Diabetes & Obesity RESEARCH REVIEW™

Making Education Easy

Issue 154 – 2022

In this issue:

Abbreviations used in this issue
CV = cardiovascular
HbA_{1c} = glycosylated haemoglobin
SGLT = sodium glucose cotransporter

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Welcome to issue 154 of Diabetes and Obesity Research Review.

NZ research is represented this month in two papers, beginning with an Auckland study attempting to identify why young patients with type 2 diabetes develop complications earlier than those with type 1 diabetes of comparable duration. Moving down the North Island, just a bit, to the Waikato, our colleagues there have researched inequities in initial use of vildagliptin in general practice for type 2 diabetes. Also very topical at the moment, there is an evaluation of blood glucose level instability in type 1 diabetics during the week following COVID-19 vaccination. We conclude this month's issue with a trial of the impact of a non-calorie-restricted low-carbohydrate diet on glycaemic control, body composition and CV disease risk factors in patients with type 2 diabetes.

We hope you enjoy this selected research, and we look forward to your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Socioeconomic status and risk factors for complications in young people with type 1 or type 2 diabetes

Authors: Wijayaratna S et al.

Summary: The reasons young people with type 2 diabetes develop complications earlier than those with type 1 diabetes were explored in this cross-sectional study of 731 and 1350 individuals, aged <40 years, diagnosed with the respective diabetes types between 15 and 30 years of age, and referred to secondary diabetes services in Auckland. Compared with the type 1 diabetes group, greater proportions of the type 2 diabetes groups were of Māori or Pasifika descent (24% and 71% [p<0.001]), and 78% were from the lowest four New Zealand Deprivation Index categories (p<0.001). BMI, mean HbA_{1c} level, macroalbuminuria and CV disease risk all increased progressively across the deprivation categories (p≤0.01). Deprivation was the strongest risk factor for poorly controlled diabetes (adjusted odds ratio 1.17 [95% CI 1.13, 1.22]), and each decile increase in the deprivation index was associated with an increased likelihood of increased urinary albumin-to-creatinine ratio (1.11 [1.06, 1.16]), and a 4% increase in CV disease risk irrespective of diabetes type.

Comment: Anyone working in diabetes will have observed the increase in rates of younger people with type 2 diabetes. Furthermore, they often have worse progression and rate of complications than older people developing type 2 diabetes or similar aged people with type 1 diabetes. This study reports an analysis of factors that might determine this from a cohort of patients referred to secondary care in the Auckland region. These data confirm the clinical observation and highlight how deprivation is an important factor in determining this increased risk. This shows how important the social determinants of health are, and critically how difficult it is to address the outcomes for these people from within the health sector alone. One caution on interpreting these data is the pattern of referral to secondary care, where as a rule all patients with type 1 diabetes are seen in secondary care, but increasingly only those with type 2 diabetes who have worse control or existing complications are referred, which would skew these findings. It would be interesting to repeat these analyses using the whole population data – if we had a national diabetes register. Wouldn't that be powerful!

Reference: BMJ Open Diabetes Res Care 2021;9:e002485
Abstract

New Year's resolutions and weight loss

Many of us make New Year's resolutions, and weight loss is a common goal.
CLICK HERE to read a timely review on the Role of Pharmacotherapy in Food Cravings.

Food craving is an important piece of the weight-loss puzzle. This article describes the issue of food cravings in patients with obesity, and the role that pharmacotherapy can play in the management of this issue.

Anthropometric and adiposity indicators and risk of type 2 diabetes

Authors: Jayedi A et al.

Summary: This systematic review with dose-response meta-analysis included 216 cohort studies (2.3 million individuals with type 2 diabetes among 26 million participants) reporting on the relationship between adiposity/bodyfat and type 2 diabetes risk in the general adult population. The risk of developing type 2 diabetes was found to increase significantly for each 5 kg/m^2 increase in BMI (relative risk 1.72 [95% CI 1.65, 1.81]), each 10cm increase in waist circumference (1.61 [1.52, 1.70]), each 0.1-unit increase in waist-to-hip ratio (1.63 [1.50, 1.78]), each 0.1-unit increase in waist-to-height ratio (1.73 [1.51, 1.98]), each unit increase in visceral adiposity index (1.42 [1.27, 1.58]), each 10% increase in bodyfat (2.05 [1.41, 2.98]), each 0.005-unit increase in body shape index (1.09 [1.05, 1.13]) and each 10% increase in body adiposity index (2.55 [1.59, 4.10]). There was a strong positive linear association identified between BMI and type 2 diabetes risk, with positive linear or monotonic associations detected in all regions and ethnicities with no marked deviation from linearity at any specific cutoff value. Indices of central fatness were also positively, linearly or monotonically associated with type 2 diabetes risk independently of overall adiposity; total and visceral fat mass were also positively, linearly or monotonically associated in a small number of studies.

Comment: Overweight and obesity are recognised and important modifiable risk factors for type 2 diabetes and CV disease. However, there are often debates about the relative utility of different measurements or estimates of body fatness, and cutoffs for each measurement. This systematic review and meta-analysis is particularly useful, because it includes a very large number of people, from very diverse populations. Whilst it confirms BMI as a very useful tool to predict risk of type 2 diabetes, what interested me was that the relationship appears more linear than what previous data have suggested as being a more exponential relationship. It also shows again that waist circumference adds additional information and nuance to the description of risk of body fatness. However, again I was interested to see that using a waist-to-height ratio may be better than waist alone or waist-to-hip ratio, which has traditionally been preferred. Despite this knowledge, waist circumference is still very poorly collected in clinical practice.

Reference: BMJ 2022;376:e067516
Abstract

Randomized trial of closed-loop control in very young children with type 1 diabetes

Authors: Ware J et al., for the KidsAP Consortium

Summary: Seventy-four children aged 1–7 years on insulin-pump therapy for type 1 diabetes received 16 weeks each of a closed-loop system and a sensor-augmented pump as control therapy in randomised order in this crossover trial. Compared with the control therapy, the closed-loop system was associated with a longer time with glucose levels in the target range (70–180 mg/dL; primary endpoint, mean adjusted difference, 8.7 percentage points [p<0.001]), a shorter time in a hyperglycaemic state (–8.5 percentage points [p<0.001]), a lower HbA_{1c} level (–0.4 percentage points [p<0.001]), and a lower mean sensor glucose level (–12.3 mg/dL [p<0.001]); time spent in a hypoglycaemic state did not differ significantly (p=0.74). During the closed-loop treatment, the median time spent in the closed-loop mode was 95%, and there was one case of severe hypoglycaemia.

Comment: The last decade has seen major advances in technology for insulin delivery and glucose sensing, but perhaps even more importantly, in algorithms for integrating the two. We are now seeing studies like this one coming through showing the benefits of this technology in achieving tight glycaemic control without risk of hypoglycaemia. Although the point of this study was to compare a closed-loop with sensor augmented pump therapy, to me the main take-home point for us in NZ is that this technology is now clearly superior to multiple daily injections. Furthermore, in this age-group where the burden of diabetes management for both the children and their parents is so high, safe and effective technology should now be the standard of care. It is great that pumps are funded in NZ, but woeful that we still have special authority criteria and more so that sensor technology is not available to those who can't afford it. It really is time that this is resolved.

Reference: N Engl J Med 2022;386:209–19
Abstract

Variation in open access vildagliptin use in Waikato patients with type 2 diabetes

Authors: Chepulis L et al.

Summary: This NZ research evaluated variations in initial vildagliptin use among adults with type 2 diabetes after the agent was approved for open access funding in October 2018. Among 3971 patients included in the analysis, 724 (18.2%) had initiated vildagliptin therapy, with a mean time to first dispensing of 192.1 days. Compared with patients of European ethnicity, those of Asian ethnicity were more likely to receive vildagliptin whereas Māori were less likely. Initiation of vildagliptin was also more likely in younger patients and those with an HbA_{1C} level of >64 mmol/mol. Across general practices, vildagliptin use ranged from 0.0% to 82.4%.

Comment: Type 2 diabetes is largely managed in primary care in NZ. In the last 3 years we have seen the availability of three new classes of medications for glucose level lowering, which have unique mechanisms of action and a diverse range of side effects. As with any new medication, it takes time for practitioners to become comfortable with prescribing them. This paper highlights some of the issues with one of these classes, the DPP (dipeptidyl peptidase)-4 inhibitors, and here vildagliptin, once it was available for unrestricted funded prescription. Compared with the SGLT-2 inhibitors and GLP (glucagon-like peptide)-1 agonists, vildagliptin is a very simple medication to use and has very few side effects to consider. Therefore it is surprising that the uptake wasn't greater. The authors highlight well reported inequities in prescription, and also enormous range between general practices. It will be interesting to see whether a similar pattern is seen with the SGLT-2 inhibitors and GLP-1 agonists. It suggests that a systematic way of educating practitioners, and proactively pro-equity approaches to introducing new medicines needs to be taken. Perhaps the new health system will enable this.

Reference: N Z Med J 2022;135(1548):77–88
Abstract

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Variety and quantity of dietary protein intake from different sources and risk of new-onset diabetes

Authors: Zhou C et al.

Summary: Associations of protein intake variety and quantity with new-onset diabetes were explored using Chinese health and nutrition survey data from 16,260 individuals free of diabetes at baseline. Over a median 9.0 years of follow-up, 1100 individuals developed diabetes. U-shaped associations were identified for total, whole grain-derived and poultry-derived protein with new-onset diabetes, J-shaped associations were seen between unprocessed or processed red meat-derived protein and new-onset diabetes, a reverse J-shaped association was evident between fish-derived protein and new-onset diabetes, L-shaped associations were detected between egg-derived and legume-derived protein with new-onset diabetes, and a reverse L-shaped association was apparent between refined grain-derived protein and new-onset diabetes (all p<0.001 for nonlinearity). Each incremental increase in a high variety score for protein source was associated with a decreased risk of new-onset diabetes (hazard ratio 0.69 [95% CI 0.65, 0.72]).

Comment: This is a really interesting perspective on the relationship between dietary protein and risk of type 2 diabetes. Historically there has been a lot of focus on macronutrient composition, as percentages of total energy intake. There has also been a plethora of studies looking at type of fat and type of carbohydrate, but relatively few studies on protein, particularly on the sources of protein. This study demonstrates how important that is, with much lower rates of new-onset diabetes where dietary protein is derived more from plant sources or fish than from red meat. These data add further weight to the changing focus from macronutrient proportions to macronutrient quality/composition. It is very likely that these differences are at least in part mediated by other components of the foods, and/or the interactions between them.

Reference: BMC Med 2022;20:6
Abstract

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Nudging customers towards healthier food and beverage purchases in a real-life online supermarket

Authors: Stuber JM et al.

Summary: Customers purchasing food via an online supermarket over a 1-month period (n=11,775) were randomised to a control condition, information nudges, position nudges or both information and position nudges. Sales data revealed no overall significant effects between the groups, although effects were modified by area-level deprivation with shoppers from deprived areas allocated to information nudges purchasing a higher percentage of healthy products of 2.4% relative to controls; no significant difference was seen for position or combined nudges. In contrast, shoppers from nondeprived areas purchased lower percentages of healthy products when exposed to information nudges and combined nudges (–1.6% and – 2.1%, respectively), but not position nudges.

Comment: Changing dietary pattern is very difficult, and multiple strategies are likely required to achieve sustained change that is big enough to make an impact on health. This paper reports and interesting approach, which has been possible because of an increasing trend in online grocery shopping. Supermarkets have used product placement as a tool to influence purchasing for a long time. Cynically this is usually to increase profits rather than improve health, but the effectiveness of this tool is well known. This paper reports using information or positional 'nudges' to try to move purchases to a more healthy profile. With the methods used here, only information nudges in more deprived population groups made any significant improvement. Given that we have seen the importance of deprivation in risk for diabetes and outcomes, this is still useful. There may also be scope for different types or styles of 'nudging' that can be tested as well.

Reference: BMC Med 2022;20:10
Abstract

The change in glycaemic control immediately after COVID-19 vaccination in people with type 1 diabetes

Authors: Heald AH et al.

Summary: Temporary instability of blood glucose levels following vaccination against SARS-COV-2 was explored in this analysis of interstitial glucose levels from 97 consecutive adults with type 1 diabetes using the FreeStyle Libre® flash glucose monitor. Compared with prevaccination values, the mean percentage of interstitial glucose levels in the target range of 3.9–10.0 mmol/L was significantly lower during the 7 days after vaccination (52.2% vs. 55.0% [p=0.030]), with 58% of participants experiencing a reduction in the time in target range in the week after vaccination, 30% having a decrease of >10% and 10% having a decrease >20%. The effect of vaccination on interstitial glucose level targets during the subsequent week was most pronounced for metformin/dapagliflozin plus basal bolus insulin recipients and for participants with an HbA_{1c} level below the median value (respective changes, –7.6% and –5.7%).

Comment: Anecdotally, people with diabetes have reported a rise in their blood glucose levels in the week after they have had their COVID vaccination, and therefore this study caught my eye. In people with type 1 diabetes who were using flash glucose monitoring, time in range during the week before the vaccine was compared with the week after the vaccine. About a third of people had a deterioration in time in range, but curiously some also had better control. This analysis doesn't take into consideration any changes in insulin dosing and attention to corrections, etc. What I found interesting was that in this UK-based study, almost a third of patients with type 1 diabetes were using either metformin or an SGLT-2 inhibitor in addition to their insulin. This is much higher than I expect will be the case in NZ, even acknowledging the funding issues for SGLT-2 inhibitors. These individuals were more likely to have worse control after the vaccine.

Reference: Diabet Med 2021:e14774
Abstract

The impact of birthweight on subsequent phenotype of type 2 diabetes in later life

Authors: Paulina C et al.

Summary: The impact birthweight has on phenotype at diagnosis of type 2 diabetes and subsequent glycaemic deterioration was explored in this analysis of 48,000 births in Scotland. Each 1kg increment in lower birthweight was associated with a 293-day younger age at type 2 diabetes diagnosis (p=0.005) and a 1.29 kg/m^2 lower BMI at diagnosis (p<0.001); there was no significant association of birthweight with diabetes progression.

Comment: As the authors say, it is well known that low birthweight is associated with later lifetime risk of developing type 2 diabetes. There are many potential reasons why that might be, including the effect of intrauterine stress influencing β-cells or gene programming related to downstream insulin-mediated glucose uptake and utilisation. This interesting study shows that individuals with low birthweight were more likely to develop type 2 diabetes at a younger age and at a lower BMI than their normal birthweight counterparts. Without conducting detailed clamp studies of β-cell function and insulin sensitivity, these data suggest the effect is more likely mediated by reduced β-cell function and/or mass rather than insulin resistance. This is the opposite of what I might have predicted, and sadly not something that is likely modifiable.

Reference: Diabet Med 2022:e14792
Abstract

Real-world evidence of efficacy and safety of sodium–glucose cotransporter 2 inhibitors as adjunctive therapy in adults with type 1 diabetes

Authors: Palanca A et al.

Summary: Real-world efficacy and safety of SGLT-2 inhibitors combined with insulin for the treatment of type 1 diabetes were reported for 199 adults from two European centres. After 12 months of this treatment, significant reductions were seen for mean HbA_{1c} level (–0.5 percentage points), bodyweight (–2.9kg) and daily insulin use (–8.5%), with the greatest reduction in HbA_{1c} level seen in patients with a baseline HbA_{1c} level of >64 mmol/mol (8.0%; reduction of –0.7 percentage points) and the greatest weight loss seen in those with a BMI >27 kg/m^2 (–3.5kg reduction). Patients with an estimated glomerular filtration rate <90 mL/min/1.73m^2 at baseline experienced an increase in this parameter of 4.5 mL/min/1.73m^2, whereas those with a urinary albumin-to-creatinine ratio >15 mg/g experienced a decrease in this parameter of –16.6 mg/g. The overall incidence of adverse events was 28.6%, including genital infections (22.6%), ketosis (2.5%) and diabetic ketoacidosis (3.5%); there were no cases of severe hypoglycaemia.

Comment: The use of SGLT-2 inhibitors in type 1 diabetes is very controversial, mainly because of the risk of ketoacidosis. I have had a small number of people with type 1 diabetes using them with mixed experience, but a generally impressive reduction in glucose level variability. This study reports data from real-world experience of their use in 200 people with type 1 diabetes. The observations confirm my experience of reductions in HbA_{1c} level, weight and insulin doses. However, there were a small number of episodes of ketoacidosis, but only 3.5%, which is much lower than many might have expected. Overall, I think these data are more reassuring than I would have expected, and suggest that there may be a place for these agents in type 1 diabetes after all. We must be cautious and extremely careful in who we select, how we educate and ensure safety, but watch this space.

Reference: Diabetes Care 2022:dc211584
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.**

Effects of a 6-month, low-carbohydrate diet on glycaemic control, body composition, and cardiovascular risk factors in patients with type 2 diabetes

Authors: Gram-Kampmann EM et al.

Summary: Patients with type 2 diabetes were randomised to a 6-month calorie-nonrestricted low-carbohydrate diet (maximum 20% total energy intake from carbohydrates; n=49) or a control diet (50–60% of total energy from carbohydrates; n=22) in this open-label trial. Compared with the control diet, the low-carbohydrate diet was associated with a 30.5% reduction in energy from carbohydrate and a 30.6% increase in energy from fat, as well as reductions in HbA_{1c} level at 3 months of 8.9 mmol/mol, which was maintained out to 6 months (–7.5 mmol/mol), bodyweight of 3.9kg, BMI of 1.4 kg/m^2 and waist circumference of 4.9cm (all p<0.01), which were accompanied by reductions in total fat mass of 2.2kg (p=0.027) and lean mass of 1.3kg (p=0.017). There were no significant changes in blood lipid levels or blood pressure after 6 months, physical activity levels were maintained, and no episodes of severe hypoglycaemia were reported.

Comment: There continues to be interest in low or very low carbohydrate diets as a way to help people with type 2 diabetes better manage their condition. There is perhaps no other diet/nutrition controversy that creates more passionate debate! Despite the interest and range of opinion, there remain few well-conducted randomised controlled trials that have been conducted specifically in people with type 2 diabetes or prediabetes. This study does that, and shows significant benefits of a low-carbohydrate diet on glycaemic control, the primary endpoint, and weight, with no adverse effects on lipid levels, blood pressure or rates of hypoglycaemia. This is all very encouraging, but once again it was only a 6-month intervention. We still need a well-conducted study of this nature that extends out to at least 2 years before we can really make conclusions. However, these data are reassuring that low-carbohydrate diets are a valid short-term approach for people with type 2 diabetes.

Reference: Diabetes Obes Metab; Published online Jan 4, 2022
Abstract

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