Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 133 – 2020

In this issue:

Abbreviations used in this issue

CGM = continuous glucose monitoring
CSII = continuous subcutaneous insulin infusion
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
MDI = multiple daily injections
RCT = randomised controlled trial
SGLT = sodium glucose cotransporter
SMBG = self-monitoring of blood glucose
SSB = sugar-sweetened beverage

Welcome to issue 133 of Diabetes and Obesity Research Review.

This issue begins with an RCT reporting longer times in the target glucose level range among participants with type 1 diabetes who use closed-loop insulin delivery systems compared with those who used sensor-augmented insulin pumps. This is followed by research reporting health benefits for employees after a workplace ban on SSB (sugar-sweetened beverage) sales was implemented. Disparities in the UK for type 2 diabetes management based on deprivation and ethnicity mirror disparities we see here in NZ. On a similar note, NZ researchers have reported lower adherence to metformin monotherapy among Māori and Pacific people with type 2 diabetes, highlighting the need to better understand the reasons for this difference.

I hope you find this update in diabetes and obesity research informative, and I look forward to receiving your feedback and suggestions.

Best regards,

Professor Jeremy Krebs
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Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes

Authors: Brown SA et al., for the iDCL Trial Research Group

Summary: Patients with type 1 diabetes were randomly assigned to treatment with a closed-loop system (n=112; in closed-loop mode for a median of 90% of the time over 6 months) or a control group using sensor-augmented pumps (n=56). Compared with the control group, the closed loop group had a significantly greater increase from baseline in the percentage of time with their glucose level within target (70–180 mg/dL [3.9–10.0 mmol/L]; primary endpoint; mean adjusted difference, 11 percentage points [p<0.001]), and also had superior outcomes for the percentage of time their glucose level was >180 mg/dL, mean glucose level, HbA_{1c} level (–0.33 percentage points [p=0.001]) and percentage of time that their glucose level was <70 mg/dL (–0.88 percentage points [p<0.001]) or <54 mg/dL. There were no serious hypoglycaemic events and there was one episode of diabetic ketoacidosis in the closed-loop group.

Comment: For some time now, it has felt like closed-loop pump systems have been on the verge of mainstream clinical practice. This carries with it a lot of hope and expectation by patients with type 1 diabetes and their healthcare teams alike. It is with that expectation that I read this paper and was slightly disappointed. The primary outcome was time in range, which has become the standard metric to report CGM data. With the closed-loop system, time in range only increased from 61% to 71%. This was significant and better than the control group, but somehow I was expecting more. Furthermore, the HbA_{1c} level reduction was minimal. Importantly, there was no major increase in hypoglycaemia or ketoacidosis, indicating that the closed-loop system is safe. Overall, I was a bit underwhelmed, particularly with the knowledge that tech-savvy people with type 1 diabetes are already doing this on their own, with older technology, but perhaps better algorithms and getting great results.

Reference: N Engl J Med 2019;381:1707–17
Abstract

Association of a workplace sales ban on sugar-sweetened beverages with employee consumption of sugar-sweetened beverages and health

Authors: Epel ES et al.

Summary: This study assessed whether an SSB sales ban and a brief motivational intervention at a Northern California university and hospital was associated with changes in SSB intake and cardiometabolic health among 214 employees. Baseline mean SSB daily intake of 1050mL declined to 540mL at follow-up (p<0.001). SSB intake was correlated with HOMA-IR (homeostatic model assessment of insulin resistance) improvements (r=0.16 [p=0.03]). Those not receiving the brief intervention reduced their SSB intake by a mean of 246.0mL compared with 762.0mL in those who received the intervention. Waist circumference declined by 2.1cm (p<0.001).

Comment: Despite the evidence that SSBs contribute to a range of adverse health conditions including obesity, diabetes and dental disease, attempts to reduce consumption have been limited in their effectiveness. Levying a tax has been very controversial, despite evidence of its effectiveness internationally. A ban on sales of SSBs in schools has been overturned under the label of 'nanny state'. At the hospital I work in, all SSBs were removed from vending machines several years ago with an unprecedented backlash from staff! They subsequently crept back in by stealth. So, I find this paper very interesting and hopefully an evidence base to further stimulate the benefit of regulation in helping us weak humans to modify our behaviour in a healthy way that we fundamentally do want to do. I suggest all of you tape a copy of this paper to the front of any vending machine with SSBs in your workplace.

Reference: JAMA Intern Med 2020;180:9–16
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.

Comparison of group medical visits combined with intensive weight management vs group medical visits alone for glycemia in patients with type 2 diabetes

Authors: Yancy WS Jr. et al.

Summary: Outpatients with type 2 diabetes, uncontrolled HbA_{1c} levels and body mass index ≥27 kg/m² were randomised to 4-week group medical visits of counselling about diabetes-related topics with medication optimisation for 16 weeks (n=136) or low-carbohydrate diet counselling with baseline medication reduction and subsequent medication optimisation every 2 weeks for 16 weeks followed by an abbreviated group medical visit intervention every 8 weeks (13 visits; n=127) in this noninferiority trial. HbA_{1c} levels improved in both groups, but the group with weight management as well as the group medical visits had a significant reduction in diabetes medication use ($p<0.001$), greater weight loss (mean difference, −3.7kg [$p<0.001$]) and ~50% fewer hypoglycaemic events ($p<0.001$) during the 48-week evaluation period.

Comment: We all struggle to find ways to facilitate weight loss and improved glycaemic control for people with type 2 diabetes, particularly for those people who don't engage in the traditional system of medical care. Therefore, finding ways that are acceptable and relevant for these people is becoming a priority. The concept of group medical visits was a new one to me until recently, but there is accumulating evidence that this model may be effective, and may appeal more to a whānau approach. Therefore, this paper caught my eye. The use of group medical visits that incorporated a weight management intervention resulted in global improvements in diabetes parameters including weight loss. Here the choice of dietary intervention was reduced carbohydrate, which although topical is not the only approach. This paper can't answer whether other dietary interventions would be equally effective. The take-home message for me was that this type of approach is something we should consider in NZ.

Reference: JAMA Intern Med 2020;180:70–9
Abstract

Diabetes care: addressing psychosocial well-being in young adults with a newly developed assessment tool

Authors: Bachmeier CAE et al.

Summary: These authors reported on the usage and acceptance of a diabetes psychosocial assessment tool with embedded validated screening tools over a 12-month period among 155 patients aged 18–25 years who were offered the tool; 96.1% had type 1 diabetes with a mean duration of 10.5 years, and their average HbA_{1c} level was 7.12 mmol/mol (8.7%). The proportion of patients who had severe diabetes-related distress was 19.4%, 14.8% had low WHO Well-Being Index-5 scores (28–50 points), 25.8% and 16.1% had evidence of anxiety and depression, respectively, according to Patient Health Questionnaire-4 responses, and 27.1%, 26.6%, 28.4% and 4.5% had evidence of significant weight, shape, eating and serious hypoglycaemia concerns, respectively.

Comment: It is easy to underestimate the degree of distress experienced by young people with type 1 diabetes. It is a hard enough time of life without the extra burden of a chronic disease that is relentless in its demands. This paper reports the use of a tool to measure the degree of distress and identified a concerning proportion of young people with significant issues. As suggested by the authors, this tool may be useful in practice to identify those at greatest need of the limited psychological supports that we have available. We have begun to use this at CCDHB, and are identifying similar rates of concerns, highlighting the need for a multidisciplinary team dedicated to young-adult diabetes care.

Reference: Intern Med J 2020;50:70–6
Abstract

Disparities in glycaemic control, monitoring, and treatment of type 2 diabetes in England

Authors: Whyte MB et al.

Summary: These researchers analysed data from a retrospective primary-care cohort of 84,452 UK adults with type 2 diabetes to identify disparities in glycaemic control, monitoring and prescribing. Compared with the least deprived individuals (assessed using the Index of Multiple Deprivation), those who were most deprived had lower HbA_{1c} levels, and were less likely to undergo annual HbA_{1c} level, blood pressure, estimated glomerular filtration rate, retinopathy and neuropathy assessments. Compared with individuals of White ethnicity: i) those of Black ethnicity had lower HbA_{1c} levels and were less likely to be prescribed SGLT-2 inhibitors or GLP-1 agonists, or undergo annual HbA_{1c} level or retinopathy testing: ii) those of Asian ethnicity were significantly less likely to be prescribed insulin, SGLT-2 inhibitors or GLP-1 agonists and were significantly less likely to undergo retinopathy and neuropathy screening, but were significantly more likely to undergo HbA_{1c} level and renal function monitoring.

Comment: We are well aware of the disparities that exist in NZ among ethnicities and level of deprivation for rates of type 2 diabetes, screening and monitoring of the disease, glycaemic control and outcomes. It is therefore of interest to read this paper from the UK examining the same issues in England, where there is a very different ethnic/cultural mix, although a similar health system, allowing for the key difference of largely free open access to primary care. The findings of this retrospective cohort study of people with type 2 diabetes over a 4-year period were remarkably similar to those we observe here in NZ. Key parameters of good diabetes care including engagement, monitoring and medication use were all worse for those of specific ethnicities and those who were more deprived. This is nothing new, but it is further reinforcement of the knowledge that we need to do better to improve equity in healthcare.

Reference: PLoS Med 2019;16:e1002942
Abstract

Preconception diabetes mellitus and adverse pregnancy outcomes in over 6.4 million women

Authors: Wei Y et al.

Summary: Associations between preconception blood fasting plasma glucose level and pregnancy outcomes were explored in a retrospective population-based cohort of 6,447,339 women aged 20–49 years in China. The respective incidences of diabetes and impaired fasting glucose levels were 1.18% and 13.15%. Of 917 women who reported a history of diabetes, 37.28% had uncontrolled diabetes (preconception fasting plasma glucose level ≥5.6 mmol/L). The proportion of women who had an adverse pregnancy outcome was 15.6%. Compared with women with normal fasting plasma glucose levels, those with impaired fasting glucose levels and those with diabetes had increased risks of spontaneous abortion (respective odds ratios 1.08 [95% CI 1.06, 1.09] and 1.11 [1.07, 1.15]), preterm birth (1.02 [1.01, 1.03] and 1.17 [1.14, 1.20]), macrosomia (1.07 [1.06, 1.08] and 1.13 [1.09, 1.16]), neonates who were small for gestational age (1.06 [1.02, 1.10] and 1.17 [1.04, 1.32]) and perinatal infant death (1.08 [1.03, 1.12] and 1.59 [1.44, 1.76]); diabetes was also associated with a higher risk of birth defects (1.42 [1.15, 1.91]). Among women without a self-reported diabetes history, positive linear associations were seen between fasting plasma glucose levels and spontaneous abortion, preterm birth, macrosomia, small for gestational age and perinatal infant death ($p<0.001$ for trend, for all).

Comment: So just a small study then! We know that pregnancy outcomes in NZ are worst for women with unknown type 2 diabetes at conception. This has driven the inclusion of HbA_{1c} level in booking bloods in early pregnancy to try to pick them up well before the usual screen for gestational diabetes at around 28 weeks. This impressive study from China of over 6 million women was able to tease out the issues of preconception dysglycaemia a bit more. When categorised by existing diabetes, prediabetes defined by impaired fasting glucose, or normal glycaemia, there were very clear increased risks of a whole range of adverse pregnancy outcomes for not only those with diabetes, but also with prediabetes. They did not have HbA_{1c} level data, which is a shame, as we cannot be sure that the same observation would apply to prediabetes defined in that way, as we do in NZ. The risk of adverse outcomes increased linearly with fasting glucose level. These data would suggest that more may need to be done to prepare women considering pregnancy to minimise their risks. The unintentional risk of that statement is an increase in disparities in outcomes for women who may not access care or plan pregnancy.

Reference: PLoS Med 2019;16:e1002926
Abstract

Glycemic outcomes in adults with T1D are impacted more by continuous glucose monitoring than by insulin delivery method

Authors: Šoupal J et al.

Summary: Three-year follow-up outcomes from the nonrandomised COMISAIR study were reported; COMISAIR prospectively followed 94 real-world patients with type 1 diabetes who used various combinations of real-time CGM, MDI, SMBG and CSII. The respective 3-year HbA_{1c} levels for those who used real-time CGM plus MDI, real-time CGM plus SCII, SMBG plus CSII and SMBG plus MDI were 53, 52, 61 and 64 mmol/mol (7.0%, 6.9%, 7.7% and 8.0%); the differences between the two CGM groups versus the two SMBG groups were statistically significant ($p\leq0.0020$), while the differences between the two real-time CGM groups and between the two SMBG groups were not (respective p values 0.61 and 0.69). The real-time CGM plus MDI, real-time CGM plus CSII and SMBG plus CSII groups also had significantly improved percentages of time in target glucose level range (70–180 mg/dL [3.9–10 mmol/mol]; 48.7–69.0% [$p<0.0001$], 50.9–72.3% [$p<0.0001$]) and 50.6–57.8% [$p=0.0114$], respectively), and the respective real-time CGM groups also had significant reductions in time spent below the target range (9.4–5.5% [$p=0.0387$] and 9.0–5.3% [$p=0.0235$]). There were five episodes of severe hypoglycaemia in the SMBG groups and two in the sensor-augmented insulin regimen groups.

Comment: The use of technology to improve care in type 1 diabetes is a hot topic. For some time now we have had evidence for the benefits of insulin pump therapy as a tool for delivering insulin, and we are lucky to have funded access to this for many patients in NZ. However, as I say to patients, an insulin pump is only another way to deliver insulin and can help solve particular problems, but it still requires a lot of effort for patients to get the best results. Pumps are not a panacea and do not suit everyone with type 1 diabetes. The emergence of more affordable real-time subcutaneous glucose monitoring devices has opened up another way of improving care through reducing the barrier to monitoring and increasing the amount of data available to a person to help them manage their glucose levels. The evidence for this has been mixed, and I think this paper provides a very useful and pragmatic perspective. This is a nonrandomised trial and therefore open to selection bias, but in a way that is a strength of the study. Participants have chosen the type of treatment they want, which is what happens in the real world. The study shows that use of CGM has more impact on HbA_{1c} level and hypoglycaemia than method of insulin delivery. Wouldn't it be great to have funded access to CGM for our patients with type 1 diabetes.

Reference: Diabetes Care 2020;43:37–43
Abstract

Adherence to metformin monotherapy in people with type 2 diabetes mellitus in New Zealand

Authors: Horsburgh S et al.

Summary: Adherence to metformin monotherapy was assessed for 85,066 NZ patients with type 2 diabetes who started such treatment between Jan 1, 2006 and Sept 30, 2014, followed until the end of 2015. Associations were identified between lower metformin monotherapy adherence and time since starting metformin, younger age and being of Māori or Pacific ethnicity, while factors associated with greater adherence were receipt of more nondiabetic medications, a history of cardiovascular disease and recent cancer registration.

Comment: It's the old maxim: a drug only works if you take it! Metformin remains the first-line therapy after lifestyle changes in the management of type 2 diabetes. For the vast majority of people, once metformin has been commenced, there are very few situations where it is appropriate to stop it. These include persistent adverse effects, end-stage kidney disease, major weight loss and achieving diabetes remission. Therefore, longitudinal adherence to metformin use may be a useful marker of general adherence and engagement with diabetes care. This study in NZ describes adherence to metformin in a longitudinal cohort. The findings echo other ways of looking at overall diabetes care – who is doing well and who is not. Consistent with other findings, younger people with type 2 diabetes and Māori and Pacific people are doing less well.

Reference: Diabetes Res Clin Pract 2019;158: 107902
Abstract

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Impact of technology on glycaemic control in type 2 diabetes

Authors: Dicembrini I et al.

Summary: This was a meta-analysis of RCTs (for which there was significant heterogeneity; I^2=90%) comparing CSII with MDI or comparing CGM or flash glucose monitoring with SMBG in patients with type 2 diabetes. No significant difference was seen between CSII and MDI for HbA_{1c} level (–0.26% [p=0.29]), whereas there was a marginally significant difference between CGM and SMBG (–0.24% [p=0.05]). No significant difference was seen between flash glucose monitoring and SMBG (one RCT) for HbA_{1c} level at study end (8.4% vs. 8.3%), although quality of life was better and hypoglycaemic events were fewer with flash glucose monitoring.

Comment: I have included studies examining the role of technology, insulin pumps and subcutaneous CGM in the management of type 1 diabetes, but it is not surprising that people with type 2 diabetes are also asking for these technologies. This meta-analysis looked at the evidence for the impact of pumps and CGM in type 2 diabetes. The conclusion is that there is only a small benefit across a range of domains, including glycaemic control, rates of hypoglycaemia and quality of life. This is perhaps not surprising as the characteristics of the population with type 2 diabetes are very diverse, the physiology of the disease is very heterogeneous and the type of insulin regimen and oral hypoglycaemic use are also very mixed. Therefore, at an individual level, there may well be people who greatly benefit from use of CGM, pumps or both, but this is lost in the clinical trial setting. That also makes it very hard at a clinical and funding level to select those who would benefit.

Reference: Diabetes Obes Metab 2019;21:2619–25
Abstract

Impact of dietary protein on postprandial glycaemic control and insulin requirements in type 1 diabetes

Authors: Paterson MA et al.

Summary: This systematic review included published studies investigating the glycaemic impact of dietary protein when consumed alone (two studies) or as part of a mixed meal (12 studies) in individuals with type 1 diabetes. No glycaemic effect was seen with protein alone until ≥75g was consumed, whereas postprandial glucose levels were affected by carbohydrate-containing meals with ≥12.5g of protein. Glycaemic responses and insulin requirements were even greater when fat was included in a high-protein meal. The glycaemic effect from dietary protein occurred in 90–240 minutes.

Comment: The 'pizza phenomenon': people with type 1 diabetes find out for themselves that, even for the most careful, the rules of carbohydrate counting go out the window with pizza and indeed many other meals with high protein and fat content. Many find an intuitive way to deal with this or avoid these foods. This meta-analysis helps to characterise the effect of protein on postprandial glucose a bit more. It shows the variability of impact of protein depending on the composition of the meal, including quantity of protein, carbohydrate and fat. This variability makes it difficult to provide advice to people on what to do with their bolus insulin. More work is needed to test different strategies to estimate the additional insulin required for protein and fat content, and to find a practical way to calculate this for people that is not too burdensome and therefore simply ignored.

Reference: Diabet Med 2019;36:1585–99
Abstract

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