Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 141 – 2021

In this issue:

Abbreviations used in this issue

BMI = body mass index
CGM = continuous glucose monitoring
CV = cardiovascular
DKA = diabetic ketoacidosis
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
HR = hazard ratio
MI = myocardial infarction
MUFA/PUFA = mono-/polyunsaturated fatty acid
RYGB = Roux-en-Y gastric bypass
SGLT = sodium glucose cotransporter

PHARMACY GUILD OF NEW ZEALAND

diabetes new zealand

NZMA New Zealand Medical Association

Welcome to issue 141 of Diabetes and Obesity Research Review, our first issue for 2021.

We begin with a cluster randomised trial showing that an online weight loss programme integrated with population health management slightly but significantly improved weight loss over usual care in patients with type 2 diabetes. Two papers from the N Z Med J highlight ethnic inequities in NZ: one reports that Māori and Pasifika people and those of lower socioeconomic status were over-represented in admissions for DKA at Middlemore Hospital, while the other found that adherence to screening guidelines for diabetes in pregnancy was worse for Māori than non-Māori. On a more positive note, another paper from the N Z Med J reports that primary-care nurses in Auckland have increased the number of foot examinations and the provision of recommended foot-care education over the last decade. The issue concludes with a secondary analysis of the EMPA-REG OUTCOME trial of empagliflozin versus placebo in participants with type 2 diabetes and atherosclerotic CV disease, showing a reduced burden of CV complications and all-cause hospital admissions.

We hope you enjoy the papers selected for this issue, and we look forward to your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Effect of an online weight management program integrated with population health management on weight change

Authors: Baer HJ et al.

Summary: Overweight/obese (BMI 27–<40 kg/m²) primary-care patients aged 20–70 years with type 2 diabetes or hypertension were randomised by cluster to an online programme with (n=298) or without (n=216) additional support from nonclinical staff to monitor progress, or to usual care (n=326) in this trial. The respective mean weight changes at 12 months in the usual care, online programme only and online programme plus support arms were –1.2, –1.9 and –3.1kg, with statistically significant differences between the online programme plus support and usual care groups (p<0.001) and between the online programme plus support and online program only groups (p=0.01); the mean weight changes for the respective study arms at 18 months were –1.9, –1.1 and –2.8kg.

Comment: We all know that achieving sustained and meaningful weight loss for people with obesity is very hard. There are so many barriers to the success of weight management programmes. One such barrier is time and access to individual or group sessions with health professionals. This makes online services theoretically attractive, but few studies have shown efficacy of online programmes. This study compared an online programme enhanced buy additional contact with an online programme alone or just simple education. Not surprisingly, the combined package resulted in greater weight loss – albeit very modest. To make this useful in clinical practice, the cost of the intervention has to be low, and that is primarily determined by staff costs. An economic analysis would help determine the utility of this approach in NZ.

Reference: JAMA 2020;324:1737–46
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. 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 FULL BIO CLICK HERE.**

Association between bariatric surgery and all-cause mortality

Authors: Doumouras AG et al.

Summary: The relationship between bariatric surgery and all-cause mortality was explored in Canadian population-based cohorts of 13,679 patients who had undergone bariatric surgery and 13,679 matched nonsurgical patients, followed for a median of 4.9 years. Compared with the nonsurgical group, the surgical group had a lower overall mortality rate (1.4% vs. 2.5%; adjusted HR 0.68 [95% CI 0.57, 0.81]), including for patients aged ≥55 years (0.53 [0.41, 0.69]), who had an absolute risk reduction of 3.3%; surgery was also associated with lower risks of CV-related mortality (0.53 [0.34, 0.84]) and cancer-related mortality (0.54 [0.36, 0.80]). The relative effects were similar between sexes, but men had a stronger association in absolute terms.

Comment: The role of bariatric surgery in weight management and metabolic health is well established. There are numerous longitudinal cohort studies and some randomised controlled trials showing benefits for weight loss, diabetes and CV disease risk. There are fewer studies reporting on mortality. This paper adds to that literature. In a case-matched design in large numbers of people undergoing bariatric surgery (80% gastric bypass), mortality was significantly lower than for matched controls after a mean of 4.9 years. The difference between cases and controls emerged early in the postoperative period and appeared to be continuing to diverge, suggesting that with longer follow-up, the benefits may be even greater.

Reference: Ann Intern Med 2020;173:694–703
Abstract

Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity

Authors: Lowe DA et al.

Summary: The 12-week TREAT trial randomised 116 participants with BMI of 27–43 kg/m² to consistent meal timing or time-restricted eating. The consistent meal timing group was instructed to eat three structured meals per day, and the time-restricted eating group to eat *ad libitum* from noon until 8:00pm and completely abstain from caloric intake from 8:00pm until noon the following day. A significant decrease in weight was seen in the time-restricted eating group (–0.94kg [p=0.01]), but there was no significant change in the consistent meal timing group (–0.68kg [p=0.07) or between groups (–0.26kg [p=0.63]). In a subgroup of 50 study participants who underwent additional in-person testing, a significant within-group decrease in bodyweight was seen for the time-restricted eating group (–1.70kg [p<0.001]) and a significant difference in appendicular lean mass index was seen between groups (–0.16 kg/m² [p=0.005]), but there was no significant change for any of the other secondary outcomes assessed within or between groups. Estimated energy intake did not differ significantly between groups.

Comment: Intermittent fasting has become a popular dietary intervention to facilitate weight loss. One popular form of intermittent fasting is the 5:2 diet, and another is time-restricted eating. This study looked at the effect of time-restricted eating on weight and metabolic outcomes after 12 weeks compared with regular mealtimes. The study design is interesting because it involved remote data collection on the majority of the participants. There was modest weight loss in both groups with no difference between them – possibly all explained simply by participating in a study focusing on diet. However, it is important to understand that neither group were actually instructed to reduce total energy intake. This may explain the degree of weight loss observed, and raises the question whether additional guidance on energy intake may have assisted and potentially resulted in more weight loss and associated improvements in metabolic parameters.

Reference: JAMA Intern Med 2020;180:1491–9
Abstract

Diabetic ketoacidosis admissions at Middlemore Hospital

Authors: Lee JH & Orr-Walker BJ

Summary: This was an observational study of cause and patient demographics for 57 patients with type 1 diabetes who had received a total of 69 diagnoses of DKA at Middlemore Hospital between July 1, 2015 and June 30, 2016; 35% of the patients were Pasifika, 23% were Māori and 56% were from the lowest socioeconomic status quintile. Nonadherence to insulin was the reason for DKA in 59%, while infections were associated with 16% of DKA cases and new diagnoses of type 1 diabetes were associated with 14%. Nonadherence was identified as the cause of DKA for greater proportions of Pasifika and Māori patients.

Comment: Admission to hospital with DKA is always an important event and highlights a person at risk for other adverse health outcomes associated with their diabetes. Of course, some present with new type 1 diabetes, but as this paper shows clearly, apart from that, nonadherence with insulin therapy is a more common and very important reason. Furthermore, in this NZ population, more Pacific and Māori patients and those with greater deprivation were more likely to present in this way. Although not presented here, mental health issues can also be a common underlying factor in these presentations and should be considered. These are important data, which unfortunately provide further evidence of worse health status and outcomes for Māori and Pacific compared with European New Zealanders.

Reference: N Z Med J 2020;133(1525):34–40
Abstract

Ethnic inequities in screening for diabetes in pregnancy in New Zealand – adherence to national guidelines

Authors: Chepulis L et al.

Summary: These NZ researchers reviewed the clinical records of 807 women without known diabetes prior to pregnancy who gave birth in hospitals or community birth centres in the Waikato region during June–August 2017. Some form of diabetes screening during pregnancy was performed for 94% of the women, with 65.3% receiving HbA_{1c} level screening at <20 weeks' gestation and 33.1% being tested for gestational diabetes mellitus at 24–28 weeks' gestation, but only around a quarter (26.4%) received all Ministry of Health guideline-recommended screening. The most common screening performed was HbA_{1c} level testing (83.9% of all pregnancies), and around three quarters of the women had undergone glucose load screening at some stage during their pregnancy. Compared with the 541 non-Māori women included in the study, a significantly lower proportion of the 263 Māori women received both HbA_{1c} level and further glucose load screening during the recommended gestational windows (17.5% vs. 31.6% [p<0.0005]).

Comment: These rates of screening for gestational diabetes mellitus across the board, let alone the ethnic differences, suggest some form of systemic failure. Whether this is due to a lack of education or understanding by young women who are pregnant or contemplating pregnancy, or more concerningly by health professionals, needs to be explored. It is pleasing to see that testing HbA_{1c} level at least is relatively good, and critical to detect women with undiagnosed type 2 diabetes, who have the worst pregnancy outcomes. However, work is required to understand and rectify the barriers to more complete glucose-based screening in the second trimester.

Reference: N Z Med J 2020;133(1525):106–113
Abstract

Improved foot management of people with diabetes by primary healthcare nurses in Auckland, New Zealand

Authors: Daly B et al.

Summary: Trends between 2006–2008 and 2016 in diabetes foot examinations performed by around a quarter of all Auckland-based primary-care nurses were assessed using self-administered questionnaires and telephone interviews. Compared with the 2006–2008 period, significantly more patients consulted by practice nurses received foot examinations (58% vs. 36%) and foot-care education (66% vs. 26%) in 2016, with significantly more nurses reporting routinely examining the feet of their patients (45% vs. 31%) and providing foot-care education (28% vs. 13%); these practices were associated with nurses undertaking >5 hours of diabetes education in the prior 5 years. No foot examination was performed in 43% of patients with diabetes in 2016, and of these, 23% had no record of a prior examination.

Comment: Good foot care and education is often forgotten in the management of diabetes. Thorough examination of the feet takes time and is therefore difficult to complete within the time constraints of a standard consultation in primary care. Therefore, it has become an important aspect of good primary-care practice nursing to provide this aspect of monitoring and care for people with diabetes. This paper reviews footcare in Auckland primary care and changes over a decade between 2006 and 2016. There have been major improvements across the board, which seem to be related to education and upskilling of practice nurses. Hopefully these improvements can be sustained and even further developed with well-structured systematic care.

Reference: N Z Med J 2020;133(1572):39–50
Abstract

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Association of types of dietary fats and all-cause and cause-specific mortality

Authors: Mazidi M et al., on behalf of the International Lipid Expert Panel (ILEP) & Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group

Summary: Associations between different types of dietary fats and mortality were explored in the NHANES cohort (n=24,144) with the results added to data from 29 prospective studies for a meta-analysis (n=1,164,029). In the NHANES cohort, inverse associations were detected, comparing the highest and lowest quartiles, between total fat and PUFA consumption and all-cause mortality (respective HRs 0.90 [95% CI 0.82, 0.99] and 0.81 [0.78, 0.84]), whereas a positive association was seen for saturated fatty acid consumption (1.08 [1.04, 1.11]). In the meta-analysis, inverse associations of total fat, MUFA and PUFA consumption with all-cause mortality were seen (respective HRs 0.89 [95% CI 0.82, 0.97], 0.94 [0.89, 0.99] and 0.89 [0.84, 0.94]). There was no significant association between total fat consumption and mortality due to CV disease (HR 0.93 [95% CI 0.80, 1.08]) or coronary heart disease (1.03 [0.99, 1.09]), but a positive association was detected between saturated fatty acid intake and death due to coronary heart disease (1.10 [1.01, 1.21]). Neither MUFA nor PUFA consumption was associated with death due to CV disease or coronary heart disease, and their consumption was inversely associated with death due to stroke (respective HRs 0.80 [95% CI 0.67, 0.96] and 0.84 [0.80, 0.90]).

Comment: There are few topics that cause more debate amongst nutritionists than the role of dietary fat in weight and health. This debate results in controversial extremes in dietary advice from high-fat, low-carbohydrate diets to low-fat diets. This paper explored the associations between dietary fat intake and mortality, and importantly looked at this by type of fat and by cause of death. The findings reinforce again the differences between an increased risk of saturated fat and the protective effects of PUFAs and MUFAs. This differential effect should underpin dietary advice, rather than a focus on proportion of total dietary fat, and is consistent with dietary patterns such as the Mediterranean diet.

Reference: Clin Nutr 2020;39:3677–86
Abstract

Potential benefits and harms of gastric bypass surgery in obese individuals with type 1 diabetes

Authors: Höskuldsdóttir G et al.

Summary: This observational registry-based cohort study compared 387 patients with type 1 diabetes and obesity who had undergone RYGB surgery with 387 matched patients who had not undergone RYGB. Compared with the nonsurgical controls, patients who had undergone RYGB had lower risks of CV disease (HR 0.43 [95% CI 0.20, 0.9]), CV-related death (0.15 [0.03, 0.68]), hospitalisation for heart failure (0.32 [0.15, 0.67]) and stroke (0.18 [0.04, 0.82]), but higher risks of serious hyperglycaemic events (1.99 [1.07, 3.72]) and substance abuse (3.71 [1.03, 3.29]).

Comment: Gastric bypass surgery is a well established treatment for obesity and also for type 2 diabetes with evidence for resolution of diabetes and improved CV outcomes. However, the role of gastric bypass as a treatment for obesity in people with type 1 diabetes is less clear. It will not resolve the diabetes and makes the management of hypoglycaemia more difficult. This is a very helpful study, albeit limited by being a retrospective case-match study rather than a prospective randomised trial. Nevertheless, it provides excellent data to show that gastric bypass confers significant benefits for people with type 1 diabetes who are obese, with reductions in risk for CV disease and death. Hypoglycaemia is of concern, but with careful individual consideration, these data do support a role for gastric bypass in this group of patients.

Reference: Diabetes Care 2020;43:3079–85
Abstract

Six months of hybrid closed-loop versus manual insulin delivery with fingerprick blood glucose monitoring in adults with type 1 diabetes

Authors: McAuley SA et al., for the Australian JDRF Closed-Loop Research Group

Summary: Adults using multiple daily insulin injections (51%) or insulin pumps without CGM for managing their type 1 diabetes were randomised to 26 weeks of a hybrid closed-loop system (n=61) or continuation of current therapy (n=59) in this trial. Participants assigned to the hybrid closed-loop system showed an increase from baseline in the time in range on CGM during the final 3 weeks (primary outcome) from 55% to 70% at 26 weeks, with no change seen in the control group (55% at both timepoints) and a significant between-group difference ($p<0.0001$). Compared with the control group, the hybrid closed-loop group also had a significantly lower median HbA_{1c} level (difference –4 mmol/mol, or –0.4% [$p<0.0001$]) and a better diabetes-specific positive well-being score ($p<0.0048$) with no deterioration in diabetes distress, perceived sleep quality or cognition. There were 19 serious adverse events in the hybrid closed-loop group, nine of which were device-related, and 13 in the control group.

Comment: Insulin pump technology continues to advance, with the evolution of better subcutaneous glucose monitoring and now better algorithms to link them into closed loops. There is great hope that such closed-loop pumps will help people with type 1 diabetes to achieve excellent glucose control and minimise hypoglycaemia, and that this will translate to better long-term outcomes and close the gap in premature mortality that stubbornly persists. This study shows some benefit in this direction, with better time in range for glucose level without increased hypoglycaemia. The benefit in HbA_{1c} level was modest and did not reduce it to a nondiabetes range. This is progress, but we are not there yet.

Reference: Diabetes Care 2020;43:3024–33
Abstract

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Associations between the time in hypoglycemia and hypoglycemia awareness status in type 1 diabetes patients using continuous glucose monitoring systems

Authors: Lin YK et al.

Summary: Patients with type 1 diabetes who were using real-time CGM systems for ≥86% of the time were included in this cross-sectional observational study with the aim of determining if those with impaired awareness of hypoglycaemia (n=49) experienced more hypoglycaemia than those with normal hypoglycaemia awareness (n=50). Compared with patients with normal hypoglycaemia awareness, patients with impaired awareness of hypoglycaemia were significantly more likely to have CGM values of <70 and of <54 mg/dL, levels for which Clarke scores were significantly positively correlated. Patients with impaired awareness of hypoglycaemia also had significantly more events with glucose levels <70 and <54 mg/dL at ≥1 timepoint or lasting ≥20 minutes, and they experienced significantly more daytime events with glucose levels <54 mg/dL, nocturnal events with glucose levels <70 and <54 mg/dL and longer daytime event durations with glucose levels <70 and <54 mg/dL.

Comment: Hypoglycaemia unawareness is a major risk for people with type 1 diabetes for severe hypoglycaemia and limits the achievement of good glycaemic control. One of the potential benefits of CGM is to detect hypoglycaemia early and give a person the opportunity to treat it before a severe event evolves. Preventing hypoglycaemia is an important strategy to improve hypoglycaemia awareness over time. However, this study shows that unfortunately patients with impaired awareness continue to have more hypoglycaemia than those with normal awareness, despite the use of CGM.

Reference: Diabetes Technol Ther 2020;22:787–93
Abstract

Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents

Authors: Cahn A et al.

Summary: Cardiac and renal outcomes in patients with type 2 diabetes treated with dapagliflozin were investigated in the placebo-controlled DECLARE-TIMI 58 trial; the impact of baseline glucose-lowering agent on the treatment effect and interactions with dapagliflozin were investigated in this *post hoc* analysis. There were 14,068 baseline metformin users, 7322 baseline sulfonylurea users, 2888 baseline dipeptidyl peptidase-4 inhibitor users, 750 baseline GLP-1 receptor agonist users and 7013 baseline insulin users. The trial's composite outcome of CV-related death and hospitalisation for heart failure was reduced with dapagliflozin versus placebo, with a greater benefit seen for baseline GLP-1 receptor agonist users (HR 0.37 [95% CI 0.18, 0.78]) versus nonusers (0.86 [0.75, 0.98]; p=0.03 for interaction). Baseline glucose-lowering agent had no impact on the composite outcome of CV-related death, MI or ischaemic stroke (which was not significantly different for dapagliflozin versus placebo; HR 0.93 [95% CI 0.84, 1.03]) or on the renal-specific outcome (which was significantly reduced with dapagliflozin versus placebo; 0.53 [0.43, 0.66]). All of the outcomes were similar between baseline metformin users versus nonusers.

Comment: There is now abundant evidence for the cardiac and renal benefits of the SGLT-2 inhibitors as a class of drugs. This study adds further evidence to that literature and strengthens the decision by PHARMAC to fund an agent in this class for people at risk of CV disease or diabetic nephropathy. Although exploratory, the additional information from this study is the potential that a combination of an SGLT-2 inhibitor with a GLP-1 agonist may confer even greater benefit. At this stage, PHARMAC has specifically excluded funding for the combination of these drug classes. However, if this evidence base increases, then one would hope that they might review that position.

Reference: Diabetes Obes Metab 2021;23:29–38
Abstract

Effects of empagliflozin on first and recurrent clinical events in patients with type 2 diabetes and atherosclerotic cardiovascular disease

Authors: McGuire DK et al.

Summary: This secondary analysis of the EMPA-REG OUTCOME trial assessed the impact of empagliflozin on total CV events and hospital admissions; in the EMPA-REG OUTCOME trial, 7020 patients with type 2 diabetes and atherosclerotic CV disease were randomly assigned to receive empagliflozin 10mg (n=2345), empagliflozin 25mg (n=2342) or placebo (n=2333). Median follow-up was 3.2 years for empagliflozin recipients (pooled) and 3.1 years for placebo recipients. Compared with placebo, empagliflozin was associated with reduced risks of all major adverse CV events (rate ratio 0.78 [95% CI 0.67, 0.91]; 12.88 events prevented per 1000 patient-years), fatal/nonfatal MI (0.79 [0.62, 0.998]; 4.97 events prevented per 1000 patient-years), fatal/nonfatal MI or coronary revascularisation (0.80 [0.67, 0.95]; 11.65 events prevented per 1000 patient-years), hospitalisation for heart failure (0.58 [0.42, 0.81]; 9.67 events prevented per 1000 patient-years) and hospitalisation for any reason (0.83 [0.76, 0.91]; 50.41 events prevented per 1000 patient-years); these risk reductions were numerically greater for total events than for first events. There was no significant difference between the empagliflozin and placebo arms for total fatal/nonfatal stroke risk (rate ratio 1.10 [95% CI 0.82, 1.49]).

Comment: This is one of the main clinical trials providing the evidence underpinning SGLT-2 inhibitors and their overwhelming benefits for people with or at risk of CV events. The evidence speaks for itself and all I can say is roll on Feb 1st when we can finally start using funded empagliflozin in NZ and see these clinical benefits for the very large number of patients who will benefit. The key thing now is to systematically roll them out and achieve the greatest coverage we can.

Reference: Lancet Diabetes Endocrinol 2020; 8:949–59
Abstract