In this issue:

Abbreviations used in this issue
BMI = body mass index
CGM = continuous glucose monitoring
GFR = glomerular filtration rate
HbA$_{1c}$ = glycosylated haemoglobin
HR = hazard ratio
SGLT = sodium glucose cotransporter

Welcome to issue 122 of Diabetes and Obesity Research Review.

First up for this issue is a systematic review and meta-analysis reporting that artificial pancreas systems are efficacious and safe for treating outpatients with type 1 diabetes. The second paper is one of two NZ research papers included in this issue – these look at a text message-based, self-management intervention for adults to manage poorly controlled diabetes, and the role of social media in promoting and marketing the products of popular food and beverage brands. There is also a research paper that found changing to metformin is better than continuing intermittent intensive insulin therapy after induction for maintaining β-cell function and glycaemic control in type 2 diabetes. This issue concludes with a review of recommendations for managing diabetes during air travel.

The input of our readers is always valued, so please send us your comments and feedback.

Best regards,

Associate Professor Jeremy Krebs
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Artificial pancreas treatment for outpatients with type 1 diabetes

Authors: Bekiari E et al.

Summary: This was a systematic review and meta-analysis of 40 studies (n=1027) that included 35 comparisons of single-hormone and nine of dual-hormone artificial pancreas systems versus any type of insulin-based treatment. The artificial pancreas systems were associated with significantly higher proportions of time in normoglycaemia (3.9–10.0 mmol/L) for both overnight and 24-hour periods (primary outcome; respective weighted mean differences 15.15% [95% CI 12.21%, 18.09%] and 9.62% [7.54%, 11.7%]), as well as favourable effects on proportions of time with sensor glucose levels >10 and <3.9 mmol/L over 24 hours (–8.52% [–11.14%, –5.9%] and –1.49% [–1.86%, –1.11%]) compared with control conditions. The findings for the primary outcome remained robust in sensitivity analyses that included only the nine trials that were assessed to be at low risk of bias or those conducted under unsupervised, normal living conditions, and the findings were also consistent in subgroup analyses of single-hormone and dual-hormone artificial pancreas systems.

Comment: In the absence of a pancreatic transplant or implantable device, a closed-loop system with an insulin pump and CGM system may be the next best thing for managing type 1 diabetes. As technology has improved in both the insulin delivery system, but more importantly the glucose sensing systems and algorithms for insulin adjustment, so have the results of these 'artificial pancreas' studies. They are now past the point of very short, laboratory-based and highly controlled studies, to free living studies. Concerns over safety remain, but are easing with time and experience. It may not be long before they are a reality in the NZ clinic situation. As with any treatment, and particularly technology-based treatment, they will only suit a subset of those with type 1 diabetes, but for those people they may make a significant difference.

Reference: BMJ 2018;361:k1310
Abstract

Independent commentary by Associate Professor Jeremy Krebs, an endocrinologist with a particular interest in obesity and diabetes. He is an Associate 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, Assoc Prof Krebs maintains active research interests in the area of obesity and diabetes, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery. **FOR FULL BIO CLICK HERE.**

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form.

One form per review read would be required. Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE.**

Effectiveness of text message based, diabetes self management support programme (SMS4BG)

Authors: Dobson R et al.

Summary: Patients aged ≥16 years with poorly controlled type 1 or 2 diabetes (HbA$_{1c}$ level ≥65 mmol/mol [8%]) were randomised to an intervention of tailored text messages for ≤9 months (SMS4BG) added to usual care (n=183) or usual care alone (n=183) in this NZ trial. Compared with usual care alone, the addition of the text messaging intervention was associated with a significantly greater mean reduction in HbA$_{1c}$ level at 9 months (primary outcome; −8.85 vs. −3.96 mmol/mol [p=0.007]) and significant improvements in four of the 21 secondary outcomes assessed, specifically foot care behaviour (adjusted mean difference 0.85 [p<0.001]), overall diabetes support (0.26 [p=0.03]), EQ-5D health status visual analogue scale score (4.38 [p=0.03]) and perceptions of illness identity (−0.54 [p=0.04]). In addition, 95% of the intervention group reported that the text messaging intervention was useful and 97% were willing to recommend the programme to other patients with diabetes.

Comment: It is always great to see high quality NZ research getting published in the BMJ. This study looks at the difficult area of finding an effective evidenced-based intervention to enhance self-management in people with diabetes. There are now many international self-management programmes and fewer NZ developed ones with an evidence base. Most are group-based face-to-face interventions and show modest improvements in HbA$_{1c}$ level and some diabetes care behaviours over 6–12 months. This study uses the novel approach of a tailored individual text message system to promote better self-management activity. Similar to previous work, the HbA$_{1c}$ level improvement is modest relative to standard care, and the most significant improvement in behaviours was in foot care. However, there was no difference in diet or activity changes and the follow-up was short. Nevertheless, the results are encouraging, and what would be useful would be an economic analysis. If this could be rolled out with low levels of health professional time required, even small benefits could be very cost effective.

Reference: BMJ 2018;361:k1959
Abstract

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Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE)

Authors: Heinemann L et al.

Summary: Patients with type 1 diabetes and a history of impaired hypoglycaemia awareness or severe hypoglycaemia during the prior year wore a masked real-time CGM (Dexcom G5 Mobile) for 28 days, after which they were randomised to continue wearing the CGM unmasked (n=75) or continued self-monitoring of blood glucose levels (controls; n=74) for 26 weeks; 75 and 66 participants from the respective groups completed the trial. In the CGM monitoring group, the mean number of hypoglycaemic events fell from 10.8 to 3.5 every 28 days, while the reduction in the control group (from 14.4 to 13.7 every 28 days) was negligible; the CGM group also had a significantly lower incidence of hypoglycaemic events (rate ratio 0.28 [95% CI 0.20, 0.39]). There were ten serious adverse events in the CGM group (one before randomisation) and seven in the control group, none of which were judged to be related to the intervention.

Comment: Severe hypoglycaemia, particularly when accompanied by unawareness, is a major risk for people with type 1 diabetes and a limitation to achieving tight glycaemic control. The development of CGM systems has provided the opportunity to reduce this risk. This study utilised the Dexcom monitor with real-time monitoring and capacity to set alerts to prompt action with excursions of glucose level. The use of CGM significantly reduced the risk of hypoglycaemic events in this very vulnerable group. Although expensive technology, these data should support the funding of such devices in selected individuals with type 1 diabetes in NZ. The evolution of flash technology devices adds to the discussion, and can only be good to create competition and choice, particularly as it is now possible to connect these to phones and watches and create alerts, which has been to date a limitation. Hopefully we will see this technology available to our patients soon and not limited to only those who can pay for it.

Reference: Lancet 2018;391:1367–77
Abstract

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

Change in overweight from childhood to early adulthood and risk of type 2 diabetes

Authors: Bjerregaard LG et al.

Summary: Whether remission of overweight status prior to early adulthood reduces the risk of subsequent type 2 diabetes was explored in a cohort of 62,565 Danish men; 5.4%, 5.5% and 8.2% of the cohort were overweight at the ages of 7 years and 13 years and during early adulthood, respectively. Being overweight was positively associated with the risk of type 2 diabetes, particularly for those overweight at older ages or diagnosed with type 2 diabetes at younger ages. Compared with men who had never been overweight, those who experienced remission of their overweight status prior to age 13 years had a similar risk of a type 2 diabetes diagnosis at age 30–60 years (HR 0.96 [95% CI 0.75, 1.21]), while those who had been overweight at 7 and 13 years of age but not during early adulthood were at increased risk (1.47 [1.10, 1.98]), although not to the extent seen for those who were persistently overweight (4.14 [3.57, 4.79]). The risk of type 2 diabetes was elevated for men whose BMI increased between the age of 7 years and early adulthood, even if their bodyweight had been normal at age 7 years.

Comment: So there is hope! Trends of overweight and obesity in childhood have largely been going in one direction, although this month we have heard some potentially positive reducing of this trend in very young children in Auckland. This retrospective analysis of Danish men shows that whilst childhood obesity is indeed associated with an increased risk of adult type 2 diabetes, this risk can be attenuated if bodyweight status can be reduced through adolescence and early adulthood. Whether this would also be seen in the NZ population, specifically in Pacific and Māori, is unknown, but given the very high rates of childhood obesity in these groups, anything that can reduce the future risk of diabetes is important. These data support calls to focus on finding effective interventions in childhood to better manage bodyweight.

Reference: N Engl J Med 2018;378:1302–12
Abstract

Volume, nature and potential impact of advertisements on Facebook and YouTube by food brands popular in New Zealand

Authors: Vandevijvere S et al.

Summary: These NZ researchers examined the extent, nature and potential impact of marketing by 45 popular packaged food, beverage and fast-food companies via Facebook posts over a 2-month period and by 15 companies via YouTube postings over 2 years. There were 762 Facebook posts made by the companies over the 2-month period, of which ~28% were videos, 63% contained ≥1 'unhealthy' food, 41% used promotional strategies, most often involving a famous sportsperson/team, and 34% promoted 'premium offers', most often competitions. It was estimated some of these posts could be viewed by 10% of NZ adolescents. The analysis of the YouTube channels revealed 300 videos by the investigated brands over the 2-year period, with ~84% containing food marketing, 77% for 'unhealthy' products. Promotional strategies and premium offers were present in 61% and 24% of these videos, respectively, with the most common marketing techniques being the same as those identified in the Facebook analyses.

Comment: Sadly the food industry, marketers and companies see only their bottom line and not the welfare of the public as their primary responsibility. I guess that is capitalism in western democracy working at its best! It shouldn't really surprise anyone that with increased academic and public attention and pressure to reduce food advertising to children on television, the food industry is simply finding alternative and unregulated media to push their toxic ware. Social media is an increasingly important aspect of young people's lives, paralleled by less time spent accessing traditional print media and television. This study highlights these issues and identifies this change in advertising patterns as an important issue for us to be aware of, and to advocate for regulation in.

Reference: N Z Med J 2018;131(1473):14–24
Abstract

Two-year trial of intermittent insulin therapy vs metformin for the preservation of β-cell function after initial short-term intensive insulin induction in early type 2 diabetes

Authors: Retnakaran R et al.

Summary: Adults with type 2 diabetes for a mean duration of 2.0 years and mean HbA_{1c} level 46 mmol/mol (6.4%) were randomised to 3 weeks of induction intensive insulin therapy (glargine, lispro) followed by either repeat treatment for ≤2 weeks every 3 months or daily metformin. Compared with continued intensive insulin therapy, changing to metformin was associated with a higher baseline-adjusted Insulin Secretion-Sensitivity Index-2 score at 2 years (primary outcome; 245.0 vs. 142.2 [p=0.008]), a lower baseline-adjusted HbA_{1c} level at 2 years (42 vs. 56 mmol/mol [6.0% vs. 7.3%; p=0.0006]) and a greater proportion of participants achieving an HbA_{1c} level of ≤42 mmol/mol (≤6.0%) at study completion (66.7% vs. 8.3% [p=0.009]), with no significant between-group difference for insulin sensitivity.

Comment: The notion of preservation of β-cell function by early aggressive use of insulin in type 2 diabetes is not a new one. What this study has done is to take that a step further and explore whether the initial benefits of intensive insulin therapy can be preserved over time by using repeated intermittent courses of the same treatment. The comparator arm of this study is continuous metformin use, which would be standard therapy for new-onset type 2 diabetes. It is notable that metformin is superior in all facets, with better 2-year glycaemic control, but also better β-cell function assessed by an oral glucose tolerance test. This is an interesting observation and could become a useful strategy. Further work is needed to better understand how this approach is working, and to optimise the initial insulin protocol.

Reference: Diabetes Obes Metab 2018;20:1399–407
Abstract

Investigating the longitudinal association between diabetes and anxiety

Authors: Smith KJ et al.

Summary: Fourteen studies (n=1,760,800) examining anxiety as a risk factor for incident diabetes were included in this systematic review and meta-analysis. Unadjusted or least-adjusted (age only) analyses detected a significant association between baseline anxiety and incident diabetes (odds ratio 1.47 [CI 1.23, 1.75]), with the association persisting with statistical significance in most adjusted analyses. No association of diabetes to incident anxiety was detected in analyses of studies that examined this relationship.

Comment: There is a well-established link between depression and type 2 diabetes, which is bidirectional. Less is known about the association with anxiety, although anxiety and depression are closely linked and often co-exist. This systematic review and meta-analysis has shown what we might predict, that anxiety is also associated with diabetes, and in this analysis with incident diabetes, therefore supporting a causal association, whereas there was little evidence to support the reverse association. Since the prevalence of anxiety is increasing, this may be an important contributing factor in the increasing incidence of diabetes and offers another opportunity for intervention to reduce this. More work is needed to understand the three-way relationship with depression and treatments of both mental health issues.

Reference: Diabet Med 2018;35:677–93
Abstract

Novel subgroups of adult-onset diabetes and their association with outcomes

Authors: Ahlqvist E et al.

Summary: This data-driven cluster analysis in 8980 Swedish patients with newly diagnosed diabetes was undertaken to identify different subgroups within type 2 diabetes. Clusters were identified based on six variables (glutamate decarboxylase antibodies, BMI, age at diagnosis, HbA_{1c} level and homeostatic model assessment-2 estimates of β-cell function and insulin resistance). These were then related to prospective data from patient records on the development of complications and prescription of medications, and repeated in three independent cohorts of 1466, 844 and 3485 individuals. Overall, five replicable clusters of patients with significantly different patient characteristics, disease progression and risk of diabetic complications were identified. Striking findings were that individuals in cluster 3, the group most resistant to insulin, exhibited a significantly higher risk of diabetic kidney disease compared with individuals in clusters 4 and 5; however, they had been prescribed similar diabetes treatment. Furthermore, those in cluster 2 (insulin deficient) had the highest risk of retinopathy. The genetic associations in the clusters differed from those seen in traditional type 2 diabetes.

Comment: We are in an age of increasing personalised medicine, determination of treatments by genetic risks, and tailoring of drug regimens and other treatments to these. In diabetes, this is still emerging. We have long recognised that type 2 diabetes is a very heterogeneous disease, sharing a common phenotype of hyperglycaemia by which it is defined, but with multiple variations of the causative components and responses to treatments. Until recently we have had limited ways of defining these differences, but more importantly limited options for treatment, which created a one-size-fits-all approach. Now, we have more treatment options with distinctly different modes of action, which in most developed countries now enables a more individualised approach to management. In order to facilitate this, it is important in day-to-day practice to be able to easily identify which patients will respond best to which approaches. This paper is therefore of great interest, that in identifying distinct clusters of people with diabetes, it begins to speak to a more targeted management approach.

Reference: Lancet Diabetes Endocrinol 2018;6:361–9
Abstract

SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment

Authors: Seidu S et al., for and on behalf of Primary Care Diabetes Europe

Summary: This was a systematic review and meta-analysis covering 40 randomised controlled trials (n=29,954) of SGLT-2 inhibitors in patients with type 2 diabetes, with and without renal impairment. Compared with placebo, SGLT-2 inhibitor use by participants with renal impairment was associated with initial decreases in estimated GFR followed by an increase and return to baseline levels and preserved or initial increases followed by return to baseline for serum creatinine levels. No significant changes in estimated GFR or serum creatinine levels were associated with SGLT-2 inhibitor use in participants without renal impairment. Compared with placebo, use of SGLT-2 inhibitors, particularly canagliflozin and empagliflozin, was associated with decreases in urine albumin level, improved albuminuria, slowed progression to macroalbuminuria and reduced risks of worsening renal impairment, kidney transplantation and death from renal disease in participants with and without renal impairment.

Comment: Of the newer drugs for type 2 diabetes, there is growing evidence that SGLT-2 inhibitors may come out on top for overall clinical benefits, ease of use and a relatively low side effect profile. Quite apart from the glucose-lowering effect, it is the other benefits of the class that are becoming more compelling. Weight loss and blood pressure lowering are important, but the cardiovascular outcome studies are the most impressive. This meta-analysis adds further to the support for SGLT-2 inhibitors demonstrating renal protection. The mechanism of action requires functional glomerular filtration, and therefore it is of note that in the group of people with renal impairment, not only were the drugs effective in lowering glucose, but additionally they provided renal protection and prevented further renal deterioration. There really is an urgent need now for funding of this class of drugs in NZ. What more do PHARMAC need to act? It is a disgrace that NZ has taken so long, and continues to stall on funding an agent with so many benefits above and beyond the simple glucose-lowering primary effect.

Reference: Prim Care Diabetes 2018;12:265–83
Abstract

Management of diabetes during air travel

Authors: Pavela J et al.

Summary: This systematic literature review identified 47 articles providing expert opinion, two observational studies, two case reports and ten device studies of current recommendations with supporting evidence regarding the management of diabetes during air travel. The travel advice provided by the articles was generally consistent, with increasing attention to preflight security, but indications for adjusting oral antihyperglycaemic therapy varied. Few recommendations were provided regarding contemporary agents and nonhypoglycaemic adverse events, and little consensus was provided on insulin adjustment protocols, with many antedating current insulin formulations. While most articles advocated adjusting insulin pump time settings on arrival at the destination, there was disagreement on timing and rate adjustments. It was also noted that although the accuracy of glucometers and subcutaneous glucose sensors is compromised at altitude, this is not to an extent that would preclude their use.

Comment: Air travel is increasingly common, and with NZ's geographical location, this frequently means long-haul flights and time-zone changes. This raises practical challenges and clinical risks for people with diabetes, especially if they are taking insulin. This is becoming increasingly complex with insulin pumps. People are wanting guidance on how best to manage their diabetes whilst travelling, and currently this is rather *ad hoc* and not evidence based. This paper therefore caught my eye in the hope that it would provide this evidence. However, while it does cover the issues and reviews what is published, what is striking is the lack of any evidenced-based recommendations. Virtually all published work is expert opinion. This raises the possibility of conducting some research in this area. I suspect that recruitment would not be an issue!

Reference: Endocr Pract 2018;24:205–19
Abstract
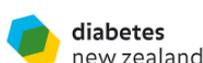
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