Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 136 – 2020

In this issue:

Abbreviations used in this issue

BMI = body mass index
CGM = continuous glucose monitoring
CV = cardiovascular
GDM = gestational diabetes mellitus
GFR = glomerular filtration rate
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
SGLT = sodium glucose cotransporter
SMBG = self-monitoring of blood glucose

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Welcome to issue 136 of Diabetes and Obesity Research Review.

This issue begins with research reporting a nearly 10-fold increased risk of developing type 2 diabetes in women who have experienced GDM (gestational diabetes mellitus). There is also research reporting that women who used real-time CGM achieved better daytime glucose level control than those who used SMBG. Supporting the ongoing call for funding of GLP-1 receptor agonists and SGLT-2 inhibitors in NZ is a large study from Denmark showing that sulfonylureas are not the safest second-line treatment option in type 2 diabetes; a GLP-1 receptor agonist added to metformin provided lower risks of major adverse CV events, severe hypoglycaemia and all-cause mortality (however, we do need to be mindful of a small increase in the risk of diabetic ketoacidosis with SGLT-2 inhibitors). This issue concludes with research providing some insights into the behavioural changes that patients with type 2 diabetes experience when they participate in a weight management intervention based on a very low energy diet.

As always, we encourage you to send us your much appreciated feedback and comments.

Best regards,

Professor Jeremy Krebs
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Progression to type 2 diabetes in women with a known history of gestational diabetes

Authors: Vounzoulaki E et al.

Summary: This systematic review and meta-analysis of 20 observational studies (n=1,332,373) with ≥12 months of postpartum follow-up evaluated progression to type 2 diabetes in women with GDM compared with those who were normoglycaemic during pregnancy. The incidence of type 2 diabetes was significantly greater in women with previous GDM than in healthy controls (relative risk 9.51 [95% CI 7.14, 12.67]). The cumulative incidence of type 2 diabetes after GDM was 16.46% in women of mixed ethnicity, 15.58% in a predominantly non-white population, and 9.91% in a white population, with no significant between-group differences. The findings were not affected by age, BMI, year of publication or length of follow-up.

Comment: It is well known that GDM is a risk factor for type 2 diabetes later in life, but estimates of the actual risk vary considerably depending on the population studied. This meta-analysis of almost 70,000 women with GDM showed a relative risk of later type 2 diabetes of nearly 10. The range of relative risks in the studies was as low as 2.19 in an Iranian study with 15 years of follow-up to 25 in a UK study with 25 years of follow-up. The authors reported no difference between ethnicities as broken down to white versus non-white, which I found surprising. However, when looking at the populations included in the studies, there were very few with populations similar to NZ, no NZ studies and not surprisingly none likely to have significant numbers of Māori or Pacific women. It is clear that GDM is an important risk factor, and therefore an important opportunity to prevent future type 2 diabetes. We need more work in NZ to know our own long-term rates, and interventions to prevent conversion to type 2 diabetes.

Reference: BMJ 2020;369:m1361
Abstract

Slowed metabolic decline after one year of oral insulin treatment among individuals at high risk for type 1 diabetes in the Diabetes Prevention Trial-Type 1 and TrialNet Oral Insulin Prevention trials

Authors: Sosenko JM et al., for the Type 1 Diabetes TrialNet Study Group

Summary: The impact of >1 year of treatment with oral insulin on the slowing of metabolic decline was evaluated in participants from the Diabetes Prevention Trial-Type 1 and TrialNet trials. Among participants at high risk for type 1 diabetes (DTPRS [Diabetes Prevention Trial Risk Score] ≥6.75), the oral insulin recipients had significant increases from baseline in C-peptide level and C-peptide/glucose level areas under the curves at 1 year, compared with the placebo recipients. No significant differences were seen for these measures among participants with DPTRS <6.75.

Comment: There is always great hope that the next prevention trial in people demonstrated to be at risk of developing type 1 diabetes will be the one. Such was the hope with the oral insulin trials, but the results were disappointing. As is often the case when you combine datasets and have larger numbers in order to drill down a bit more, additional findings come to light. Here the combined data from the oral insulin studies, when analysed by a somewhat arbitrary risk score for development of type 1 diabetes, showed that for those at higher risk of type 1 diabetes, oral insulin does appear to have some benefit in delaying the inevitable. That may sound pessimistic, but the reality is that what people want is true prevention of disease, not simply a few more months before they need to go on insulin for the rest of their lives. These are interesting data, but it's back to the drawing board for a real prevention strategy.

Reference: Diabetes; Published online May 21, 2020
Abstract

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Research Review publications are intended for New Zealand health professionals.

Continuous glucose monitoring in pregnancy: importance of analyzing temporal profiles to understand clinical outcomes

Authors: Scott EM et al., on behalf of the CONCEPTT Collaborative Group

Summary: These researchers applied standard summary metrics and a functional data analysis to SMBG (n=100) and real-time CGM (n=100) data recorded at baseline and 24 and 34 weeks' gestation in the CONCEPTT trial to determine temporal differences in 24-hour glucose level profiles. Compared with participants randomised to SMBG, those assigned to real-time CGM had significantly lower glucose levels (0.4–0.8 mmol/L, or 7–14 mg/dL) for 7 hours per day (0800–1200h and 1600–1900h). Glucose levels were higher (0.4–0.9 mmol/L, or 7–16 mg/dL) for 12 hours per day (0300–0600h, 1300–1800h and 2030–0030h) at 24 weeks but not 34 weeks' gestation among participants who used insulin pumps compared with those who used MDIs. Glucose levels were also higher in women who gave birth to large-for-gestational age infants by: 0.4–0.7 mmol/L, or 7–13 mg/dL, for 4.5 hours per day at baseline; 0.4–0.9 mmol/L, or 7–16 mg/dL, for 16 hours per day at 24 weeks' gestation; and 0.4–0.7 mmol/L, or 7–13 mg/dL, for 14 hours per day at 34 weeks' gestation.

Comment: With increasing technology in diabetes management in pumps and CGM devices, with associated incremental costs compared with injectable insulin and finger prick monitoring, there are important questions to ask about the optimal utility of these devices. Insulin pumps have been in use for several decades and are continually being refined for functionality. More recently, CGM has become mainstream, and there is increasing demand from consumers and pressure from industry to utilise and fund these devices. Therefore this study is of interest, comparing the impact of either technology on maternal glucose levels and foetal size in pregnancies in women with type 1 diabetes. As has been seen in some nonpregnancy studies, CGM may have a greater beneficial impact than pump therapy. In NZ pumps are funded and CGM is not. Perhaps its time to review that.

Reference: Diabetes Care 2020;43:1178–84
Abstract

Risk of major adverse cardiovascular events, severe hypoglycemia, and all-cause mortality for widely used antihyperglycemic dual and triple therapies for type 2 diabetes management

Authors: Jensen MH et al.

Summary: Major adverse CV events, severe hypoglycaemia and all-cause mortality with antihyperglycaemic dual and triple therapies were investigated in a cohort of 66,807 real-world patients with type 2 diabetes in Denmark who received metformin plus second- and third-line therapies. Metformin plus sulfonylurea recipients had the highest risks of major adverse CV events and all-cause mortality, whereas metformin plus basal insulin recipients had the highest risk of hypoglycaemia. Recipients of GLP-1 receptor agonist-containing regimens had the lowest risk of major adverse CV events. Compared with metformin plus basal insulin recipients, those who additionally received a GLP-1 receptor agonist had a lower risk of all three endpoints, especially severe hypoglycaemia. The lowest risk of all three endpoints was seen in recipients of a combination of metformin, an SGLT-2 inhibitor and a GLP-1 receptor agonist.

Comment: …and so the evidence mounts. For many years there has been doubt about the CV safety of sulfonylureas, but they have remained the second-line agent in type 2 diabetes after metformin. Let's face it, they are cheap. Despite newer, more expensive agents becoming available, in NZ we have been largely limited to metformin, sulfonylureas and insulin. With increasing evidence for the CV and renal benefits of the GLP-1 receptor agonists and SGLT-2 inhibitors, PHARMAC is now looking to fund these agents, which is a great relief. This is further supported by this study of real-world data from Denmark, which demonstrates that ideally we should not be using sulfonylureas as second-line drugs, and that, as per the ADA/EASD guideline, SGLT-2 inhibitors or GLP-1 receptor agonists should be preferred. Let's hope those negotiations between PHARMAC and Pharma are going well.

Reference: Diabetes Care 2020;43:1209–18
Abstract

Independent commentary by Professor Jeremy Krebs
MBChB, FRACP, MD

Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He is a Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established.

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Renal and cardiovascular outcomes after weight loss from gastric bypass surgery in type 2 diabetes: cardiorenal risk reductions exceed atherosclerotic benefits

Authors: Liakopoulos V et al.

Summary: Renal and CV outcomes were compared between 5321 patients with type 2 diabetes who had undergone bariatric surgery and 5321 matched patients with type 2 diabetes who had not. Patients who had undergone gastric bypass experienced small decreases in creatinine level and albuminuria with stable estimated GFRs during the first postsurgical years, and they had lower incident rates of most renal function, CV and mortality outcomes; the risks of heart failure and CV-related death were particularly reduced (respective hazard ratios 0.33 [95% CI 0.24, 0.46] and 0.36 [0.22, 0.58]). Gastric bypass recipients also had reduced risks of a composite of severe renal disease or halved estimated GFR (hazard ratio 0.56 [95% CI 0.44, 0.71]) and nonfatal CV events (0.82 [0.70, 0.97]). Gastric bypass was associated with generally reduced risks for key outcomes across estimated GFR strata, including <30 mL/min/1.73m^2.

Comment: I haven't included many studies on bariatric surgery in recent reviews, but this paper caught my eye. It shows the value of 'big data' and the ability to combine sources of data. In this Scandinavian study, the authors used data from diabetes and surgical registries combined with medical services to explore CV and renal outcomes after gastric bypass surgery. Although this is therefore a retrospective and case-matched observational study rather than a prospective randomised trial, the findings are still notable and consistent with other data from bariatric surgery. All of the CV and renal parameters studied were dramatically better in those who had undergone gastric bypass. Why this caught my eye, is that the figures are remarkably similar to the data from the SGLT-2 studies reported in the last couple of years – it is tempting to ponder whether there may be similar mechanisms at play.

Reference: Diabetes Care 2020;43:1276–84
Abstract

Whole-grain processing and glycemic control in type 2 diabetes

Authors: Åberg S et al.

Summary: Adults with type 2 diabetes were randomised in a crossover manner to two 2-week interventions of normal grain food consumption and replacing this with nutrient-matched whole-grain products of wheat, oats and brown rice that differed in their degree of processing; 28 of the 31 enrolled participants completed both interventions. The participants also wore CGM systems, and were provided with no other lifestyle advice. There was no significant difference between the interventions for increase in alkylresorcinol levels or reported energy intake. Compared with consumption of meals of finely milled grains, consumption of less-processed whole-grain meals was associated with 9% and 6% reductions in postprandial glucose level response following breakfast and all meals, respectively, and a reduction in 24-hour glycaemic variability. Mean bodyweight increased during the finely milled intervention and decreased during the less-processed whole-grain intervention, with a difference of 0.81kg between interventions; bodyweight changes were not a mediating factor for the glycaemic variables considered.

Comment: While there is constant media attention to dietary variation in macronutrient composition, carbohydrate content particularly, the importance of dietary fibre and degree of processing is often overlooked. This NZ research keeps this issue on the table. This neatly designed, short intervention crossover study compared the effect of processing on the effect of whole grains on glucose metabolism in people with type 2 diabetes. Even over just 2 weeks, there was a significant difference in weight, and there were benefits in glycaemic variables that were independent of the weight change. These data highlight again that the quality of carbohydrate is a very important aspect of the health effects of the quantity consumed.

Reference: Diabetes Care; Published online May 18, 2020
Abstract

Regression from prediabetes to normal glucose levels is more frequent than progression towards diabetes

Authors: Lazo-Porras M et al.

Summary: The CRONICAS cohort study estimated the prevalence of prediabetes among its participants (who were from four diverse geographical settings in Peru) according to different definitions, and evaluated factors associated with regression to normal glycaemia or progression to type 2 diabetes. The respective baseline prevalences of prediabetes according to the WHO, ADA and UK NICE criteria were 6.5%, 53.6% and 24.6%, and the respective ranges for the cumulative 2-year incidences of regression to euglycaemia and progression to type 2 diabetes were 31.4–68.9% and 5.5–28.8%. Age, BMI and insulin resistance were the factors associated with regression to normal glucose levels and progression to diabetes.

Comment: …messy, messy, messy. Conceptually, the notion of progression from normal, through prediabetes to type 2 diabetes makes sense. The problem is that we try to place cutoffs to define these states when in reality it is a biological continuum. This is highlighted when comparisons are made between different criteria, as was done very elegantly in this paper. The rates of prediabetes and type 2 diabetes are much higher when using the ADA criteria compared with the WHO criteria, because the cutoffs are set lower. The concept of a biological continuum is further highlighted in this paper with demonstration of high rates of regression from abnormal to normal states even without active intervention. These data must be taken into account when interpreting data of studies reporting the impact of interventions designed to achieve regression to normal glycaemia, and reinforce the importance of a controlled trial design. These data also have important implications when designing health systems to monitor and/or intervene at an individual as opposed to a population level for the early stages of prediabetes.

Reference: Diabetes Res Clin Pract 2020;163:107829
Abstract

Text message intervention for teens with type 1 diabetes preserves HbA1c

Authors: McGill DE et al.

Summary: Patients aged 13–17 years with type 1 diabetes were randomised using a 2×2 factorial design to a problem-solving intervention aimed at improving type 1 diabetes self-care for blood glucose level monitoring and insulin bolus dosing ('Teenwork'), text reminders (to check blood glucose levels), the problem-solving intervention plus text reminders or usual care. HbA_{1c} level changes from baseline to 12 months (primary outcome) did not differ significantly between the study groups. There was evidence of responsiveness to text reminders in both groups in which they were included for predicting glycaemic benefit.

Comment: Anyone working with young adults with type 1 diabetes will agree that this is a particularly challenging age to have diabetes and to do well. There are so many challenges that young people face that do not go well with good glycaemic control. It is often suggested that use of mobile phone technology is a useful mechanism to assist with management in this age group, and here is another study to test this. One of the main challenges that health professionals face is getting the message that glucose level testing is important and one of the main tools to achieving good control. Reminder text messaging seems like a logical tool to assist with this. Whilst in some cases it is helpful, the impact is not as great as we would like to see. Sadly that is shown again in this study. Although spun to be more impressive, the impact of text messaging reminders is not a game changer. Most studies of text messaging conclude a short-term benefit, but saturation and decline of effect over time.

Reference: Diabetes Technol Ther 2020;22:374–82
Abstract

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Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes

Authors: Liu J et al.

Summary: This was a systematic review and meta-analysis of 39 randomised controlled trials assessing the effects of SGLT-2 inhibitors on diabetic ketoacidosis (85 events) in 60,580 patients with type 2 diabetes. There was high-quality evidence that compared with controls, SGLT-2 inhibitor use was associated with an increased risk of diabetic ketoacidosis (0.18% vs. 0.09%; odds ratio 2.13 [95% CI 1.38, 3.27]); the results of sensitivity analyses were similar, and the relative effect was greater in patients aged ≥60 years and those who had used SGLT-2 inhibitors for >52 weeks.

Comment: As the data for the benefits of SGLT-2 inhibitors mount and there is high probability (I would like to say certainty) that we will finally get funded access to them in NZ, it is important to ensure that we remember and are aware of the potential side effects. Perhaps the most important is ketoacidosis. This meta-analysis reviewed the evidence for an increased risk of ketoacidosis in type 2 diabetes. Whilst there is a doubling of risk in those taking an SGLT-2 inhibitor compared with not, the absolute risk still remains very low. Clearly it is important to ensure that patients are aware of the risk and to be aware of the possibility in acute situations; however, the benefits are such that it is equally important not to overstate the risk.

Reference: Diabetes Obes Metab; Published online May 4, 2020
Abstract

Behaviour change during dietary type 2 diabetes remission: a longitudinal qualitative evaluation of an intervention using a very low energy diet

Authors: Rehackova L et al.

Summary: These researchers conducted semistructured interviews with 18 individuals with type 2 diabetes who participated in a weight loss intervention of a very low energy diet for 2 months followed by a 6-month structured weight maintenance phase; the interviews were conducted at baseline and after each phase of the intervention, and 11 participants completed all three interviews. The respondents identified the following four themes of change in their narratives: i) 'building behavioural autonomy' (increasing confidence to engage in health behaviours that are not dependent on those of others; ii) 'behavioural contagion' (how one's new health behaviours affect those of others); iii) 'from rigid to flexible restraint' (reflecting the attitudinal and behavioural changes needed to successfully adapt from weight loss to weight maintenance); and iv) 'shift in identity' (representing changes in self perception).

Comment: Achieving weight loss through diet or physical activity is fundamentally all about behavioural change. Hidden within most dietary intervention studies are individuals who do very well and others who do poorly with any prescribed diet. Much of this variation is determined by aspects of personal response to behavioural change rather than the actual elements of the diet. This study adds some insight into the elements that are important to sustained behavioural change and therefore success of dietary intervention. Although studied in the setting of a very low calorie diet, it is likely the same themes apply more universally to weight loss diets.

Reference: Diabet Med 2020;37:953–62
Abstract

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