Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 132 – 2019

In this issue:

Abbreviations used in this issue
BMI = body mass index
CGM = continuous glucose monitoring
CV = cardiovascular
DKA = diabetic ketoacidosis
DPP = dipeptidyl peptidase
GI = gastrointestinal
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
HR = hazard ratio
PIP = Prediabetes Intervention Package
SGLT = sodium glucose cotransporter
UTI = urinary tract infection

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Diabetes & Obesity Research Review

Welcome to issue 132 of Diabetes and Obesity Research Review.

Metabolic surgery results in significant reductions in cardiometabolic risk, but concerns have been raised regarding other late adverse events, including CV events. The first two papers in this issue are large retrospective analyses that have reported on such outcomes. There is also a systematic review and meta-analysis on plant-based diets, suggesting benefits for type 2 diabetes primary prevention, particularly when they are rich in healthy plant-based foods. Two papers reporting NZ research are also included: one compared outcomes associated with the differing DKA (diabetic ketoacidosis) protocols used at North Shore Hospital and Auckland Hospital, while the second was a cost-effectiveness analysis of the PIP (Prediabetes Intervention Package) in NZ primary care. This issue concludes with research reporting evidence for increased diabetes remission 1 year after a lifestyle intervention, supporting the need for further large-scale research.

I hope you enjoy this research update. Please keep sending us your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Long-term adverse events after sleeve gastrectomy or gastric bypass

Authors: Thereaux J et al.

Summary: This 7-year observational study reported late adverse events after gastric bypass or sleeve gastrectomy for a cohort of 8966 patients who had undergone these procedures (55% gastric bypass, 45% sleeve gastrectomy) in France in 2009, matched to 8966 obese nonsurgical control patients as comparators. Mean follow-up was 6.8 years. Compared with controls, patients who underwent gastric bypass or sleeve gastrectomy had reduced mortality (respective HRs 0.64 [95% CI 0.52, 0.78] and 0.38 [0.29, 0.50]), but higher risks of invasive GI surgery or endoscopy (respective incidence rate ratios 2.4 [95% CI 2.1, 2.7] and 1.5 [1.3, 1.7]), GI disorders not leading to invasive procedures (1.9 [1.7, 2.1] and 1.2 [1.1, 1.4]) and nutritional disorders (4.9 [3.8, 6.4] and 1.8 [1.3, 2.5]). There were no significant associations between bariatric surgery and psychiatric disorders with the exception of a greater risk of alcohol dependence after gastric bypass (incidence rate ratio 1.8 [95% CI 1.1, 2.8]).

Comment: With an increase in the use of bariatric surgery in a wider range of people for obesity and type 2 diabetes management, it is important to keep reviewing the evidence for long-term adverse outcomes. This study reports the relative outcomes for individuals undergoing either gastric bypass or sleeve gastrectomy compared with matched controls who did not undergo surgery. A strength of the study is the large numbers and duration of follow-up. However, a weakness is the lack of randomisation and retrospective matching of controls, which introduces the potential for bias. Nonetheless, there was an impressive reduction in risk of mortality for both surgical treatments. This comes at the expense of an approximately doubling in the risk of hospital admission, mainly for GI complications. The study also confirms other data showing an increase in alcohol dependence following surgery. So whilst there are clear benefits of bariatric surgery, there are still some important long-term adverse effects that need to be discussed with patients.

Reference: Lancet Diabetes Endocrinol 2019;7:786–95
Abstract

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Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity

Authors: Aminian A et al.

Summary: This research reported major adverse CV events among 2287 obese adults with type 2 diabetes who had undergone metabolic surgery, with 11,435 matched nonsurgical controls used for comparisons. Over median follow-up of 3.9 years, the cumulative 8-year incidence of a primary endpoint event (death from any cause, coronary artery events, cerebrovascular events, heart failure, nephropathy and atrial fibrillation) was lower among surgical patients than the nonsurgical controls (30.8% vs. 47.7%; adjusted HR 0.61 [95% CI 0.55, 0.69]), as was each of its components, including all-cause mortality (10.0% vs. 17.8%; 0.59 [0.48, 0.72]), and a composite endpoint of myocardial infarction, ischaemic stroke and death.

Comment: This is a similar study to the previous retrospective follow-up analysis from France. This one is from the US and more focussed on CV outcomes, which is the standard to which new drugs in diabetes are held to. Once again, the study is limited by the retrospective nature of matching to controls rather than being a prospective randomised trial. Whilst the authors have done their best to address this by matching each patient to five controls, and the variables measured were balanced between groups, it doesn't completely remove the potential for unrecognised confounders. It is as good as you can get though. We see a very impressive reduction in the risk for CV events. This was robust across the individual components of the combined primary outcome, with an approximately 40% relative risk reduction compared with nonsurgical management. Much of these data come from prior to widespread use of SGLT-2 inhibitors or GLP-1 agonists, which we see have major benefits and would likely attenuate the differences in outcomes described in this paper.

Reference: JAMA 2019;322:1271–82
Abstract

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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.

As well as clinical and teaching activities, Professor Krebs maintains active research interests in the area of obesity and diabetes, with a particular focus on the association between obesity and type 2 diabetes, both from an aetiology and management perspective, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery.

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

Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY)

Authors: Matthews DR et al., for the VERIFY study group

Summary: VERIFY was a 5-year trial investigating first-line combination vildagliptin/metformin therapy versus metformin monotherapy in patients with newly diagnosed (within 2 years) type 2 diabetes. Adult participants (HbA_{1c} level 48–58 mmol/mol; BMI 22–40 kg/m^2) were randomised to 5 years of treatment with metformin 1000mg, 1500mg or 2000mg daily with (n=998) or without (n=1003) vildagliptin 50mg twice daily. Participants whose initial metformin monotherapy treatment failed (defined as HbA_{1c} level ≥53 mmol/mol) as assessed at two consecutive visits 13 weeks apart were moved to the dual treatment arm. Dual combination treatment provided more favourable clinical results compared with initial metformin monotherapy, with reduced rates of initial treatment failures (43.6% vs. 62.1%) and a significantly increased median time to treatment failure (beyond study duration vs. 36.1 months [p<0.0001]).

Comment: I am including this study not because of the specific drug, but because of the concept. The traditional model of care for type 2 diabetes has been a progressive additive pathway of lifestyle, monotherapy usually with metformin and then a second-line drug when the patient's HbA_{1c} level increases. There has been much written about treatment inertia and calls for an earlier combined therapy approach. This may make some sense, but also exposes individuals to the risk of more side effects from the drugs, and hasn't been demonstrated to actually make a difference to long-term diabetes-related outcomes. This study was set up to try to answer some of these issues. It happens to use vildagliptin, which is the DPP-4 inhibitor that we have funded here in NZ, a class of agents with very few side effects and good tolerability. What I struggle with in this type of study is that it should not come as any surprise that if you treat a person with two glucose-lowering drugs compared with one, their glycaemic control is better and remains below any chosen cutoff value for longer. You are just treating earlier, but what does interest me about this study is that there just may be some additional benefit on longer-term further progression of diabetes and need for a third-line agent. I think there will be a lot of discussion about this trial, and sadly a lot of hyperbole. Nevertheless, for a drug that is easy to take and has very few side effects, there may be a place for early combined treatment; especially if the HbA_{1c} level is very high at diagnosis.

Reference: Lancet 2019;394:1519–29
Abstract

Association between plant-based dietary patterns and risk of type 2 diabetes

Authors: Qian F et al.

Summary: This systematic review and meta-analysis included nine studies (n=307,099) that reported data on the relationship between adherence to plant-based dietary patterns and type 2 diabetes incidence among adults; there were 23,544 cases of incident type 2 diabetes across the studies. There was a significant inverse association between higher versus lower adherence to a plant-based dietary pattern and type 2 diabetes risk (relative risk 0.77 [95% CI 0.71, 0.84]; I^2=44.5% [p=0.07] for heterogeneity). This association was: i) similar in a fixed-effects model (relative risk 0.80 [95% CI 0.75, 0.84]); ii) consistent across predefined subgroups; and iii) stronger when the definition of plant-based patterns was restricted to healthy plant-based foods (e.g. fruits, vegetables, whole grains, legumes and nuts; 0.70 [0.62, 0.79]). Most studies were judged to be of good quality in terms of dietary assessment, disease outcomes and statistical adjustment for confounders.

Comment: I must first declare that I am not a vegetarian. In fact, I love meat – red meat. Don't shoot me. So I debated about even including this study; however, there is increasing focus, debate and discussion about the merits of a more plant-based diet generally across the population, fuelled more by climate change than health, but nonetheless topical and important. This systematic review and meta-analysis of observational epidemiological studies shows that adherence to a plant-based diet has a 'dose-dependent' benefit in association with lower rates of type 2 diabetes. There was as much as a 30% reduction in risk where the plant-based diet included elements with known benefits such as fruit, wholegrains and legumes. This is impressive and warrants attention. However, as with any observational data, we must be careful to watch for confounders. Particularly here where it is highly probable that those adopting a very healthful plant-based diet will also be more likely to adopt other healthy lifestyle characteristics, such as regular exercise, not smoking and less likely to be overweight. So yes, I love a good steak. Should I eat less of it, probably. Tough.

Reference: JAMA Intern Med 2019;179:1335–44
Abstract

Differing protocols of managing adult diabetic ketoacidosis outside of the intensive care unit make no difference to the rate of resolution of hyperglycaemia and acidosis

Authors: Braatvedt G et al.

Summary: Outcomes were compared between 26 patients aged >16 years with type 1 diabetes admitted for DKA to the general ward of North Shore Hospital (30 admissions), which uses a UK weight-based ketone centric protocol, with those of 35 patients admitted to the general ward of Auckland Hospital (41 admissions), which uses a protocol based on glucose measurements alone; the degrees of ketoacidosis and hyperglycaemia at admission were similar between the two hospitals. The hospitals were similar for the duration of insulin and 10% dextrose infusions, but patients admitted to North Shore Hospital received a greater total number of units of insulin infused and a higher hourly rate of dextrose, with similar hypokalaemia and hypoglycaemic event rates at each site. There was also no significant difference between the two hospitals for hyperglycaemia and acidosis resolution rates or length of stay.

Comment: There is often debate about the most appropriate way to manage DKA, with some suggesting a focus on fluid and glucose treatment and others targeting ketone resolution. There are many different protocols in circulation, all with variations on a theme, and ardent supporters, fuelled mostly by those who have derived them or worked in a particular hospital as a junior doctor! This study reports the outcomes of two different DKA protocols in hospitals within the greater Auckland area. The bottom line is that it didn't really matter which protocol you use; the outcomes were similar. I think that what this highlights is that for DKA, the most important thing is having a protocol that is followed by the medical and nursing teams. In teaching medical students, I focus on the principles of management and say that any hospital they work in will have a protocol, so find it and follow it. This study supports that mantra.

Reference: N Z Med J 2019;132(1504):13–23
Abstract

A cost-effectiveness analysis of the Prediabetes Intervention Package (PIP) in primary care

Authors: Connor D et al.

Summary: The cost effectiveness of NZ's PIP programme, piloted in Hawke's Bay, was evaluated from a health funder perspective using 2015 NZ dollars, with costs and per kilogram weight change at 6 months analysed at an individual participant level. Using multiple imputation and bootstrapping, a significant 1.87kg difference was seen for median bodyweight between intervention and control groups at 6 months. The programme was associated with an incremental cost-effectiveness ratio of $170.90 for each 1kg of bodyweight lost; the incremental cost-effectiveness ratio for lower-cost scenarios ranged from $95.33 to $120.74.

Comment: Preventing the progression of prediabetes to diabetes is an important health goal for NZ as we try to turn around the rates and morbidity of type 2 diabetes. With an estimated 25% of the adult population affected with prediabetes, this should be a health priority. Finding cost-effective ways to do this at both individual and public health levels is the challenge. The PIP study is a pragmatic, relatively simple lifestyle intervention that was designed to be able to be delivered in the NZ primary-care setting. As such, it is translating evidence that such interventions can be effective, but also showing how to actually deliver this in the diverse population of Hawkes Bay. This is very promising, and we eagerly await the results of the bigger trial of this that is currently running.

Reference: N Z Med J 2019;132(1504):24–34
Abstract

Text messaging and brief phone calls for weight loss in overweight and obese English- and Spanish-speaking adults

Authors: Godino JG et al.

Summary: English- and Spanish-speaking adults with BMI 27.0–39.9 kg/m^2 were randomised to a 1-year weight loss intervention using SMS text messages (ConTxt; n=101), the same intervention combined with health coaching calls (n=96) or a control group of standard print materials on weight reduction (n=101); 6- and 12-month follow-up visits were attended by 87.2% and 84.9% of the participants, respectively. Compared with the control group, participants from the SMS plus health coaching group experienced a significantly greater mean percent bodyweight loss at 12 months (difference, –3.0 [p=0.003]) but the difference for the SMS only group was not significant (–1.07 [p=0.291]); there was also no significant difference between the SMS plus health coaching and the SMS only groups (–1.95 [p=0.057]). Similar findings were seen for changes in absolute weight, BMI and percentage bodyfat at 12 months. Exploratory analyses suggested that the English-speaking participants responded less favourably to SMS plus health coaching than the Spanish-speaking participants.

Comment: With widespread use of personal smart phones, the option of technology-based personalised interventions has become very popular for the management of a wide range of long-term conditions. The effectiveness and durability of impact reported has been variable. Many studies using nonselective motivational SMS messages have not shown effectiveness. This study compared text messages with or without additional personal contact with a health coach to standard printed advice on weight loss. It shows that the combination of the two is superior and facilitates a mean weight loss of about 3.6kg. This is comparable to most effective diet and lifestyle weight-loss studies. For those who like this, it may be a good alternative. The old fart in me suspects the personal real-human contact with the health coach is the more critical element in the long term. I would like to see a cost effectiveness analysis of this study and comparison with other interventions.

Reference: PLoS Med 2019;16:e1002917
Abstract

Nationwide trends in pancreatitis and pancreatic cancer risk among patients with newly diagnosed type 2 diabetes receiving dipeptidyl peptidase 4 inhibitors

Authors: Lee M et al.

Summary: Associations between DPP-4 inhibitors and both pancreatitis and pancreatic cancer were explored for a population-based cohort of Korean patients with newly diagnosed type 2 diabetes treated with DPP-4 inhibitors (n=10,218) and other antidiabetic agents (n=22,990). DPP-4 inhibitor use was associated with significantly increased risks of pancreatitis and pancreatic cancer (adjusted HRs 1.24 [95% CI 1.01, 1.52] and 1.81 [1.16, 2.82]) with a 6-month drug use lag period; these risks were generally consistent during the first 12 months and 1 year after the initial prescription with no evidence of an increasing trend according to duration of exposure.

Comment: The issue of pancreatitis and pancreatic cancer with the incretin-based therapies, the DPP-4 and GLP-1 drugs, won't go away. Early signals from some of the phase 3 clinical trials raised the possibility of an increased risk, but post-registration large registry-based studies have been reassuring. Both pancreatitis and pancreatic cancer are both more common in people with diabetes than those without, but the issue is whether these drugs further increase that risk. This study, from a Korean insurance database, again suggests that there may be an increased risk of both pancreatitis and cancer with DPP-4 inhibitors. There may be an ethnicity risk at play here compared with European registry data, but it does suggest we need to keep a very open mind about this issue. However, the actual rate remains very low, and even a 24% increased relative rate of pancreatitis does not translate to a major risk across the population.

Reference: Diabetes Care 2019;42:2057–64
Abstract

Improvement in psychosocial outcomes in children with type 1 diabetes and their parents following subsidy for continuous glucose monitoring

Authors: Burckhardt M-A et al.

Summary: This prospective Australian research sought to determine the impact of CGM on psychosocial outcomes for 38 children aged >12 years with type 1 diabetes; 60 parents also contributed data to the study. CGM use was found to decrease parental total fear of hypoglycaemia from baseline (p=0.004), including the 'worry' subscore (p=0.004), and both the parents and children reported increased satisfaction with diabetes treatment. There was also a significant improvement in parental sleep and significant decreases in overnight finger prick testing, impaired hypoglycaemic awareness among children and HbA_{1c} level (from 68 to 65 mmol/mol [p=0.036]).

Comment: The ongoing development of technologies for CGM has the potential to revolutionise diabetes management. This is possibly most acutely seen in paediatric patients with type 1 diabetes where there is such an impact of the disease on both the child and the parents. The need for invasive finger pricking to monitor glucose levels, the fear of hypoglycaemia for both parent and child and the general burden of all this on the family are all issues that sit in the context of health professionals giving the message that tight control is important and reduces risks of long-term complications. This study reports the effect of availability of funded CGM on these variables in Australia. CGM certainly reduces the negative aspects for both child and parent, but not by as much as I might have expected. This is another study coming out that raises more questions for me about the utility of CGM and how we can best use it, best select patients for it and be aware that there are sometime unintended negative effects too. It is not the holy grail.

Reference: Diabetes Technol Ther 2019;21:575–80
Abstract

Sodium-glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections

Authors: Dave CV et al.

Summary: This population-based cohort study compared severe UTI events among new SGLT-2 inhibitor, DPP-4 inhibitor and GLP-1 agonist users using US insurance claims data. Two cohorts of adults with type 2 diabetes were created and matched 1:1 on propensity score: SGLT-2 inhibitor versus DPP-4 inhibitor users (cohort 1; n=123,752) or GLP-1 agonist users (cohort 2; n=111,978). In cohort 1, the respective incidence rates for severe UTI events among new SGLT-2 inhibitor and DPP-4 inhibitor users were 1.76 and 1.77 per 1000 person-years; HR 0.98 [95% CI 0.68, 1.41]), and in cohort 2, the respective incidence rates for SGLT-2 inhibitor and GLP-1 agonist users were 2.15 and 2.96 per 1000 person-years; 0.72 [0.53, 0.99]); these findings were robust across sensitivity analyses. Furthermore, there was no increased risk of outpatient UTIs among SGLT-2 inhibitor users in either cohort 1 or cohort 2 (respective HRs 0.96 [CI 0.89, 1.04] and 0.91 [0.84 to 0.99]).

Comment: As we are hopefully on the brink of getting better access to the SGLT-2 inhibitors, it is useful to learn more about the real-world experience of their use in clinical practice rather than just clinical trials. One expected and reported adverse effect of these drugs is UTIs secondary to increased urinary glucose levels. This study reports the rates of observed UTIs requiring hospitalisation or outpatient treatment from insurance claims databases in the US, for those initiating an SGLT-2 inhibitor compared with a DPP-4 inhibitor or GLP-1 agonist as a second-line therapy in type 2 diabetes. There was no increased risk compared with DPP-4 inhibitors and a marginal decrease compared with GLP-1 agonists. So it appears that for bacterial UTIs, the concerns surrounding the SGLT-2 inhibitors are largely unfounded. That does not address the increase in fungal skin infections – these can be minimised with good perineal hygiene.

Reference: Ann Intern Med 2019;171:248–56
Abstract

Type 2 diabetes remission 1 year after an intensive lifestyle intervention

Authors: Ried-Larsen M et al.

Summary: This secondary analysis assessed remission of type 2 diabetes for participants of a randomised controlled trial comparing a 12-month lifestyle intervention that included 5- to 6-weekly, 30- to 60-minute sessions of aerobic and combined aerobic and strength training sessions and individualised dietary plans aiming for a BMI of ≤25 kg/m² (n=64) with standard care (n=34) in patients with insulin nondependent type 2 diabetes; 93 of the participants completed 12 months of follow-up after the 12-month study period. There was a nonsignificant trend for a higher rate of type 2 diabetes remission at follow-up in the intervention arm compared with the standard care arm (odds ratio 4.4 [95% CI 0.8, 21.4]); when the five participants lost to follow-up were assumed to have relapsed, the association achieved statistical significance (4.4 [1.0, 19.8]).

Comment: There is good evidence from the DiRECT study that a very low-calorie diet for people with early type 2 diabetes can induce remission. This study adds further evidence to the DiRECT study results. Here the intervention was very early after diagnosis, which may have the advantage of targeting people when they are most motivated to reverse things. The intervention was a mixed physical activity and dietary intervention along similar lines to those used in diabetes prevention studies. After 2 years, the second of which had no active intervention, almost a quarter of those in the treatment group had remission of diabetes compared with 7% in the standard-care group. In this study, there was more of a focus on physical activity and physical fitness rather than weight loss. Although the overall rates of remission are lower than DiRECT, it does provide evidence that there is scope for either or both approaches. The real and outstanding question though is how can we actually translate both of these approaches into the real world in NZ. There is an urgent need to conduct good translational research in this area.

Reference: Diabetes Obes Metab 2019;21:2257–66
Abstract