Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 138 – 2020

In this issue:

Abbreviations used in this issue
CGM = continuous glucose monitoring
CV = cardiovascular
HbA_{1c} = glycosylated haemoglobin
HR = hazard ratio
RYGB = Roux-en-Y gastric bypass
SGLT = sodium glucose cotransporter
SMBG = self-monitoring of blood glucose

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Diabetes & Obesity Research Review

Welcome to issue 138 of Diabetes and Obesity Research Review.

Two studies considering the effects of healthy eating patterns in type 2 diabetes begin this issue: the first reports the impact of whole-grain food consumption on overall risk, and the second has investigated plasma biomarkers to assess the effect of fruit and vegetable intake on type 2 diabetes incidence. There is also a systematic review on diabetes outpatient appointment nonattendance, and a quantitative analysis has identified and categorised the main barriers to maintenance of bodyweight loss. The issue concludes with a trial investigating associations between time spent in hypoglycaemia and various mean glucose and HbA_{1c} levels in patients with type 1 diabetes on multiple daily insulin injections randomised to CGM or SMBG.

I hope you enjoy the research selected, and I look forward to receiving your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Intake of whole grain foods and risk of type 2 diabetes

Authors: Hu Y et al.

Summary: Data from the US Nurses' Health Study I and II (n=158,259) and Health Professionals Follow-Up Study (n=36,525) were analysed to explore associations between whole-grain food intake (five categories) and type 2 diabetes risk; 18,629 participants self-reported a diagnosis of type 2 diabetes over 4,618,796 person-years of follow-up. Compared with participants in the lowest whole-grain intake category, those in the highest category had a 29% lower rate of type 2 diabetes. Compared with consumption of <1 serving per month, type 2 diabetes risk was lower for consumption of ≥1 serving per day of whole-grain cold breakfast cereal (adjusted HR 0.81 [95% CI 0.77, 0.86]) and dark bread (0.79 [0.75, 0.83]), and for consumption of ≥2 servings per week of oatmeal (0.79 [0.75, 0.83]), brown rice (0.88 [0.82, 0.94]), added bran (0.85 [0.80, 0.90]) and wheat germ (0.88 [0.78, 0.98]). These associations were stronger in lean individuals than overweight or obese individuals (p=0.003 for interaction), and were not significantly modified by physical activity, smoking status or family history of diabetes.

Comment: If you thought the world of politics was controversial, then how about nutrition! At a time when there is resurgence of low-carbohydrate diets for weight loss, my attention was drawn to this paper in the BMJ. The Nurses Health Studies and Health Professionals Follow-Up Study have a wealth of longitudinal data. Here the analysis is of whole-grain consumption and incident type 2 diabetes. The data are consistent with previous observations that higher whole-grain consumption is associated with lower rates of diabetes. So there is the challenge, how do you do 'keto' and have whole grains? I am all for a range of dietary options that can be tailored to individuals' preferences, but it is important to remember that the more extreme a dietary pattern, the more likely it is that important elements with proven benefits will be eliminated.

Reference: BMJ 2020;370:m2206

Abstract

Association of plasma biomarkers of fruit and vegetable intake with incident type 2 diabetes

Authors: Zheng J-S et al.

Summary: This prospective case-cohort study explored the relationship between fruit/vegetable intake, assessed using plasma vitamin C and carotenoid levels, and type 2 diabetes risk in 9754 individuals with type 2 diabetes and a subcohort of 13,662 individuals from the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. Each standard deviation increase in vitamin C level was associated with reduced type 2 diabetes risk (HR 0.82 [95% CI 0.76, 0.89]), as was each standard deviation increase in total carotenoid level (0.75 [0.68, 0.82]). The risk of developing type 2 diabetes also decreased as a composite biomarker score that categorised vitamin C and individual carotenoid levels into five groups increased (respective HRs 0.77, 0.66, 0.59 and 0.50 for groups 2–5 versus group 1, the lowest group). For the composite biomarker score groups 1, 3 and 5, the respective self-reported median fruit and vegetable intakes were 274, 396 and 508 g/day, and each standard deviation difference in the score, equivalent to a 66 g/day difference in total fruit and vegetable intake, was associated with a reduced risk of developing type 2 diabetes (HR 0.75 [95% CI 0.67, 0.83]).

Comment: One of the eternal challenges of nutrition research is having accurate quantitative data on actual food intake. All of the self-reported dietary food records are subject to reporter bias both qualitatively and quantitatively. Therefore having a measurable biomarker would help to solve this issue. Unfortunately there are few such biomarkers, although plasma vitamin C and carotenoid levels can be used as a proxy of fruit and vegetable intake. Most 'healthy food guidelines' include a recommendation for five or more portions of fruit and vegetables per day. This prospective observational study from Europe relates the biomarker score to incident diabetes and supports previous evidence and the call for increasing fruit and vegetable intake as part of a healthy diet.

Reference: BMJ 2020;370:m2194
Abstract

Effects of diet versus gastric bypass on metabolic function in diabetes

Authors: Yoshino M et al.

Summary: Metabolic regulators of glucose homeostasis before and after weight loss of ~18% following gastric bypass or dietary intervention were evaluated in 22 obese patients with diabetes. There was no significant difference between the diet and surgery groups for weight loss-induced increases in mean suppression of glucose production from baseline during clamp stage 1 or 2, increases in insulin-stimulated glucose disposal, increases in β-cell function or decreases in the areas under the curves for 24-hour plasma glucose and insulin levels. There were no major complications recorded in either group.

Comment: The theory that RYGB (Roux-en-Y gastric bypass) surgery conveys some additional metabolic benefit over and above weight loss has been around for many years. This was largely based on the observation that glucose metabolism improves well before any significant weight loss ensues. However many authors have shown similar benefits from dietary weight loss, including the DIRECT study achieving resolution of diabetes in some people. This small study compared the metabolic benefits of RYGB and diet-induced weight loss. Although not a randomised trial, the degree of weight loss was well matched between groups. Using the reference method for measuring insulin sensitivity and pancreatic function, the authors found that there were no important differences between the metabolic effects. This argues against any magical effects of RYGB, but of course this doesn't take into account hunger, and the real issue, as we all know, is maintaining the weight loss achieved through dietary change.

Reference: N Engl J Med 2020;383:721–32
Abstract

A randomized trial of closed-loop control in children with type 1 diabetes

Authors: Breton MD et al., for the iDCL Trial Research Group

Summary: Children aged 6–13 years with type 1 diabetes were randomised to use of a closed-loop insulin delivery system (n=78; in closed loop mode for a median of 93% of the time) or a sensor-augmented insulin pump (controls; n=23) in this 16-week, open-label trial. Compared with the control group, participants assigned to the closed-loop group had a greater increase in mean percentage of time in target glucose level range (70–180 mg/dL) from baseline (mean adjusted difference, 11 percentage points, equivalent to 2.6 hours per day [p<0.001]). Both the closed-loop and control groups had low median percentages of time with glucose levels <70 mg/dL (1.6% and 1.8%, respectively). There were no diabetic ketoacidosis or severe hypoglycaemic episodes recorded in either group.

Comment: It's getting closer… There is no doubt that the greatest advances in the management of type 1 diabetes in the last few years have been in the technology space. Improvements in subcutaneous glucose sensors have facilitated the progress of algorithms for closed-loop insulin delivery with insulin pumps. This is slowly trickling down to real-world clinical practice, with the availability of insulin suspension for low glucose levels. Although we know that innovative do-it-yourselfers are already using their own closed-loop systems safely and effectively, they haven't quite reached us yet. This study adds to the growing literature showing safety and benefit across a range of ages for people with type 1 diabetes. Once the technology is available, there will be growing calls for PHARMAC to fund the sensor side of the loop as well as the pumps themselves.

Reference: N Engl J Med 2020;383:836–45
Abstract

High adherence to a Mediterranean diet at age 4 reduces overweight, obesity and abdominal obesity incidence in children at the age of 8

Authors: Notario-Barandiaran L et al., on behalf of the INMA Project

Summary: Associations between adherence to a Mediterranean diet at 4 years of age and overweight, obesity and abdominal obesity were explored for a cohort of children, including 1801 and 1527 who attended follow-up visits at ages 4 and 8 years, respectively. Cross-sectional analyses revealed no significant association between adherence to a Mediterranean diet and overweight, obesity or abdominal obesity at the age of 4 years; however, longitudinal analyses revealed that greater adherence to a Mediterranean diet at age 4 years was associated with lower incidences of these three outcomes at 8 years of age (respective HRs 0.38 [95% CI 0.21, 0.67], 0.16 [0.05, 0.53] and 0.30 [0.12, 0.73]).

Comment: There are well-documented benefits of a Mediterranean dietary pattern in adults with lower rates of obesity and metabolic disease. Although not universal, and possibly increasingly less common, families will tend to consume a similar diet. Therefore, if adults are habitually following a Mediterranean diet, there is a greater chance that their children will also. This study is very interesting and adds to the evidence supporting this dietary pattern by showing that children who are already following a Mediterranean diet at age 4 years are much less likely to develop obesity by age 8 years than those who are not. This evidence supports the idea of a whānau-based intervention to promote the uptake of a Mediterranean dietary pattern for the benefit of the whole family.

Reference: Int J Obes 2020;44:1906–17
Abstract

Age-specific associations of glycated haemoglobin variability with cardiovascular disease and mortality in patients with type 2 diabetes mellitus

Authors: Wan EYF et al.

Summary: Relationships between increased HbA_{1c} level variability and the risks of CV disease and mortality were explored for a cohort of 147,811 patients with type 2 diabetes. After median follow-up of 7.4 years (1.02 million person-years), the respective incidences of CV disease events and deaths from any cause were 27,793 and 23,175, with positive log-linear associations detected between HbA_{1c} level variability for both outcomes across all age groups. An inverse association was seen between age and HbA_{1c} level variability for the composite of CV disease and all-cause mortality, with each percentage point increase in HbA_{1c} level variability increasing the likelihood of either outcome to a greater extent for patients aged 45–54 years (HR 1.28 [95% CI 1.21, 1.35]) than for those aged 75–84 years (1.14 [1.11, 1.17]). A subgroup analysis showed that patients whose HbA_{1c} levels were usually <53 mmol/mol had an ~8-fold increased risk than those whose levels were usually ≥64 mmol/mol.

Comment: The question of whether glycaemic variability or simply the overall control reflected by HbA_{1c} level is the most important factor determining risks for complications of diabetes is often raised by patients. Until the recent development and use of more reliable and affordable CGM, this has been a difficult question to study. Some data using 7-point capillary monitoring have suggested that variability may be an independent risk factor over and above HbA_{1c} level. This study has looked at the variability in HbA_{1c} level over time as another measure of glucose variability, and shows that it is strongly related to CV disease and mortality in type 2 diabetes. Interestingly, this is particularly true if the usual HbA_{1c} level is lower. This is somewhat counterintuitive, but emphasises the importance of consistently maintaining good control. At higher usual levels of HbA_{1c}, the overall glucose burden dominates the risk rather than the variability. It would be nice to see a similar analysis using time in range for glucose levels from a CGM system across the spectrum of usual HbA_{1c} levels.

Reference: Diabetes Obes Metab 2020;22:1316–27
Abstract

Long-term efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study)

Authors: Mathieu C et al.

Summary: The 52-week results were reported for the phase 3 DEPICT-2 trial, which randomised 813 adults with type 1 diabetes 1:1:1 to receive dapagliflozin 5mg, dapagliflozin 10mg or placebo; the study completion rate was 88.2%. Compared with placebo, reductions in HbA_{1c} levels at 52 weeks were significantly greater in the dapagliflozin 5mg and dapagliflozin 10mg arms (respective differences –0.20% [95% CI –0.34, –0.06] and –0.25% [–0.38, –0.11]), as were adjusted mean percentage decreases in bodyweight (–4.42% [–5.19, –3.64] and –4.86% [–5.63, –4.08]). Most adverse events were mild or moderate and resolved with treatment. The respective serious adverse event rates in the dapagliflozin 5mg, dapagliflozin 10mg and placebo arms were 11.8%, 7.0% and 5.9%, with diabetic ketoacidosis more frequent in the dapagliflozin arms (4.1%, 3.7% and 0.4%). Similar proportions of participants from the treatment groups were affected by hypoglycaemic events, and severe hypoglycaemia was uncommon.

Comment: Most of the literature and evidence for benefits of the SGLT-2 class of drugs has come from people with type 2 diabetes. It is that group for who we are likely to now get funded access. Whilst there is important glucose level lowering, the major benefits are seen in reduced CV and renal events. People with type 1 diabetes are also at greater risk of these and may benefit from SGLT-2 agents. Furthermore, anecdotally people with type 1 diabetes have found them useful for weight and stabilising glucose control as well. This study reports a randomised controlled trial of an SGLT-2 agent in type 1 diabetes that confirms these benefits. However, particularly in type 1 diabetes, the major concern is the increased risk of ketoacidosis. This is especially important because it often occurs with relatively normal or mild hyperglycaemia, therefore potentially going unrecognised. This study shows an important increased risk, with an incidence of ketoacidosis of around 4%. I think we need to be cautious with the use of these agents in type 1 diabetes.

Reference: Diabetes Obes Metab 2020;22:1516–26
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.**

Non-attendance at diabetes outpatient appointments

Authors: Brewster S et al.

Summary: These authors systematically reviewed 15 observational, one randomised controlled, nine qualitative, five survey and four service improvement studies that reported outpatient appointment nonattendance data for adults and young people with type 1 or 2 diabetes. Appointment management strategies, service improvements, patient navigators and WebCam appointments were included in the interventions. The studies provided variable definitions of nonattendance. Nonattendance was more common among younger adults, smokers and those with financial pressures. Patients who failed to attend their outpatient appointments had higher HbA_{1c} levels, with other outcomes also being typically worse but more variable across studies. Reasons for nonattendance in qualitative studies were categorised as balancing the costs and benefits of attendance, coping strategies and the relationship between the patient and healthcare professional.

Comment: DNA – no, not the code that defines us all, but that annoying 'did not attend'. This is a universal challenge we have in trying to support and help patients with diabetes. There are many reasons for a DNA, including easily identifiable and missed reminders or letters in one-off blips for people who usually attend. However, the more difficult situation is the serial offender! As this systematic review shows, this is more commonly in younger people and typically associated with worse glycaemic control and other outcomes. This review gives some insight into the determinants, but more work is needed to understand this better and to then formulate ways to overcome the barriers to engaging with structured care. That may well require other forms of delivery of that care such as we have seen with more telehealth this year because of COVID. Although my experience already is that those who DNA a hospital clinic are tending to now also DNA a virtual one!

Reference: Diabet Med 2020;37:1427–42
Abstract

Four main barriers to weight loss maintenance? A quantitative analysis of difficulties experienced by obese patients after successful weight reduction

Authors: Fischer M et al.

Summary: These researchers identified major barriers to weight maintenance for 88 patients with nonsurgical weight loss for morbid obesity; the patients' mean baseline body mass index was 49.5 kg/m^2, their weight loss over 12 months was 24.3% and they were followed for 1.48 ±0.6 years. The researchers identified four solid factors that were composed of 21 items and explained 56% of the variance; these were extracted and interpreted as 'hedonic hunger', 'mental distress', 'binge eating' and 'demoralisation'. Weight regain of 12.4 ±12% was correlated with each of these factors, but most closely with 'mental distress' (r=0.38); however, 'binge eating' was the most important predictor after controlling for age and follow-up time (adjusted R^2=0.297).

Comment: Most people who really choose to apply themselves to adhering to energy restriction through whatever dietary pattern they select are able to lose weight. However, as we see clinically and the literature reflects, the challenge then is to maintain that weight loss. This paper tried to quantify the relative contributions of the many factors that have been previously identified as the barriers to weight loss maintenance, and thus enable the development of tools to address these. It is clear that it is multifactorial, but mental distress and binge eating were the most important factors together with hunger and demoralisation – all things we would intuitively pick and frequently observe. However, they are difficult to address within an under-resourced health system. The behavioural components require individualised plans that ideally the individual can implement when required. This is not an easy task, but worthy of research.

Reference: Eur J Clin Nutr 2020;74:1192–200
Abstract

The association between HbA_{1c} and time in hypoglycemia during CGM and self-monitoring of blood glucose in people with type 1 diabetes and multiple daily insulin injections

Authors: Ahmadi SS et al.

Summary: Patients with type 1 diabetes treated with multiple daily insulin injections (n=161) were randomised to CGM or conventional SMBG in the GOLD-4 trial, with an evaluation period of 16 months. Both treatment arms were associated with increases in time spent in hypoglycaemia. In the CGM arm, 57.1% of participants with HbA_{1c} levels <58 mmol/mol (<7.5%) had <1.0% time spent with glucose levels <3.0 mmol/L and 54.8% had <4.0% of time spent with glucose levels <3.9 mmol/L. The estimated respective mean times spent in hypoglycaemia for participants with mean HbA_{1c} levels of 52 mmol/mol (7.0%) were 5.4% and 1.5% for <3.9 mmol/L and <3.0 mmol/L during CGM, and the corresponding values during SMBG were 9.2% and 3.5%. Participants with mean glucose levels of 8 mmol/L spent 4.9% and 2.8% more units of time with glucose levels <3.9 and <3.0 mmol/L, respectively, during SMBG than during CGM.

Comment: One of the main limiting factors for people with type 1 diabetes achieving tight glycaemic control is the corresponding increase in hypoglycaemic events as their HbA_{1c} level comes down. This was shown very clearly in the DCCT trial 30 years ago and remains a problem. While we wait for closed loops to solve the problem, preventing hypoglycaemia comes down to frequent glucose level monitoring. The rise of flash CGM has made this more achievable. This study shows that using CGM can help reduce the time spent hypoglycaemic when maintaining HbA_{1c} levels in or close to target. Ask a person with type 1 diabetes if that should be enough to persuade PHARMAC to fund them, and I know what they would say.

Reference: Diabetes Care 2020;43:2017–24
Abstract