 4.42]); HF (12.90 [7.39, 22.51] vs. 5.07 [3.55, 7.22]); and atrial fibrillation (1.17 [0.62, 2.20] vs. 1.18 [0.79, 1.77]). Reductions in life expectancy due to the development of type 1 diabetes before age 10 years were 17.7 and 14.2 life-years for women and men, respectively.

Comment: There have been several publications in the last 12 months indicating that despite many advances in diabetes care, premature mortality in people with type 1 diabetes remains higher than those without diabetes. This study from registry data in Sweden further adds to this concern. Not only does type 1 diabetes increase the risk of CV events, it is further increased by earlier age of onset and greatest for women. I have long struggled with what to advise young people with type 1 diabetes on CV risk management, and statin therapy in particular. Because age is such a dominating factor in risk calculators, it is rare for a person under the age of 40 years to have a risk estimate that triggers intervention. However, based on studies such as this one, perhaps we should be proactively more aggressive at a younger age. It is difficult, however, to persuade young people to take statins as primary prevention. It is time for a well-conducted, large long-term outcome study. The only problem is who is going to fund it?

Reference: Lancet 2018;392:477–86
Abstract

ERRATUM: Please note that in the August 2018 issue (#123) there was an error in the commentary for the paper below.

Ludvigsson JF et al. Periconception glycaemic control in women with type 1 diabetes and risk of major birth defects. BMJ 2018;362:k2638. Abstract

The comment stated that preconception HbA1c level should be maintained at 'below 6.5%, or 68 mmol/mol'. The correct figures are 'below 6.5%, or 48 mmol/mol'.

Closed-loop insulin delivery for glycemic control in noncritical care

Authors: Bally L et al.

Summary: Hospitalised adults with type 2 diabetes requiring subcutaneous insulin therapy were randomised to closed-loop insulin delivery (n=70 patients) or conventional subcutaneous insulin therapy according to local practice (n=66). Compared with the control group, the closed-loop group experienced a significantly longer mean time with the sensor glucose level measurement in the target range of 100–180 mg/dL, or 5.6–10.0 mmol/L, for ≤15 days or until hospital discharge (primary endpoint; 65.8% vs. 41.5% [p<0.001]), a significantly lower proportion of participants who exceeded the target range (23.6% vs. 49.5% [p<0.001]) and a significantly lower mean glucose level (154 vs. 188 mg/dL, or 8.5 vs. 10.4 mmol/L [p<0.001]). No significant between-group difference was seen for the duration of hypoglycaemia or the amount of insulin that was delivered, and there were no episodes of severe hypoglycaemia or clinically significant hyperglycaemia with ketonaemia in either group.

Comment: People with type 2 diabetes have increased hospitalisation, increased length of stay and poorer outcomes for most acute conditions than people without diabetes. This observation has driven many studies to determine whether interventions to tighten glucose level control during hospitalisation in those with known diabetes and in those with so-called 'stress hyperglycaemia' improve these parameters. Whilst the evidence has been mixed, the current general consensus is that aiming for very tight control may actually be harmful. This has been attributed to increased rates of hypoglycaemia. Therefore on this background, this current study is of interest. Closed-loop technology with glucose sensors paired with insulin pumps are receiving a lot of interest in community management of people with type 1 diabetes. Here, the same concepts are applied to in-hospital management of those with type 2 diabetes. The results show improved control with less time hyperglycaemic, and no increase in hypoglycaemia. This is encouraging, but the real question is given the cost of such management, did this reduce length of stay or improve outcomes?

Reference: N Engl J Med 2018;379:547–56
Abstract

Smoking cessation, weight change, type 2 diabetes, and mortality

Authors: Hu Y et al.

Summary: This analysis included data from 171,150 men and women enrolled in the US Nurses' Health Study, the Nurses' Health Study II and the Health Professionals Follow-Up Study to determine whether bodyweight gain after smoking cessation attenuates the health benefits of quitting. The researchers identified study participants who had reported quitting smoking and prospectively assessed changes in smoking status and bodyweight. Smoking cessation-related diabetes risk was greater among recent quitters (2–6 years since smoking cessation) compared with current smokers (HR 1.22 [95% CI 1.12, 1.32]); the risk peaked 5–7 years after quitting and then gradually decreased. The temporary increase in the risk of type 2 diabetes was directly proportional to bodyweight gain; no increased risk was seen among quitters who did not gain bodyweight (p<0.001 for interaction). Quitters did not have a temporary increase in mortality, regardless of bodyweight change after quitting. Compared with current smokers, the respective HRs for death from CV disease among recent quitters without bodyweight gain and those with bodyweight gains of 0.1–5.0kg, 5.1–10.0kg and >10.0kg were 0.69 (95% CI 0.54, 0.88), 0.47 (0.35, 0.63), 0.25 (0.15, 0.42) and 0.33 (0.18, 0.60), and among longer term quitters (>6 years since smoking cessation), the HR was 0.50 (0.46, 0.55). Similar associations were seen for all-cause mortality.

Comment: One of the unwanted consequences of stopping smoking is frequently weight gain. For many smokers the reason they continue to smoke or restart again after quitting is control of weight. This study asks the very important question whether weight gain following stopping smoking offsets the gains in health from quitting. The results are compelling. Although the weight gain proportionately increases the risk of developing diabetes, this adverse effect peaks at 5–7 years and then declines. However, despite weight gain, the benefits of stopping smoking on CV and all-cause mortality are not significantly impacted by weight gain. This reinforces the very simple and important message that in smokers, stopping smoking is probably the most important single intervention that they can do to improve their long-term health.

Reference: N Engl J Med 2018;379:623–32
Abstract

Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes

Authors: Rawshani A et al.

Summary: Reductions in excess deaths and CV events were explored for a cohort of 271,174 Swedish registry patients with type 2 diabetes and 1,355,870 matched controls. There were 175,345 deaths during median follow-up of 5.7 years. Stepwise decreases were seen among patients with type 2 diabetes for the excess risks of death, acute MI, stroke and HF hospitalisation for each evaluated risk-factor variable, namely Hb_{A1c} level, low-density lipoprotein cholesterol level, albumin level, smoking status and BP, within the target range. Compared with controls, patients with type 2 diabetes who had all five of these variables within target ranges had an increased risk of death from any cause (HR 1.06 [95% CI 1.00, 1.12]), a lower risk of acute MI (0.84 [0.75, 0.93]) and no difference for the risk of stroke (0.95 [0.84, 1.07]). The HF hospitalisation risk was consistently higher among patients with diabetes than controls (HR 1.45 [95% CI 1.34, 1.57]). The strongest predictor of acute MI and stroke in the patients with type 2 diabetes was an Hb_{A1c} level not in target, and the strongest predictor of mortality was smoking.

Comment: This large Swedish registry study in people with type 2 diabetes asks the important question whether the known increased risk of adverse CV outcomes associated with having type 2 diabetes is reduced or eliminated by achieving targets for glucose, BP, lipids and smoking. We have plenty of evidence from studies like the UKPDS and Steno 2 amongst others that targeting these parameters reduces the risk in highly controlled intervention trials, but does that translate to the real world and can the risk be completely eliminated? With the notable exception of admissions for HF, the answer is yes! Those who achieved targets had no excess risk of other outcomes. This study is of course open to many confounding variables that may have important contributions to this outcome, such as other patient or system variables that influence the probability of attaining the targets. Nonetheless, it is useful information to underpin patient discussions about the benefit of targeting goals in each of the risk factor areas. Now what about HF? Apparently there is a 'new' diabetes drug that is particularly good at reducing that outcome too. Just saying Pharmac.

Reference: N Engl J Med 2018;379:633–44
Abstract

Prognostic implications of single-sample confirmatory testing for undiagnosed diabetes

Authors: Selvin E et al.

Summary: The prognostic utility of a single-sample confirmatory definition of undiagnosed diabetes (fasting glucose level ≥7.0 mmol/L [126 mg/dL] and Hb_{A1c} level ≥6.5% from a single blood sample) was explored in a prospective cohort of 13,346 participants from the Atherosclerosis Risk in Communities study over 25 years of follow-up. Among participants without diagnosed diabetes (n=12,268), 978 had an elevated fasting glucose or Hb_{A1c} level at baseline, and of these, 39% had both, meeting study criteria for undiagnosed diabetes, leaving the rest classified as unconfirmed undiagnosed diabetes. The respective sensitivity and specificity values of the confirmatory definition for identifying cases of diabetes during the first 5 years of follow-up were 54.9% and 98.1%, with the specificity value increasing to 99.6% by 15 years. The 15-year positive predictive value was 88.7% versus 71.1% for unconfirmed cases. Significant associations were seen between confirmed undiagnosed diabetes and CV disease, kidney disease and mortality, and these were stronger than those seen with unconfirmed diabetes.

Comment: This area is a pet love and hate of mine at the same time. At the heart of it is the question 'what is diabetes?' Any study that purports to answer whether a specific test, combination of tests or single, duplicate or stepwise testing is better than another is ultimately flawed, because there is no single reference method or gold standard test. Each of the current methods is a biological continuum to which we impose arbitrary and controversial cutoff points with various justifications, mainly derived from observed risks of microvascular and or macrovascular complications. Furthermore, each has inherent measurement error and biological variability. I get very annoyed when people claim that one test is superior to another, when none can perfectly separate out those at risk from those not at risk of these complications, and therefore none can truly be considered the reference method. There is no doubt that each method defines a slightly different group of individuals, with overlap but also with discrepancy, at least at the lower levels. No doubt there will continue to be debate and changes in criteria over the years. With my pragmatist hat on, I support the use of Hb_{A1c} level as a screening test because of its simplicity and ability to perform on a nonfasting sample. This alone helps to reduce inequity, and when the risks of diabetes and its complications are greatest in Māori, Pacific, Indian and areas of high deprivation, this has got to be a priority.

Reference: Ann Intern Med 2018;169:156–64
Abstract

Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care

Authors: O'Brien R et al.

Summary: Relationships between bariatric surgery and incident microvascular complications of type 2 diabetes were explored in a retrospective cohort of 4024 adults who had undergone bariatric surgery (76% gastric bypass, 17% sleeve gastrectomy and 7% adjustable gastric banding) and 11,059 matched controls. Compared with the nonsurgical controls, bariatric surgery recipients had a significantly lower risk of incident microvascular disease at 5 years (16.9% vs. 34.7%; adjusted HR 0.41 [95% CI 0.34, 0.48]) and lower 5-year cumulative incidences of diabetic neuropathy (7.2% vs. 21.4%; 0.37 [0.30, 0.47]), nephropathy (4.9% vs. 10.0%; 0.41 [0.29, 0.58]) and retinopathy (7.2% vs. 11.2%; 0.55 [0.42, 0.73]).

Comment: Bariatric surgery is an excellent treatment for type 2 diabetes. Multiple studies, including RCTs comparing surgery with optimal medical management, have demonstrated that bariatric surgery dramatically improves glucose control, to the point that many people have normal glycaemia off all medication. Some call this 'cure', but as this current study reinforces, I don't think we can think of it in that way. Although glycaemia is normalised or improved, the accumulated risk of micro- and macrovascular complications accrued prior to surgery is not completely eliminated. This study shows that these risks are significantly reduced. One important message to take from this study is that even if glucose levels are normalised after surgery, individuals should continue to be screened for complications of diabetes.

Reference: Ann Intern Med 2018;169:300–10
Abstract

Intergenerational changes in adolescents' physical fitness and weight in New Zealand

Authors: McAnally HM et al.

Summary: Fitness parameters and bodyweights were compared for cohorts of two generations of adolescents (968 aged 15 years from the Dunedin Study and 343 of their children aged 15–16 years from the Next Generation Study) in this research to determine continuity and changes across the two generations. On average, participants from the Next Generation adolescents had been heavier and had a higher BMI than those from the Dunedin Study. There was no significant difference between the generations for unadjusted VO_{2max} values for boys, but girls from the Next Generation cohort had lower values than those from the Dunedin Study. After adjustment for bodyweight, VO_{2max} values in the Next Generation cohort were 25% lower for girls and 15% lower for boys compared with their parents.

Comment: Back in my day… This study provides evidence of what we all suspect. We are breeding a bunch of lazy teenagers, and we weren't! This is a nice study that deals with some of the confounding that would occur if we simply compared two age cohorts. The use of the offspring of the first cohort as the comparator to some extent accounts for the genetic effect, and suggests a more environmental factor at play in the observed differences in fitness seen in the younger generation. The findings raise the question, what is driving the differences, and the father of a teenage boy in me observes in a trial of n=1 that screen time, social media and transport options are key factors. Of course there may be bias in that assessment!

Reference: N Z Med J 2018;131(1482):16–28
Abstract

Canagliflozin and renal outcomes in type 2 diabetes

Authors: Perkovic V et al.

Summary: This was an exploratory analysis of renal outcomes from the two CANVAS trials, which together randomised 10,142 patients with type 2 diabetes and a high risk of CV events to receive canagliflozin (100mg or 300mg) or placebo. Compared with placebo, canagliflozin recipients had: i) a lower rate of a composite outcome of sustained doubling of serum creatinine level, end-stage kidney disease and death from renal causes (1.5 vs. 2.8 per 1000 patient-years; HR 0.53 [95% CI 0.33, 0.84]), a finding that was consistent across prespecified patient subgroups; ii) a slower decline in annual estimated GFR; iii) a lower mean urinary albumin-to-creatinine ratio; and iv) no significant difference for serious renal-related adverse events (2.5 vs. 3.3 per 1000 patient-years; 0.76 [0.49, 1.19]).

Comment: There really is quite a buzz around the SGLT-2 inhibitors. Whilst there is always a risk of overestimating and overstating the benefits of a new class of drugs, and the appearance of more side effects with greater use in a wider range of patients than the carefully selected clinical trials, all the evidence so far points to some real advantages of the SGLT-2 inhibitors over some other classes of antidiabetic drugs. The two primary ones being a reduction in presentation with HF and, as reported here with canagliflozin as the example, a reduced risk of adverse renal outcomes. Time will tell whether this is a class effect, as more evidence from the phase 3 trial programmes for each of the agents comes through, but to date it does appear to be the case. It is notable that in the latest consensus document from the ADA and EASD released this month that in patients with established HF or renal impairment, SGLT-2 inhibitors are now the recommended second-line agents after metformin. Again, just saying Pharmac.

Reference: Lancet Diabetes Endocrinol 2018;6:691–704
Abstract