Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 134 – 2020

In this issue:

Abbreviations used in this issue

BMI = body mass index
BP = blood pressure
CV = cardiovascular
DKA = diabetic ketoacidosis
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
HF = heart failure
RCT = randomised controlled trial
SGLT = sodium glucose cotransporter

Welcome to issue 134 of Diabetes and Obesity Research Review.

This issue begins with research reporting a lower risk of gout in recipients of SGLT-2 inhibitors (for type 2 diabetes) than GLP-1 receptor agonist recipients. NZ research is included in the form of a retrospective review describing differences in glycaemic control according to age, gender, rurality and ethnicity in patients with type 1 diabetes from the Waikato region. Also relevant to NZ's Pacific population is research from our trans-Tasman neighbours reporting on the value of a church-based lifestyle intervention programme targeting Samoans living in Sydney. This issue concludes with a large umbrella analysis of meta-analyses providing us with a comprehensive assessment of CV outcomes associated with a range of glucose-lowering medications.

We hope you enjoy this update in diabetes and obesity research, and our recent special report on COVID-19 and diabetes. We would be delighted to hear your thoughts and feedback.

Best regards,

Professor Jeremy Krebs
jeremykrebs@researchreview.co.nz

Assessing the risk for gout with sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes

Authors: Fralick M et al.

Summary: Gout rates were compared between cohorts of adults newly prescribed SGLT-2 inhibitors versus GLP-1 receptor agonists for type 2 diabetes in this population-based study using US insurance claims data (n=295,907). Compared with propensity score-matched GLP-1 receptor agonist recipients, SGLT-2 inhibitor recipients had a significantly lower incidence rate of gout (4.9 vs. 7.8 events per 1000 person-years; hazard ratio 0.64 [95% CI 0.57, 0.72]).

Comment: Gout is a common comorbidity of type 2 diabetes and very relevant in NZ, with Māori more likely to have both conditions. There is increasing evidence for additional – non-glucose-lowering – CV and renal benefits of the SGLT-2 inhibitor class of medications that have been well reported and discussed previously. Blockade of SGLT-2 not only reduces glycaemia, but also reduces serum uric acid levels, which may therefore reduce the incidence of gout. This study focuses on this question, using an insurance database from the US, and a propensity matching design as opposed to a true RCT. That said, the sample size was very large, with almost 300,000 people split between those starting an SGLT-2 inhibitor or a GLP-1 agonist. There were 40% fewer new cases of gout in those using an SGLT-2 inhibitor, but the overall rates were actually very low. How this might translate to the NZ context, and particularly for Māori, would be very interesting. The benefits may potentially be greater, and when combined with reduced risks of CV events and renal failure, may significantly improve equity.

Reference: Ann Intern Med 2020;172:186–94
Abstract

Covid-19 Response: Our heartfelt thanks

All of us at Research Review want to thank you for the part you are playing in the Covid-19 crisis. Our hats go off to you, and we are proud to be associated with you. Our role in all of this is to support you by keeping you informed and up to date as much as we possibly can.

Antimicrobial stewardship in diabetic ketoacidosis

Authors: Gassiep I et al.

Summary: This retrospective chart review of 111 patients with type 1 diabetes who presented with DKA a combined total of 249 times to a single centre reported on infections precipitating DKA, microbiological aetiology and antimicrobial prescribing practices over a ~3-year period ending mid-2018. Infections were suspected for 40% of the presentations, with 14.5% being proven or probable infections. Skin and soft tissue infections were present in 25% of presentations, UTIs in 22% and respiratory tract infections in 19%. Of 100 presumed infections, pathogens were identified in 24; these included *Staphylococcus aureus* (46%), *Klebsiella pneumoniae* (17%) and *Escherichia coli* (13%); no viral pathogens were detected. Three-quarters of the 80 prescriptions for empirical antimicrobials did not conform with guidelines for the management of suspected infections. Single-agent ceftriaxone was the most frequently prescribed antimicrobial, and was appropriately prescribed in 30% of cases.

Comment: Historically, infection has been the most common trigger of ketoacidosis in people with type 1 diabetes. I teach medical students to hunt hard for a source of infection once they have addressed fluids, insulin and potassium. This report from northern Australia suggests that infection may not be as common a trigger as we might imagine. This retrospective audit of over 100 cases of DKA revealed only 15% of confirmed infections, with the majority of cases of DKA precipitated by poor adherence to insulin regimens. It also demonstrated inappropriate antibiotic prescription in many of the cases of DKA that were not related to infection. Therefore, whilst we must be vigilant and continue to actively look for infection, care must be exercised in use of antibiotics where none is found, with more targeted questioning about adherence and/or self-harm.

Reference: Intern Med J 2020;50:173–7
Abstract

Glycaemic control across the lifespan in a cohort of New Zealand patients with type 1 diabetes mellitus

Authors: Tamatea JAU et al.

Summary: Differences in glycaemic control according to age, gender, rurality and ethnicity were retrospectively reviewed for 1303 patients with type 1 diabetes entered into the Waikato Regional Diabetes Database. The patients' median HbA_{1c} level was 67 mmol/mol (8.3%) with those aged 15–29 years having the highest levels and 85.3% of all patients having a level that exceeded clinical recommendations. Patients on insulin pump therapy had a lower median HbA_{1c} level than those receiving multiple daily injections (63 vs. 69 mmol/mol, or 7.9% vs. 8.5% [p<0.001]), although Māori and males were significantly less likely to be on insulin pump therapy (respective p values 0.003 and <0.0001). An association was seen between worsening glycaemic control and increasing social deprivation (p<0.001); this was not influenced by rural versus urban living.

Comment: The evidence for the benefit of tight glycaemic control in type 1 diabetes dates back several decades. However, despite this and advances in available insulins and technology for monitoring glucose and administering insulin, people with type 1 diabetes continue to struggle to achieve their goal. This is further highlighted in this paper from Waikato, where 85% of people had an HbA_{1c} level above target. It is notable that young adults had the highest HbA_{1c} levels, an observation that we all see in our clinics. The authors point to Māori ethnicity and social deprivation as important factors, as well as reduced access to pumps. Whilst these may accentuate the difficulties people face, I think it is more complex than this when 85% do not meet their target. Managing type 1 diabetes is tough and relentless, no matter who you are.

Reference: Intern Med J; Published online March 16, 2020
Abstract

Establishment and validation of a risk prediction model for early diabetic kidney disease based on a systematic review and meta-analysis of 20 cohorts

Authors: Jiang W et al.

Summary: These authors used data from a meta-analysis of studies reporting on diabetic kidney disease risk factors in 41,271 patients with type 2 diabetes to derive a model for predicting this complication. Factors that were significantly predictive of diabetic kidney disease and were included in the model were age, BMI, smoking, diabetic retinopathy, HbA_{1c} level, systolic BP, high-density lipoprotein cholesterol level, triglyceride levels and urinary albumin-to-creatinine ratio; estimated glomerular filtration rate was also predictive but was significantly heterogeneous among the studies so was not included in the model. The individual risk factors were assigned scores according to their weightings; the highest score was 37.0. Validation undertaken in an external cohort of Chinese patients with median follow-up of 2.9 years revealed respective sensitivity and specificity values of 0.847 and 0.677 at a cutoff value of 16.

Comment: Diabetic nephropathy is one of the most debilitating and costly complications of diabetes that we try to prevent. Currently we screen for the risk of developing nephropathy in people with diabetes by regular urine microalbumin testing. While this is useful for detecting early disease, and identifying people who need more aggressive BP and glycaemic management, it doesn't differentiate those at greatest risk or rapid progression of renal failure. Any tool that could optimise this would be very useful. This paper reports a risk prediction tool for diabetic kidney disease derived from readily available clinical data from over 40,000 people with type 2 diabetes. The scoring tool was then validated in a separate cohort. The parameters included in the model were all predictable factors, but the strength of the tool is in the relative weighting and collation of them together. This has the potential to be useful clinically, but as with any such tool, this will only be the case if it is easy to use in an automated practice management system, otherwise it is very unlikely to be actually used.

Reference: Diabetes Care 2020;43:925–33
Abstract

A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers

Authors: Frykberg RG et al., on behalf of the TWO2 Study Group

Summary: Patients with diabetes and chronic diabetic foot ulcers (n=220) were randomised to multimodal cyclical pressure topical wound oxygen home therapy or sham therapy added to optimal standard care in the TWO2 study. At first analysis, there was a significant difference between the active versus sham therapy arm for ulcer closure (41.7% vs. 13.5%; adjusted odds ratio 6.00 [97.8% CI 1.44, 24.93]), with a significantly greater likelihood of ulcer healing by week 12 (adjusted hazard ratio 4.66 [1.36, 15.98]) and a greater 12-month ulcer closure rate (56% vs. 27% [p=0.013]).

Comment: I confess that I know nothing about this treatment, but the study caught my eye because it was well designed and addressed an important issue that causes a lot of morbidity and cost. Topical oxygen therapy was >4 times more effective than standard care in healing ulcers at 12 weeks. This benefit was attenuated but still twice as likely to result in persistent closure of the ulcers at 12 months. This looks to be a highly effective treatment. It may already be being used around the country, but I have not come across it. It is something that should be considered and explored by podiatrists and multidisciplinary foot clinic teams.

Reference: Diabetes Care 2020;43:616–24
Abstract

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

Effects of bariatric surgery in early- and adult-onset obesity in the prospective controlled Swedish obese subjects study

Authors: Kristensson FM et al.

Summary: This analysis of data from participants from the prospective Swedish Obese Subjects study sought to establish if obesity status at age 20 years has an influence on later-life bariatric surgery outcomes. Study participants were aged 37–60 years with BMI ≥34 kg/m² for men or ≥38 kg/m² for women at enrolment, with 2007 assigned to bariatric surgery and 2040 to usual care, and stratified as normal weight (BMI <25 kg/m²), overweight (25–29.9 kg/m²) or obese (≥30 kg/m²), calculated using self-reported bodyweight values, at age 20 years. Small but statistically significant differences were seen for bodyweight reductions among the subgroups after bariatric surgery (p=0.032 for interaction), with participants who were obese at age 20 years having the greatest reductions. For the respective subgroups with normal weight, overweight and obesity at aged 20 years, bariatric surgery was associated with increased likelihoods of type 2 diabetes remission (odds ratios 4.51, 4.90 and 5.58 [p=0.951 for interaction]) and reduced type 2 diabetes incidence (0.15, 0.13 and 0.15 [p=0.972 for interaction]), and reductions in microvascular complications independent of obesity status at age 20 years (p=0.650 for interaction). Associations between bariatric surgery and CV disease were similar among the subgroups (p=0.674 for interaction), as were surgical complications.

Comment: There is now overwhelming evidence that bariatric surgery is a highly effective treatment for type 2 diabetes. This is true for several different procedures and for people of different levels of obesity at the time of surgery. The Swedish Obesity Study is the longest running prospective study of bariatric surgery and although not randomised has given us a wealth of data and in insight into the relationship between obesity and diabetes and the longitudinal effects of surgery on that. This report focuses on the question of whether early obesity influences the metabolic benefits of surgery much later in life. The hypothesis being that early obesity may diminish the benefits. However, it is interesting that that does not appear to be the case. It supports the idea that β-cell function and failure are the most important factors and that obesity and insulin resistance reveals or hastens the metabolic decline/reversal. This is further supported by the observation that remission following surgery is less common in those already requiring insulin therapy – and thus are further down the pathway of β-cell failure. It's good to inherit an abundance of β-cells!

Reference: Diabetes Care 2020;43:860–6
Abstract

Outcomes of a church-based lifestyle intervention among Australian Samoans in Sydney

Authors: Ndwiga DW et al.

Summary: These researchers reported on the effectiveness of the Le Taeao Afua diabetes prevention programme, a culturally adapted, church-based lifestyle intervention delivered by community coach and peer support facilitators aimed at preventing and promoting self-management of type 2 diabetes, and targeted towards Samoans living in Australia. Of 107 participants enrolled, 68 (63.5%; mean age 48.9 years; 57.2% female) had before and after intervention data for analysis. Participants with diabetes experienced a fall from baseline in HbA_{1c} level after completing the programme (from 65 to 57 mmol/mol, or from 8.1% to 7.4% [p=0.040]); the reduction for those with newly diagnosed diabetes did not reach statistical significance (from 64 to 54 mmol/mol, or 8.0% to 7.1% [p=0.131]). Among participants without diabetes, weekly moderate and vigorous physical activity increased (from 316.1 to 562.4 min [p=0.007]) as did their knowledge of diabetes (p<0.001). There was no significant change for BP, BMI or waist circumference associated with completion of the programme.

Comment: In NZ, the highest rates of type 2 diabetes are seen in the Pacific population, who also have high rates of diabetes complications. Therefore anything that might be effective in preventing diabetes or assisting in self-management and improved outcomes needs to be tried and assessed. Because the church community is very important for many Pacific people, it is often touted as an environment where interventions could be delivered. However, the evidence to support the effectiveness of such an approach has been lacking. It is therefore great to see this study. The authors acknowledge that this is an observational cohort design and that an RCT is required, but the initial results are encouraging that a community approach, delivered in a church setting, can be effective in improving health measures for Pacific people with and without diabetes.

Reference: Diabetes Res Clin Pract 2020;160:108000
Abstract

A food-based, low-energy, low-carbohydrate diet for people with type 2 diabetes in primary care

Authors: Morris E et al.

Summary: Thirty-three patients with type 2 diabetes and BMI ≥30 kg/m² were randomised 2:1 to an 800–1000 kcal/day, food-based, low-carbohydrate (<26% energy) diet for 8 weeks, followed by a 4-week weight maintenance period and four 15- to 20-minute appointments with a nurse, or to usual care, in this feasibility trial; 32 participants completed follow-up. Compared with usual care, the intervention was associated with greater reductions in mean weight loss (9.5 vs. 2kg [p<0.001]) and mean HbA_{1c} level (16.3 vs. 0.7 mmol/mol [p<0.001]).

Comment: The popularity of reduced carbohydrate diets ebbs and flows over time. There have been many iterations of these diets and its extreme version, the 'keto diet', is currently de rigueur. Whenever you mention 'low-carb diets' in nutrition circles, you get a very polarised response. However, there is no doubt that for some individuals, following a low-carbohydrate diet is achievable, preferable and successful in facilitating weight control. For people with type 2 diabetes, the potential benefit of this approach is even greater, with less demand on pancreatic insulin production. This study is a feasibility study to establish whether prescription and support of a low-carbohydrate energy-restricted diet within primary care is achievable. The results were encouraging, with greater weight loss and impressive reductions in HbA_{1c} level than standard care. It is of course important to realise that this was over 12 weeks and the real test is what happens at 12 months and 2 years. I'm sure the authors are already planning or conducting such a trial, and we await the outcome.

Reference: Diabetes Obes Metab 2020;22:512–20
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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Inhibition of food craving is a metabolically active process in the brain in obese men

Authors: Wang G-J et al.

Summary: Using fluorodeoxyglucose-PET, brain responses during attempted cognitive inhibition of craving on exposure to food cues were compared between 16 obese men and 11 age-matched nonobese men in this research. While in a food-deprived state, the men's brain glucose metabolism was measured with no food stimulation, food stimulation with no inhibition and food stimulation with attempted inhibition on separate days, with individualised favourite food items presented prior to and after the fluorodeoxyglucose injection for 40 minutes. In both groups, food stimulation versus no stimulation was associated with increased glucose metabolism in the inferior and superior frontal gyri, default mode network and cerebellum, and attempted inhibition versus no inhibition was associated with suppressed metabolism in the right subgenual anterior cingulate, orbitofrontal areas and bilateral insula and temporal gyri. However, the obese men exhibited increased metabolism in the pregenual anterior cingulate cortex and caudate during attempted inhibition versus no inhibition, whereas the nonobese men did not. Negative correlations between changes in food desire from no inhibition to attempted inhibition and changes in metabolism in the pregenual anterior cingulate cortex/caudate were also seen in the obese men and not in their nonobese counterparts.

Comment: Well this is a fun little paper. Energy intake is such a complex interaction between genetics, environment and behaviour. How this battle plays out largely determines our weight. Of course energy expenditure is the other critical player. This is an interesting experiment to determine whether there are any important differences between obese and lean men in terms of brain activity during active attempted inhibition of food intake. The use of PET scanning to measure actual metabolic brain activity is a strength. It shows that for obese men, there is more interaction between food stimuli and brain activity, and a more energy-dependant process to overcome the positive stimulus of food. We are hard-wired to conserve energy, so this observation may in part explain how obese men may be less successful in their attempts to resist food when available. I'm just trying to decide which of my many favourite foods I would choose for this experiment!

Reference: Int J Obes 2020;44:590–600
Abstract

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Association of glucose-lowering medications with cardiovascular outcomes

Authors: Zhu J et al.

Summary: This umbrella review and evidence map included 232 meta-analyses of RCTs examining the CV safety of ten classes of antidiabetes drugs. Six risk and 38 protective associations with high evidence strength were identified. Glimepiride was associated with significantly increased stroke risk, rosiglitazone with MI and HF risk and pioglitazone with HF risk. The protective associations included significantly lower risks of: i) major adverse CV events with GLP-1 receptor agonists (including albiglutide, exenatide, liraglutide and semaglutide specifically), SGLT-2 inhibitors (including canagliflozin and empagliflozin specifically) and pioglitazone; ii) death from CV disease with GLP-1 receptor agonists and SGLT-2 inhibitors (including canagliflozin and empagliflozin specifically); iii) MI with GLP-1 receptor agonists (including albiglutide specifically), SGLT-2 inhibitors and pioglitazone; iv) HF with GLP-1 receptor agonists (including albiglutide specifically) and SGLT-2 inhibitors (including canagliflozin, dapagliflozin and empagliflozin specifically); and v) stroke with GLP-1 receptor agonists (including dulaglutide and semaglutide specifically) and pioglitazone.

Comment: I have included this study for two reasons. Firstly, it pulls together all of the evidence for positive and negative effects of diabetes medications on CV outcomes, and secondly because I couldn't resist the cute concept of an 'umbrella review'! There really is so much evidence now for the broad benefits of the SGLT-2 inhibitors and the GLP-1 agonists. As this review reports, this is in contrast to adverse effects of the sulfonylureas routinely used as the comparator in Pharma trials, and the thiazolidinediones; although pioglitazone has mixed effects. These findings continue to keep the focus on the need for PHARMAC to fund either or both SGLT-2 inhibitors and GLP-1 agonists. It also raises concerns that the US FDA has removed their requirement for new drugs in the diabetes area to undergo CV outcome trials. It was only because of this requirement, brought in after the postmarketing negative effects of rosiglitazone were reported, that we have had these major trials conducted, which have given us such useful evidence for these new drugs. Sadly, without the FDA requirement, I think it is unlikely that the Pharma industry will continue to conduct such trials and they are unlikely to be funded by other sources.

Reference: Lancet Diabetes Endocrinol 2020;8:192–205
Abstract

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