Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 137 – 2020

In this issue:

Abbreviations used in this issue

BMI = body mass index
BP = blood pressure
CGM = continuous glucose monitoring
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
RCT = randomised controlled trial
RYGB = Roux-en-Y gastric bypass
SGLT = sodium glucose cotransporter

Welcome to issue 137 of Diabetes and Obesity Research Review.

This issue begins with a paper comparing CGM with standard glucose level monitoring in adolescents and young adults with type 1 diabetes. Some of the other papers selected for this issue focus on the relationship between obesity and type 2 diabetes risk. One reports a significantly increased risk of type 2 diabetes in early adulthood in individuals who are severely obese during adolescence – a finding that while hardly surprising needs to be considered in the context of the increasing number of adolescents who are obese. Meanwhile, the contribution of obesity to type 2 diabetes risk has been highlighted by a large Danish study, which found that obesity was associated with a greater risk for type 2 diabetes than either lifestyle or genetic predisposition. This issue concludes with a paper looking into differences in bodyweight loss after RYGB versus vertical sleeve gastrectomy according to preoperative desire for consuming sweetened beverages.

We hope you find these and the other selected papers interesting, and we look forward to receiving any feedback you may have.

Best regards,

Professor Jeremy Krebs
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Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes

Authors: Laffel LM et al., for the CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group; CDE10

Summary: Adolescents and young adults with type 1 diabetes were randomised to CGM (n=74) or usual care using a blood glucose meter for glucose level monitoring (n=79) in this trial; 93% of the participants completed the study, and 68% of the CGM group used it for ≥5 days per week during the sixth month. Compared with usual care, CGM was associated with a greater reduction in HbA_{1c} level at 26 weeks (adjusted between-group difference, –0.37% [p=0.01]), along with significant differences in three of seven binary HbA_{1c} level outcomes, eight of nine CGM metrics and one of four patient-reported outcomes. There were three severe hypoglycaemic events in the CGM group and two in the usual care group, hyperglycaemia/ketosis occurred in one participant from the CGM group and four from the usual care group, and diabetic ketoacidosis occurred in three participants from the CGM group and in one from the usual care group.

Comment: Anyone working with adolescents and young adults with type 1 diabetes knows that they can be a challenging group. Perhaps more than other age groups with diabetes, finger prick testing frequently goes out the window. Therefore, continuous subcutaneous glucose monitoring could offer an ideal way of maintaining data to guide insulin dosing. Anecdotally we have all seen people for whom CGM has been the tool that has made the difference and enabled a young adult to achieve excellent control. It was therefore with hope and expectation that I read this paper. Unfortunately whilst the outcome is a statistically significant improvement in HbA_{1c} level compared with finger-prick testing, the magnitude is not going to excite PHARMAC to fund them for everyone with type 1 diabetes. We need a way to differentiate those who benefit the most and target funding for them.

Reference: JAMA 2020;323:2388–96
Abstract

Intermittent energy restriction is comparable to continuous energy restriction for cardiometabolic health in adults with central obesity

Authors: Pinto AM et al.

Summary: The Met-IER trial randomised 43 nonsmokers aged 35–75 years to an intermittent energy restriction diet (2 days of 600 kcal/day followed by 5 days of healthy eating advice) or a continuous energy restriction diet (–500 kcal/day healthy eating advice) for 4 weeks. Compared with the intermittent energy restriction diet, the continuous energy restriction diet was associated with a decrease in fasting plasma glucose levels (mean difference, –4.8% [p<0.05]) and higher fasting plasma nonesterified fatty acid levels (mean difference, 0.15 mmol/L [p<0.005]), but no significant difference for the primary outcome of revised quantitative insulin sensitivity check index score, which increased in both groups, or for bodyweight loss (–2.6% vs. –2.9% [p=0.464]), lipid levels, adipokine/inflammatory markers, ambulatory BP or heart rate variability.

Comment: The concept of intermittent fasting as a means to reduce total energy intake over time and thus promote weight loss has become a popular option in weight management for those who are overweight generally and also in those with diabetes. There are theoretical reasons why each may have greater benefits on the components of glucose metabolism. This study examined the relative effects of continuous versus intermittent energy restriction designed to achieve the same reduction in total energy, on markers of glucose metabolism. Both achieved similar weight loss. The small diametrically opposed differences in fasting glucose and fatty acid levels are difficult to explain, with the overall results suggesting similar metabolic effects, with the achievement of weight loss the driver to change rather than the approach.

Reference: Clin Nutr 2020;39:1753–63
Abstract

Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes

Authors: Zhang Y et al.

Summary: This was a systematic review with meta-analysis of eight RCTs (n=4896) comparing vitamin D supplementation with placebo with respect to the development of new-onset type 2 diabetes in individuals with prediabetes. Compared with placebo, supplementation of vitamin D was associated with a significant reduction in the risk of developing type 2 diabetes (risk ratio 0.89 [95% CI 0.80, 0.99]), a benefit that was restricted to nonobese participants (0.73 [0.57, 0.92]) and not those who were obese (0.95 [0.84–1.08]; p=0.048 for interaction); vitamin D supplementation was also associated with a greater proportion of participants who reverted from prediabetes to normoglycaemia (21.2% vs. 14.1%; risk ratio 1.48 [1.14, 1.92]).

Comment: Vitamin D deficiency has been blamed for many health problems, and supplementation the panacea. However, well-conducted RCTs to back up the observational studies have largely failed to confirm the findings. This systematic review and meta-analysis looked at the RCTs examining the effects of vitamin D supplementation on risk of developing type 2 diabetes and or reversion of prediabetes. The findings do support the use of supplementation overall, but there may be important differences in response between those who are obese versus normal weight. It is interesting to hypothesise why such a difference may be relevant. Vitamin D is a fat soluble vitamin, which could suggest that baseline body stores may be higher in obese individuals. Conversely, the pathogenesis of diabetes in nonobese individuals may be more related to pancreatic insulin deficiency rather than insulin resistance, which may be where vitamin D has a role. This is worthy of more research.

Reference: Diabetes Care 2020;43:1650–8
Abstract

For more information, please go to www.medsafe.govt.nz

Adolescent obesity and early-onset type 2 diabetes

Authors: Twig G et al.

Summary: The relationship between adolescent obesity and incident type 2 diabetes during early adulthood was explored in this Israeli population-based study of 1,462,362 individuals who were adolescents during 1996–2016. A total of 2177 individuals developed type 2 diabetes over 15,810,751 person-years, with a significant interaction among BMI, sex and incident type 2 diabetes (p=0.023). The likelihood of developing type 2 diabetes was increased for individuals in the 50th–74th percentile, 75th–84th percentile, overweight, mildly obese and severely obese BMI subgroups for men (respective adjusted hazard ratios 1.7 [95% CI 1.4, 2.0], 2.8 [2.3, 3.5], 5.8 [4.9, 6.9], 13.4 [11.5, 15.7] and 25.8 [21.0, 31.6]) and women (2.2 [1.6, 2.9], 3.4 [2.5, 4.6], 10.6 [8.3, 13.6], 21.1 [16.0, 27.8] and 44.7 [32.4, 61.5]). There was an inverse graded relationship between baseline BMI and mean age at type 2 diabetes diagnosis (for men and women, respectively, 27.8 and 25.9 years for severe obesity and 29.5 and 28.5 years for the 5th–49th [reference] percentile). The respective projected proportions of adult-onset type 2 diabetes attributable to ≥85th BMI percentile at adolescence for men and women were 56.9% and 61.1%.

Comment: It's not new to show that obesity increases the risk of type 2 diabetes. Similarly, we know that the age of diagnosis of diabetes is decreasing and in NZ this is particularly true for Pacific people as well as Māori. This study from Israel reports the relative risks of developing diabetes as young adults for those who are overweight or obese in adolescence. Not surprisingly, the relative risk for severe obesity is 25-fold in men and 44-fold in women. This is consistent with many other datasets. It must be noted however that the absolute risk of developing diabetes across the group was only 0.1%. Thus, while this is important at a population level for wide-scale interventions to prevent obesity in adolescents and young adults, the relative risks in isolation paint an overly dramatic picture. However, note the later study in this issue that shows that obesity trumps all in terms of risk of developing diabetes eventually.

Reference: Diabetes Care 2020;43:1487–95
Abstract

The association between age of onset of type 2 diabetes with the long-term risk of end-stage kidney disease

Authors: Morton JI et al.

Summary: The effect of age of type 2 diabetes onset on the cumulative incidence of end-stage kidney disease was estimated using data from 1,113,201 patients with type 2 diabetes entered in an Australian registry. Between 2002 and 2013 (7,839,075 person-years of follow-up), 7592 incident cases of end-stage kidney disease were recorded. During the first 10–15 years following the onset of diabetes, the highest incidence of end-stage kidney disease was seen in patients with an older age of diabetes onset, whereas the incidence increased among those with younger-onset diabetes over longer durations of diabetes. After 40 years of diabetes, the respective cumulative incidences of end-stage kidney disease in patients diagnosed with diabetes at ages 10–29 years and 30–39 years were 11.8% and 9.3%. When death from end-stage kidney disease without renal replacement therapy was considered, a higher incidence of end-stage kidney disease persisted in patients with older-onset diabetes for the initial 20 years, with no clear age effect thereafter.

Comment: Diabetic nephropathy and end-stage kidney disease are some of the complications of diabetes that patients most fear. They are associated with major morbidity and mortality and are very costly for individuals and the health system. This paper looks at the incidence of kidney disease in Australia and shows that short term, the highest incidence was in those of older age at diagnosis of diabetes. However, over time younger age at diagnosis and therefore longer duration of exposure to risk factors of hyperglycaemia and hypertension became more important. This is highly relevant and of great concern in NZ where the mean age of diagnosis of type 2 diabetes continues to come down. Furthermore, Māori and Pacific people are at greater risk of kidney disease than Europeans, and are disproportionately represented in those diagnosed at a younger age. These observations further support aggressive management of glucose levels and BP.

Reference: Diabetes Care 2020;43:1788–95
Abstract

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Blood-based analysis of 84 microRNAs identifies molecules deregulated in individuals with type-2 diabetes, risk factors for the disease or metabolic syndrome

Authors: Avgeris M et al.

Summary: These researchers explored the profiles of 84 type 2 diabetes-related micro-RNAs in the peripheral blood of six individuals with and six without the disease. Compared with nondiabetics, individuals with type 2 diabetes had lower levels of miR-214-3p, miR-24-3p and let-7f-5p. In patients with type 2 diabetes or metabolic syndrome/type 2 diabetes risk factors, micro-RNA levels correlated with serum insulin and HbA_{1c} levels, while in controls, they correlated with higher BMI, dyslipidaemia and family history of type 2 diabetes.

Comment: Here is one for the scientists amongst you. Micro-RNAs are a class of small noncoding RNAs that are involved in the regulation of gene expression at the post-transcriptional level by degrading their target mRNAs and/or inhibiting their translation. Micro-RNAs can therefore be implicated in the pathogenesis of disease by modifying the expression of key genes; for example, the production of insulin or the insulin receptor, or downstream signalling proteins. Although they work at the tissue level, they can be isolated from circulating blood. Therefore, this gives the potential for a simple blood sample to be analysed for a range of micro-RNAs that could give a map of the particular metabolic defects at play in that individual. Ultimately this could generate targets for individualised treatments. It is an exciting area of research.

Reference: Diabetes Res Clin Pract 2020;164:108187
Abstract

What training, support, and resourcing do health professionals need to support people using a closed-loop system?

Authors: Kimbell B et al., on behalf of the CLOuD Consortium

Summary: These authors reported a descriptive analysis of responses to interviews conducted with 22 health professionals involved in the delivery of the CLOuD (Closed Loop from Onset in Type 1 Diabetes) trial after they had ≥6 months of experience supporting participants using a closed-loop system. The respondents reported that while use of the closed-loop system could be initially more time-consuming than other insulin regimens, there was less need for participant contact with the clinical team after the initial adjustment period. However, the respondents also noted that a reduced need for *ad hoc* clinical input could result in new challenges, including fewer opportunities to reinforce users' knowledge about diabetes and to detect potential psychosocial problems. They also reported that the constant availability of data increased some parents' anxiety and created unrealistic expectations regarding the systems' capabilities. The respondents generally believed that diabetes teams should be empowered to deliver closed-loop system care, but highlighted the importance of comprehensive technology training and standardised clinical guidance for health professionals to support the use of closed-loop systems.

Comment: It's out there and best we be ready! The dream of real-time closed loop technology for people with type 1 diabetes has been just that for so long, but we are right on the verge of this becoming the standard of care. The technology exists, the algorithms exist, some patients are already doing it on their own with hacked equipment, and the latest pump-sensor pairings available in NZ do half the job automatically of preventing hypoglycaemia. So how are we going to manage this change in approach to management in our clinical services? This qualitative study provides some insights taken from a clinical trial setting. One interesting observation was the stress created by the abundance of data, something we are certainly seeing with the wider use of CGM systems generally.

Reference: Diabetes Technol Ther 2020;22:468–75
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. **FOR FULL BIO CLICK HERE.**

Efficacy and tolerability of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists

Authors: Hussein H et al.

Summary: This systematic review and network meta-analysis included 64 trials (n=31,384) reporting changes in HbA_{1c} level after ~24 and/or ~52 weeks of SGLT-2 inhibitors and/or short- or long-acting GLP-1 receptor agonists for adults with type 2 diabetes; 53 trials were 24 weeks; seven were 52 weeks and four reported both 24- and 52-week outcomes. HbA_{1c} levels were improved by all treatments compared with placebo. Compared with short-acting GLP-1 receptor agonists and SGLT-2 inhibitors, long-acting GLP-1 receptor agonists were associated with reduced HbA_{1c} levels, with semaglutide associated with reductions versus placebo (–1.49 and –1.68 percentage points at 24 and 52 weeks, respectively) and all other treatments. Bodyweight and waist circumference reductions were best with long-acting GLP-1 receptor agonists, whereas SGLT-2 inhibitors were associated with reduced BP. Significant between-class differences in tolerability were more genital infections with SGLT-2 inhibitors than with long-acting GLP-1 receptor agonists (odds ratio 5.26 [95% credible interval 1.45, 25.00]), and more diarrhoea with both short- and long-acting GLP-1 receptor agonists than with SGLT-2 inhibitors (1.65 [1.09, 2.49] and 2.23 [1.51, 3.28]).

Comment: As we wait with bated breath for the outcome of the Pharmac RFP (request for proposals) for access to SGLT-2 inhibitors and GLP-1 agonists, there are more data and trials coming out informing us about their relative benefits and optimal utility. This meta-analysis examined the relative effects of the agents on glucose level, BP, weight and adverse effects. As has been previously reported, it appears that the long-acting GLP-1 agonists may have advantages over the shorter acting ones and SGLT-2 inhibitors, particularly with weight and glucose level control, whereas SGLT-2 inhibitors have the edge on BP, which may in part explain their relatively greater benefits on renal function. I can't wait till we can use them more widely in NZ.

Reference: Diabetes Obes Metab 2020;22:1035–46
Abstract

Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes

Authors: Schnurr TM et al.

Summary: The role of genetic predisposition on the associations of obesity and unfavourable lifestyle with type 2 diabetes risk was explored in 4729 individuals who developed type 2 diabetes over a median 14.7 years of follow-up (cases) and a randomly selected cohort of 5402 controls. A genetic risk score based on 193 known type 2 diabetes-associated (excluding BMI-associated) loci was used to stratify participants into low, intermediate and high genetic risk, and the lifestyle score used considered smoking status, alcohol consumption, physical activity and diet. Associations of BMI ≥30 kg/m² and unfavourable lifestyle with increased incident type 2 diabetes risk were not significantly affected by genetic predisposition. Obesity had the greatest impact on type 2 diabetes risk (hazard ratio 5.81 [95% CI 5.16, 6.55] vs. 2.00 [1.76, 2.27] and 1.18 [1.06, 1.30] for high genetic risk and unfavourable lifestyle, respectively); even obese individuals with low genetic risk and a favourable lifestyle had an 8-fold increased risk of developing type 2 diabetes compared with their normal-weight counterparts.

Comment: Many epidemiological studies have shown that the three key risk factors for developing type 2 diabetes are family history (a proxy for genetics), sedentary lifestyle and obesity. This study uses data from a larger cohort study in Denmark to test which of these factors dominates and what interaction there is between them. Using a retrospective case-control design with an approximately 15-year follow-up period, obesity came up trumps as the dominant risk factor. I must say I was surprised to see that, as I would have expected genetics to be dominant. Even in those with low genetic risk, obesity significantly increased the risk of diabetes. As the authors conclude, having a normal bodyweight is crucial to prevent diabetes. This is work in progress in NZ.

Reference: Diabetologia 2020;63:1324–32
Abstract

Preoperative liking and wanting for sweet beverages as predictors of body weight loss after Roux-en-Y gastric bypass and sleeve gastrectomy

Authors: Perez-Leighton CE et al.

Summary: Subjective liking and wanting ratings of sucrose solutions and aspartame-sweetened flavoured beverages were ascertained for 66 candidates for RYGB or vertical sleeve gastrectomy. The patients who underwent RYGB had lost more bodyweight at postoperative months 3 and 12 than those who underwent vertical sleeve gastrectomy ($p<0.001$). At both timepoints, weight loss after RYGB was greater than after vertical sleeve gastrectomy among those with a high desire for sucrose, but not aspartame, yielding a significant cluster by surgery interaction. Categorisation according to supervised classification using liking ratings for sucrose or aspartame revealed no significant bodyweight loss effects between RYGB and vertical sleeve gastrectomy.

Comment: Bariatric surgery is a highly effective treatment for obesity and diabetes. Sleeve gastrectomy is the current vogue operation, but I have my concerns about its efficacy and longevity in people with diabetes over the long term. This study is an interesting look at this issue, examining whether hedonic behaviour might predict the likelihood of response to surgery; specifically liking sweetened beverages. Perhaps not surprisingly, those who crave sugar lose less weight, and as predicted, this was more of an issue for sleeve gastrectomy. The additional component of malabsorption and risk of dumping syndrome with RYGB helps to make this more effective in weight loss – although perhaps not in satisfaction after surgery. These data should certainly be included in the preoperative discussion about type of surgery.

Reference: Int J Obes 2020;44:1350–9
Abstract

CONGRATULATIONS TO

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