Diabetes & Obesity RESEARCH REVIEW™

Making Education Easy

Issue 155 – 2022

In this issue:

Abbreviations used in this issue
CV = cardiovascular
GIP = gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
HF = heart failure
HR = hazard ratio
ICER = incremental cost-effectiveness ratio
MI = myocardial infarction
QALY = quality-adjusted life-year
RCT = randomised controlled trial
RYGB = Roux-en-Y gastric bypass
SGLT = sodium glucose cotransporter

Welcome to issue 155 of Diabetes and Obesity Research Review.

Individuals with type 2 diabetes are at increased risk of developing some cancers, and the first paper selected for this issue explores how these risks vary by ethnicity in NZ. Other included research has reported on lifetime CV and renal disease risks for individuals with type 2 diabetes. Research from Norway found that supplying free fruit and vegetables to schoolchildren had no notable beneficial effect in terms of bodyweight. The penultimate paper in this issue is a large UK analysis reporting that SGLT-2 inhibitors with and without GLP-1 receptor agonists appear to provide beneficial primary prevention of major adverse cardiac and cerebrovascular events and HF, and GLP-1 receptor agonists alone help reduce HF events. Another analysis of CV and renal outcomes with GLP-1 receptor agonists follows, reporting on associations of these outcomes with HbA_{1c} level and bodyweight reductions.

Please feel free to send any comments or feedback regarding this issue.

Best regards,

Professor Jeremy Krebs
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Ethnic differences in cancer rates among adults with type 2 diabetes in New Zealand from 1994 to 2018

Authors: Yu D et al.

Summary: This NZ research investigated cancer risks for population-based matched cohorts of 33,524 adults with type 2 diabetes according to ethnicity. Compared with NZ European individuals with type 2 diabetes, Māori had higher rates of thyroid cancer (HR 15.36 [95% CI 4.50, 52.34]), gallbladder cancer (7.94 [1.57, 40.24]), cervical cancer (4.81 [1.08, 21.42]), lung cancer (1.97 [1.30, 2.99]) and liver cancer (1.81 [1.08, 3.03]), and lower rates of colon cancer (0.56 [0.35, 0.90]) and malignant melanoma (0.11 [0.04, 0.27]). Compared with NZ European individuals with type 2 diabetes, Pasifika had higher rates of gallbladder cancer (HR 25.10 [95% CI 3.14, 200.63]) and thyroid cancer (4.47 [1.25, 16.03]), and lower rates of colon cancer (0.48 [0.30, 0.78]), rectal cancer (0.21 [0.09, 0.48]), malignant melanoma (0.21 [0.07, 0.65]) and bladder cancer (0.01 [0.01, 0.10]).

Comment: It is already known that people with type 2 diabetes have an increased risk of developing some cancers compared with those without diabetes. This study adds to that understanding by using a relatively large population cohort that includes enough Māori and Pacific people to be able to make some comparisons by ethnicity with European people in NZ. There are some interesting observations that require more work to understand their significance. Both Māori and Pacific people with type 2 diabetes are at greater risk of thyroid cancer and gallbladder cancer, but at less risk of melanoma and colon cancer. Whether this is specific to people with type 2 diabetes or more generalisable by ethnicity cannot be determined from these data, but there is certainly a striking difference that requires wider exploration.

Reference: JAMA Netw Open 2022;5:e2147171
Abstract

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Estimated cost-effectiveness of medical therapy, sleeve gastrectomy, and gastric bypass in patients with severe obesity and type 2 diabetes

Authors: Lauren BN et al.

Summary: These researchers compared estimated cost effectiveness of medical therapy, sleeve gastrectomy and RYGB (Roux-en-Y gastric bypass) for severely obese patients with type 2 diabetes, stratified by diabetes severity. To achieve this, they used a microsimulation model to project outcomes over 5 years, with time horizons of 10–30 years in sensitivity analyses, applied to 1000 simulated cohorts of 10,000 patients, 16%, 56% and 28% with mild, moderate and severe type 2 diabetes at baseline, respectively. Compared with medical therapy over 5 years, there was a mean of 0.44 QALYs gained with RYGB overall; for mild, moderate and severe type 2 diabetes at baseline there were means of 0.59, 0.50 and 0.30 QALYs gained, respectively. For the overall population, RYGB was the preferred strategy with an ICER of $46,877 per QALY overall; ICERs were $36,479, $37,056 and $98,940 per QALY for mild, moderate and severe baseline diabetes, respectively (73.7%, 85.6% and 40.2% probability preferred, respectively). RYGB was also associated with better cost effectiveness over a longer time horizon.

Comment: I confess that I don't understand this modelling approach and cynically feel it's a bit like randomly throwing up all the cards in a pack and seeing what patterns emerge. However, I believe that it is a valid method. The purpose of this study was to explore whether cost effectiveness of weight management by medical versus different surgical procedures varies by severity of underlying type 2 diabetes – a question we ask clinically all the time with respect to efficacy. Remembering that these data are derived from a US population and the US medical system and therefore may not accurately reflect NZ practice or cost. Nonetheless, the findings reinforce my long-held bias that RYGB is more effective and cost effective for weight management in people with type 2 diabetes when compared with medical therapy or sleeve gastrectomy. This is particularly the case in more severe type 2 diabetes. I know that sleeve gastrectomy has become the procedure of choice for most surgeons, but these data add support to the use of RYGB when surgery is considered the preferable management.

Reference: JAMA Netw Open 2022;5:e2148317
Abstract

Lifetime risk of cardiovascular-renal disease in type 2 diabetes

Authors: Zhang R et al.

Summary: The lifetime risks of individual and combined major adverse renal CV events were assessed for a population-based cohort of 473,399 individuals with type 2 diabetes from England. The lifetime risk of major adverse renal CV events was 80% in patients who were free from CV and renal diseases at baseline, and the respective risks in those with HF, chronic kidney disease, MI, stroke and peripheral arterial disease at baseline were 97%, 93%, 98%, 89% and 91%. Among patients free from CV and renal diseases, the respective lifetime risk of chronic kidney disease was highest at 54%, followed by CV-related death (41%), HF (29%), stroke (20%), MI (19%) and peripheral arterial disease (9%). In patients with HF only, three quarters of major adverse renal CV events following index type 2 diabetes were attributable to HF after adjusting for age, gender and comorbidities. It was also estimated that compared with patients with >1, <3 and ≥3 modifiable health risk behaviours, achievement of ideal CV health could reduce major adverse renal CV events by around 41.5%, 23.6% and 17.2%, respectively, in patients with type 2 diabetes.

Comment: I commonly start tutorials with medical students by posing the question 'why do we care about blood glucose?'. The answer of course is that persistently elevated glucose is associated with increased risk of micro- and macrovascular complications, but it is the CV and renal complications that increase the risk of premature mortality. I'm not sure that this study tells us anything new in that regard, other than some scarily high numbers. In some ways, we are less interested in lifetime risk reported here – since we all have to die of something! – but we are very interested in premature risk and therefore the opportunity to intervene and delay onset, severity or impact of complications. I guess this study has confirmed that CV and renal outcomes are the most important, and therefore we need to focus on screening for CV disease and renal risk factors and treatments to reduce these. It's a good thing that we have an SGLT-2 inhibitor and a GLP-1 agonist in our armoury now.

Reference: BMC Med 2022;20:63
Abstract

Effects of personalized diets by prediction of glycemic responses on glycemic control and metabolic health in newly diagnosed T2DM

Authors: Rein M et al.

Summary: Twenty-three adults with newly diagnosed type 2 diabetes consumed personalised postprandial-targeting and Mediterranean-style diets, each for 2 weeks, in a randomised crossover manner. The personalised postprandial-targeting diet was associated with significant reductions in average personal postprandial glucose response (mean difference versus the Mediterranean diet, –19.8 mg/dL·h [p<0.001]), mean glucose level (–7.8 mg/dL [p<0.001]) and daily time with a glucose level >140 mg/dL (–2.42 h/day [p<0.001]), as well as a significantly greater reduction in blood fructosamine level (–16.4 µmol/dL [p<0.0001]). There was also a 6-month evaluation of the personalised postprandial-targeting diet in 16 individuals, which showed significant improvements in a number of metabolic health parameters, including HbA_{1c} level (mean change –0.39% [p<0.001]), fasting glucose level (–16.4 mg/dL [p=0.02]) and triglyceride level (–49 mg/dL [p<0.001]), as well as a diabetes remission rate of 61%. Clinical improvements were significantly associated with gut microbiome changes.

Comment: The optimal dietary approach for people with type 2 diabetes to control or reverse the metabolic derangement continues to be hotly debated. It is generally accepted that populations who follow a Mediterranean dietary pattern have a lower incidence of type 2 diabetes. There are many other approaches for which there is some evidence, which include low-fat/high-carbohydrate, or the opposite low-carbohydrate/high-fat or protein. What is perhaps the most overwhelming conclusion of the literature is that adherence to dietary pattern is more predictive of better outcomes than the specifics of the prescription itself. The authors of this paper have previously published a personalised dietary prescription approach that incorporated multiple variables into an algorithm that individualises a dietary approach. Here they report a very short-term crossover study of this approach versus a Mediterranean diet in people with newly diagnosed type 2 diabetes, then they continue on with a single-arm 6-month intervention of their personalised approach. Their conclusion is that their approach is superior, but whilst I think this is an interesting idea, I am cynical. The intervention was very intensive and uncontrolled in the 6-month study. When you delve into the supplementary files to find what foods were actually prescribed/consumed, the overall macronutrient composition resembles a low-carbohydrate diet. So while I am all for personalised medicine, I am not convinced by this study that this is any better than simply working with a person to understand their preferred approach and supporting them with dietary change and adherence.

Reference: BMC Med 2022;20:56
Abstract

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A nationwide school fruit and vegetable policy and childhood and adolescent overweight

Authors: Øvrebø B et al.

Summary: This quasi-natural experimental study required that Norwegian combined schools (grades 1–10) but not elementary schools (grades 1–7) provide students with free fruit and vegetables, with longitudinal or cross-sectional anthropometric data for 11,215 children from the Norwegian Growth Cohort analysed. After adjustment for pre-exposure BMI standard deviation, there was little evidence that free fruit and vegetables for 1–2.5 years provided any benefit for the outcomes of BMI standard deviation score, overweight/obesity, waist circumference and weight-to-height ratio for either sex, with similar findings after 4 years of the free fruit and vegetables policy.

Comment: It is generally agreed that some intervention is required at a public health level to try to reverse the trend of increasing childhood and adolescent obesity. Many ideas have been proposed, including providing fruit and vegetables in a school setting to try to modify dietary intake and behaviour. This study used a difference in policy at a national level in Norway, which created a difference between schools in whether fruit and vegetable were provided, thus generating a nonrandomised cluster trial. Although there are many potential confounders, which the authors recognise, the result was no difference in weight over time. This shows again how a good idea doesn't always translate into the desired outcome when it comes to obesity prevention. Many such interventions in isolation may have relatively weak effects that are overcome by other factors. It is likely that a broad-based multi-interventional approach is required. In that setting, this policy may have a greater effect.

Reference: PLoS Med 2022;19:e1003881
Abstract

Weight loss did not modify macronutrient specific response of hormones and satiety in overweight and obese people without metabolic disease

Authors: Li L et al.

Summary: Thirty-two overweight or obese individuals underwent meal tests before and after a weight loss intervention to investigate GLP-1, GIP, ghrelin and insulin levels and satiety response to meals according to macronutrient composition. The following macronutrient-specific response patterns were seen: GLP-1 (protein>fat=carbohydrate), GIP (carbohydrate=fat>protein), and insulin (carbohydrate>protein=fat). There was no difference between meals for postprandial decline in ghrelin level. Hunger, desire to eat, and prospective food consumption were greatest following carbohydrate intake at baseline. After weight loss, there were decreases in fasting and postprandial GLP-1 and insulin levels and concomitantly increased ghrelin levels, but with no change in macronutrient-specific hormonal response pattern. Weight loss was associated with increased hunger and desire to eat, but loss of macronutrient-specific differences. The greater the weight loss, the greater the decline of protein-induced GLP-1 response (p=0.024).

Comment: The role of different macronutrients in appetite and weight loss has been long debated. Apart from differences in energy density, differential effects on satiety hormones and glucose-regulating hormones have been examined. This study adds to that literature by using three different test meals high in carbohydrate, protein or fat, and measuring range of hormones and measures of satiety before and after a period of weight loss. There were interesting differences in the macronutrient stimulation of incretin hormones (GLP-1 and GIP) and insulin that favour higher protein content. This pattern persisted after weight loss, though the magnitude of the hormone response was modified. Notably, before weight loss, higher intake of carbohydrate was associated with greater subsequent food intake, but this difference between macronutrients was lost after weight loss when hunger generally was increased. These data support the idea of a higher protein diet being beneficial for weight and glycaemic management, but this has not been seen in large community RCTs, highlighting the complexity of the relationships between our food and these outcomes.

Reference: Clin Nutr 2022;41:948–57
Abstract

Baseline haemoglobin A1c and the risk of COVID-19 hospitalization among patients with diabetes in the INSIGHT Clinical Research Network

Authors: Min JY et al.

Summary: Associations of baseline glucose level control with COVID-19 hospitalisation and in-hospital death were explored for a retrospective cohort of adults with diabetes, stratified according to an HbA_{1c} level of 39–46 (n=50,016), 48–57 (n=54,729), 58–85 (n=47,640) and ≥86 (n=16,418) mmol/mol. Compared with patients from the lowest HbA_{1c} level group, the risk of hospitalisation was increased for the two highest groups (respective propensity score adjusted HRs 1.19 [95% CI 1.06, 1.34] and 1.40 [1.19, 1.64]), and the risk of COVID-19 in-hospital death was greater for those in the 58–85 mmol/mol group (1.29 [1.06, 1.61]).

Reference: Diabet Med 2022;e14815
Abstract

Glycemic control and clinical outcomes in U.S. patients with COVID-19

Authors: Wong R et al., for the N3C Consortium

Summary: The association between HbA_{1c} level and severity of COVID-19 outcome was reported for 39,616 adults with comorbid type 2 diabetes in this retrospective observational US study. The risk of requiring hospital admission for COVID-19 increased as HbA_{1c} level increased, but plateaus were seen for the risk of death once HbA_{1c} level exceeded 8%, and for requirement for extracorporeal membrane oxygenation once HbA_{1c} level exceeded 9%. HbA_{1c} level had no significant impact on length of hospital stay.

Reference: Diabetes Care 2022;dc212186
Abstract

Comment: It has been well documented that people with diabetes have a greater risk of more severe disease with COVID-19, including hospitalisation, ICU admission and death. What these two studies add are data to show that baseline HbA_{1c} level has an important modifying effect on that risk. As expected, risk was greater for those with worse control and higher HbA_{1c} level. These data from the INSIGHT clinical research network in New York are now somewhat historical (my how quickly things change in the COVID world) being taken from early in the pandemic during the original strain and before vaccines. The second study, also from the US, shows a threshold effect for increased risk of mortality of 64 mmol/mol (8%) and for intensive care of 75 mmol/mol (9%). Both studies support the effort that everyone is making to help people achieve the best glycaemic control they can to minimise their risk.

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Influences of decisions to attend a national diabetes prevention programme from people living in a socioeconomically deprived area

Authors: Begum S et al.

Summary: Thirty-five adults with prediabetes from socioeconomically deprived areas who had attended initial assessments for the UK's NHS Diabetes Prevention Programme completed semistructured interviews on key influences regarding decisions to attend the programme; 23 of the respondents went on to attend the first session and 12 did not. The responses showed that motivation to attend the diabetes prevention programme was affected by understanding of type 2 diabetes, making lifestyle changes, comparisons with others, and having support and certain self-perceptions. Both motivation and attendance were also affected by accessibility and practical factors.

Comment: There is enthusiasm to promote self-management courses for people with prediabetes and diabetes to help them develop knowledge and skills to improve their health. On the surface this seems like a very sensible strategy. This study reports a qualitative study on what were determinants of whether people from a deprived community attended a diabetes prevention programme in the UK. Several themes were identified, including prior knowledge, and importantly level of support and self-perception, in addition to practical issues of accessibility. This is very important to consider in NZ if we are to set up and promote these types of programmes, because we already have important inequities in rates of diabetes and outcomes by deprivation. If we don't get it right, there is a high risk that we will only further exacerbate these.

Reference: Diabet Med 2022;e14804
Abstract

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Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes

Authors: Wright AK et al.

Summary: Associations of current SGLT-2 inhibitor and GLP-1 receptor agonist use (on their own or combined) with major adverse cardiac and cerebrovascular event and HF risk were explored using data from patients with type 2 diabetes from three UK nested case-control studies, each matched to ≤20 controls. For patients with type 2 diabetes and no CV disease at baseline (n=336,334), 5.5% experienced a major adverse cardiac and cerebrovascular event, and for those without HF at baseline (n=411,206), 4.2% experienced an HF event during follow-up. Compared with other combination regimens, use of SGLT-2 inhibitors on their own and with GLP-1 receptor agonists reduced the major adverse cardiac and cerebrovascular event risk (respective adjusted pooled odds ratios 0.82 [95% CI 0.73, 0.92] and 0.70 [0.50, 0.98]), but GLP-1 receptor agonist use did not significantly reduce the risk (0.93 [0.81, 1.06]), whereas all three of these regimen types significantly reduced the risk of HF (0.49 [0.42, 0.58], 0.43 [0.28, 0.64] and 0.82 [0.71, 0.95], respectively).

Comment: Much has been written about the benefits of SGLT-2 inhibitors and GLP-1 agonists with respect to CV events and HF, with critical evidence coming from multiple large RCTs largely conducted in people with previous disease or at high risk of events. These studies have underpinned the decision by PHARMAC to fund these agents and the special authority criteria we now have. However, what has been less clear is whether the benefits are more broadly seen across a primary prevention setting, and importantly whether there is additional benefit of combining agents. This paper goes some way to answering this from real-world primary-care data in the UK comparing people with outcome events for CV disease and HF against multiple controls. It is striking how similar the odds ratios were for both agents compared with the large clinical trial data. It is also important that combining classes resulted in a 30% overall reduction in major CV and cerebrovascular events, adding weight to calls to use them together. At present people will have to self-fund one agent if they are to do that. SGLT-2 agents had a clearly superior effect on risk for HF over GLP-1 agents and there was not the same additional benefit of combination.

Reference: Diabetes Care 2022;45:909–18
Abstract

Effects of glucagon-like peptide-1 receptor agonists on cardiovascular and renal outcomes

Authors: Yoshiji S et al.

Summary: This was a meta-analysis and meta-regression analysis of data from eight studies of GLP-receptor agonists (n=60,800) reporting major adverse CV events (CV-related mortality, stroke and MI) as the primary outcome. Reductions in the risks of major adverse CV events and a composite renal outcome were seen with GLP-1 receptor agonists (respective HRs 0.86 [95% CI 0.80, 0.93] and 0.80 [0.73, 0.87]); each percentage point reduction in HbA_{1c} level was associated with 26% and 35% decreases in the logarithm of the HRs for the two endpoints, respectively, but weight reduction was not significantly associated with any outcome.

Comment: This study pooled all the major CV outcome trials across the range of GLP-1 agonists, with a total of over 60,000 patients. In the meta-analysis, the HR for major CV events was 0.86, or a 14% lower risk compared with placebo, and a 20% lower risk of combined renal outcomes. Further analysis showed that these effects were associated with the reduction in HbA_{1c} level but not with any reduction in bodyweight, which is another benefit of this class of drugs. This may be important when evaluating the effectiveness of the addition of a GLP-1 agonist in an individual, especially when weighing up whether to use a GLP-1 agonist or an SGLT-2 inhibitor. Having said that, please see the evidence from the real-world data using a combination of the two agents.

Reference: Diabetes Obes Metab; Published online Feb 8, 2022
Abstract

Independent commentary by Professor Jeremy Krebs MBChB, FRACP, MD

Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He trained in Endocrinology at Wellington Hospital in New Zealand and then did his doctorate with the Medical Research Council - Human Nutrition Research unit in Cambridge England. His thesis was on the impact of dietary factors on obesity and insulin resistance. Professor Krebs returned to New Zealand in 2002 to take up a consultant Endocrinology post at Wellington Hospital, where he was Clinical Leader of Endocrinology and Diabetes. He heads the research group and is 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.**