Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 147 – 2021

In this issue:

Abbreviations used in this issue

AUC = area under the curve
BMI = body mass index
BP = blood pressure
CGM = continuous glucose monitoring
CV = cardiovascular
GDM = gestational diabetes mellitus
HbA_{1c} = glycosylated haemoglobin
RCT = randomised controlled trial
RR = relative risk
SGLT = sodium glucose cotransporter

Welcome to issue 147 of Diabetes and Obesity Research Review.

This month's issue begins with research investigating the use of CGM in primary-care adult patients with type 2 diabetes treated with basal insulin without prandial insulin. Local research is well represented this month, including: i) a paper published in the Lancet looking into overestimation of CV risk predicted by equations derived prior to widespread screening; ii) interviews of Māori, Pacific and non-Māori/Pacific patients seeking to determine factors associated with adherence and persistence to metformin monotherapy; and iii) a retrospective clinical record review of patients with type 1 diabetes from the Waikato region exploring differences in glycaemic control according to age, gender, rurality and ethnicity. The issue concludes with research that has defined BMI cutoffs specific to a range of different ethnicities in the population of England for defining obesity based on type 2 diabetes risk.

We hope this slightly longer issue helps to keep you abreast of the latest research in diabetes and obesity. We always appreciate your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin

Authors: Martens T et al., for the MOBILE Study Group

Summary: Adults from primary care with type 2 diabetes treated with 1–2 long- or intermediate-acting basal insulin injections each day without prandial insulin, with or without noninsulin glucose-lowering medications, were randomised to CGM (n=116) or monitoring with a traditional blood glucose meter (n=59) in this trial; the trial completion rate was 94%. Compared with traditional blood glucose level monitoring, CGM was associated with a greater decrease in mean HbA_{1c} level at 8 months (adjusted difference, –0.4% [p=0.02]), a greater percentage of time in the target glucose level range of 70–180 mg/dL (59% vs. 43% [p<0.001]), a smaller mean percentage of time with a glucose level >250 mg/dL (11% vs. 27% [p<0.001]) and a lower mean glucose level (179 vs. 206 mg/dL [p<0.001]). Severe hypoglycaemic events occurred in 1% and 2% of the CGM and traditional blood glucose level monitoring groups, respectively.

Comment: Clinically, we all have plenty of examples of patients with type 1 diabetes who have turned their diabetes around with the use of CGM. The role for CGM in people with type 2 diabetes is much less well defined, although again for some people, it seems to be a tool that enables them to achieve better control. This may be simply due to better awareness of glucose response to food and activity, or may be related to informing insulin dosing. Increasing our understanding of which factors predict a good response will help in discussions with patients, and also potentially inform the debate about funding. This study shows that CGM compared with regular capillary monitoring helped achieve better reduction in HbA_{1c} level in people with poorly controlled type 2 diabetes on basal insulin but not using bolus insulin. Whilst statistically significant, the difference between groups was pretty small (–0.4%, or ~5 mmol/mol). As with any such group mean data, there would have been individuals within the CGM group who did much better than this, and understanding their characteristics would be very helpful.

Reference: JAMA 2021;325:2262–72
Abstract

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Comparative effectiveness of sodium-glucose cotransporter 2 inhibitors vs sulfonylureas in patients with type 2 diabetes

Authors: Xie Y et al.

Summary: The effectiveness of SGLT-2 inhibitors versus sulfonylureas and associated risks of all-cause mortality were explored in a cohort of patients with type 2 diabetes; there were 23,870 SGLT-2 inhibitor recipients and 104,423 sulfonylurea recipients included in the analyses. Compared with sulfonylurea users, SGLT-2 inhibitor users had a lower risk of death from any cause (hazard ratio 0.81 [95% CI 0.75, 0.87]; –5.15 fewer deaths per 1000 person-years), irrespective of CV disease status, estimated glomerular filtration rate and the presence of albuminuria, microalbuminuria or macroalbuminuria. Continued SGLT-2 inhibitor use was also associated with a lower mortality risk compared with continued sulfonylurea use in a per-protocol analysis (hazard ratio 0.66 [95% CI 0.60, 0.74]; –10.10 fewer deaths per 1000 person-years), with a difference also seen for SGLT-2 inhibitor with versus without metformin use (0.70 [0.50, 0.97]; –7.62 fewer deaths per 1000 person-years).

Comment: There have been many papers published on the role of SGLT-2 inhibitors, and I have reviewed many of these previously. We have excellent large RCTs showing benefit of these agents in those with or at high risk of CV disease or renal disease. I have included this trial because it is real-world data and makes a comparison between SGLT-2 inhibitors and sulfonylureas, which until very recently have been the most commonly used second-line agents in NZ. It isn't an RCT, but nonetheless adds useful data to the discussion about the place of these agents. Not only does it show superiority of SGLT-2 inhibitors, but this benefit is across the board and not limited to those with high risk or established CV or renal disease. This is very relevant to NZ where we have chosen to only fund these agents in high-risk individuals.

Reference: JAMA Intern Med; published online June 28, 2021
Abstract

Effect of a smartphone app on weight change and metabolic outcomes in Asian adults with type 2 diabetes

Authors: Lim SL et al.

Summary: Adults with type 2 diabetes and a BMI of ≥23 kg/m² were randomly allocated to diet and physical activity advice with (n=99) or without (n=105; controls) use of a smartphone app to track bodyweight, diet, physical activity and blood glucose level data, which were communicated with dieticians. Compared with controls, at 6 months participants who used the smartphone app had achieved significantly greater reductions in mean bodyweight (–3.6 vs. –1.2kg) and mean HbA_{1c} level (–0.7% vs. –0.3% overall, and –1.8% vs. –1.0% for participants with a baseline level ≥8%), and a greater proportion had reduced their diabetes medications (23.3% vs. 5.4%). There were also between-group differences for fasting blood glucose level, diastolic BP and dietary changes favouring the smartphone app group.

Comment: Use of smartphone apps to support patient management has become very popular across a wide range of long-term conditions. With high rates of smartphone use across the population, these are potentially very powerful tools. However, the results from RCTs using apps to support management of weight or diabetes have been very mixed, and generally underwhelming compared with their potential. This study is another RCT of a phone app-based intervention to facilitate weight loss in people with type 2 diabetes in Singapore. This particular study did show modestly greater weight loss and better metabolic outcomes using a culturally customised app. Once again, we need to know what the factors are that determine which patients are most likely to use these apps to achieve better results.

Reference: JAMA Netw Open 2021;4:e2112417
Abstract

Cardiovascular risk prediction in type 2 diabetes before and after widespread screening

Authors: Pylypchuk R et al.

Summary: This derivation and validation study from NZ sought to determine if CV risk prediction equations derived prior to widespread screening would significantly overestimate CV risk in screen-detected patients. Patients aged 30–74 years with type 2 diabetes and no known CV disease, heart failure or substantial renal impairment (n=46,652; PREDICT-1° Diabetes subcohort) were identified from the PREDICT primary-care cohort study, which covered the periods before and after widespread screening; 31.8% were not receiving oral hypoglycaemic medications or insulin at baseline. New sex-specific equations derived from this cohort returned median 5-year CV risk estimates of 7.1% and 4.0% for men and women, respectively, compared with respective risk estimates of 17.1% and 14.2% according to an older equation derived in the 2000–2006 NZDCS (New Zealand Diabetes Cohort Study). The new PREDICT-1° Diabetes equations were significantly superior to the NZDCS equation for measures of model and discrimination performance.

Comment: This is a very important paper in the context of NZ primary care management of CV risk. For many years we have used a risk estimate of individuals derived from the Framingham study, which is historical and not derived from a NZ population. Various modifications and additions to this have been made over the years to try to build diabetes into the equations, recognising that people with diabetes may be at greater risk of CV disease than the rest of the population. This paper now describes a contemporary calculator for estimating CV disease risk in type 2 diabetes derived from real-world population data that are truly representative of the NZ population. It is clear from these data that the older calculators overestimated CV disease risk for many people with type 2 diabetes. This tool will provide a more accurate estimate of risk for guiding patient management.

Reference: Lancet 2021;397:2264–74
Abstract

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What helps and hinders metformin adherence and persistence

Authors: Parkin L et al.

Summary: Face-to-face, audio-recorded, semistructured interviews were conducted with ten Māori, ten Pacific and ten non-Māori non-Pacific metformin monotherapy initiators for type 2 diabetes to determine factors influencing adherence and persistence. The reported perceived benefits of metformin included better glycaemic control, preventing or slowing type 2 diabetes progression and avoidance of serious complications, and the most frequently reported disadvantage was side effects (predominantly gastrointestinal). Interviewees reported use of a range of strategies to facilitate regular metformin use. The main reasons for initial suboptimal adherence and persistence were side effects and failing to accept their diagnosis of type 2 diabetes. Subsequent omission of missing doses was usually due to forgetfulness. Other important contributors to suboptimal adherence among Pacific people were changes in their routine due to community and church events or shift work. Some Māori interviewees indicated that they would have preferred to use traditional medicines.

Comment: Metformin is the first agent for the management of type 2 diabetes in any algorithm. However, uptake and ongoing use of metformin is not universal. This NZ study explores why that is, from a patient perspective. The main reason that emerged relates to gastrointestinal side effects, which we know are common. It is interesting that not accepting the diagnosis of diabetes was also an important finding. Forgetfulness and changes in routine are likely not specific to metformin, and may be overcome to some extent by use of blister packs or self-generated phone prompts. These are useful findings to assist in patient care.

Reference: N Z Med J 2021;134(1536):25–40
Abstract

The effects of dietary and lifestyle interventions among pregnant women with overweight or obesity on early childhood outcomes

Authors: Louise J et al.

Summary: This was an individual participant data meta-analysis from six trials that had randomised women with a singleton, live gestation between 10+0 and 20+0 weeks and a BMI of ≥25 kg/m^2 in early pregnancy to either a diet and/or lifestyle intervention or standard antenatal care, and that reported longer-term maternal (n=2383) and child (n=2529) follow-up (3–5 years of age) outcomes. A BMI z-score in the >90th percentile was seen in ~30% of the children, with no significant difference between the intervention and control groups for this primary childhood outcome (adjusted RR 0.97 [95% CI 0.87, 1.08]) or for any of the secondary childhood outcomes assessed (skinfold thickness measurements, body circumferences, fat-free mass, diet and physical activity patterns, BP and neurodevelopment).

Comment: There are many studies showing the association between maternal obesity, GDM and childhood obesity in the offspring. There continues to be the eternal debate over how much of this is related to genetics versus environment, with studies supporting both hypotheses, and most concluding that each is important. Further to this debate is whether interventions during pregnancy might influence the intrauterine environment and modify the childhood outcome. This study reports a meta-analysis of individual participant-level data from diet and or lifestyle intervention studies in pregnant women. Disappointingly, there is no evidence that weight management during pregnancy reduces childhood obesity.

Reference: BMC Med 2021;19:128
Abstract

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. **FOR FULL BIO CLICK HERE.**

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

Authors: Chepulis L et al.

Summary: Differences in glycaemic control according to age, gender, rurality and ethnicity were explored in this retrospective review of clinical records of 1303 patients with type 1 diabetes from the Waikato region. Median HbA_{1c} level was 67 mmol/mol (8.3%), with the highest levels seen in patients aged 15–29 years and levels in excess of clinical recommendations seen in 85.3% of all participants. Compared with patients on multiple daily injections, those on insulin pumps had a lower median HbA_{1c} level (63 vs. 69 mmol/mol, or 7.9% vs. 8.5% [p<0.001]), although Māori and men were significantly less likely to be insulin pump users. Glycaemic control worsened significantly as social deprivation increased, but was not significantly affected by rural versus urban living.

Comment: It is always good to have NZ data and studies to include in this review. Here is a retrospective review of glycaemic control in people with type 1 diabetes included in the diabetes register in the Waikato region. We know that control varies over time as various factors come to play for people with type 1 diabetes. Here the authors have simply taken the most recent HbA_{1c} level as representative. Despite all of the effort made by individuals with diabetes and the team helping them, it is striking that <15% were achieving target control. This highlights just how hard it is. Although those who were using an insulin pump had slightly better control, the difference is not huge and in this type of study cannot necessarily be attributed to the pump itself rather than other factors. It is notable that other determinants of health were related to control, as is seen in so many health outcomes.

Reference: Intern Med J 2021;51:725–31
Abstract

Dietary potato intake and risks of type 2 diabetes and gestational diabetes mellitus

Authors: Guo F et al.

Summary: This was a meta-analysis of 19 studies reporting data on associations of potato consumption with type 2 diabetes and GDM; 13 studies reported on 21,357 cases of type 2 diabetes among 323,475 participants, and six reported on 1516 cases of GDM among 29,288 pregnancies. Significant positive associations were seen for type 2 diabetes risk with intake of any potato (RR 1.19 [95% CI 1.06, 1.34]), baked/boiled/mashed potato (1.08 [1.00, 1.16]) and French fries/fried potato (1.33 [1.03, 1.70]) among Western populations, with significant 10%, 2% and 34% increased risks of type 2 diabetes for each 80 g/day serving of any potato, unfried potato and fried potato intake, respectively (p values for trends, <0.001, 0.02 and <0.001). There were also nonsignificant increases in GDM risk for any potato and fried potato intake (respective RRs 1.19 [0.89, 1.58], and 1.03 [0.97, 1.09]) in Western countries, with significant associations seen for each 80 g/day increase in consumption (1.22 [1.06, 1.42] and 1.26 [1.07, 1.48], respectively [p values for trends, 0.007 and 0.006]).

Comment: The poor old humble potato! Potato has been a staple carbohydrate for many Western diets for centuries. Rates of type 2 diabetes have only really increased significantly over the last 30–40 years. So can we really blame the potato? This meta-analysis suggests that there is a dose-response relationship between daily potato consumption and risk of diabetes. Notably, this is driven mostly by fried potato consumption and would suggest a contribution if not interaction between fat and carbohydrate intake and/or total energy intake as the important factor. It would be interesting to see a similar analysis for other staple carbohydrates such as rice, bread or pasta, and to see this adjusted for total energy.

Reference: Clin Nutr 2021;40:3754–64
Abstract

Dietary interventions and blood pressure in overweight or obese individuals

Authors: Arnotti K et al.

Summary: This systematic review and meta-analysis included ten RCTs (n=6862) investigating the effects of interventions of increased fruit and vegetable consumption on BP in participants with a BMI of ≥25 kg/m^2. Overall, fruit and vegetable consumption interventions were associated with decreases in systolic and diastolic BP of 2.16 and 0.55mm Hg (p values <0.001 and 0.39), respectively. Greater decreases in systolic BP were evident in participants from the community and medical schools rather than healthcare/programmes, with interventions that used the DASH diet, and when fruit and vegetable consumption was recorded in food diaries. Decreases in systolic BP were less when concealed allocation was used and fidelity checked. The greater the fruit and vegetable consumption, the greater were the decreases in systolic and diastolic BP.

Comment: Fruit and vegetable consumption has been associated with many positive health outcomes in many population studies. This meta-analysis has specifically focussed on studies that have used a fruit and vegetable intervention on BP in overweight or obese individuals. Given the extensive body of dietary intervention literature, it is surprising that there were only ten studies that met the inclusion criteria. Furthermore, the quality of the studies identified and the possibility that there is a publication bias means that it is difficult to draw confident conclusions. However, as expected it appears that there is a dose-response effect of increased fruit and vegetable intake on BP in overweight and obesity.

Reference: Clin Nutr; published online June 10, 2021
Abstract

Frequency of interruptions to sitting time: benefits for postprandial metabolism in type 2 diabetes

Authors: Homer AR et al.

Summary: Twenty-three adults with medication-controlled type 2 diabetes participated in this three-arm randomised, crossover trial with 6- to 14-day washout. The study arms consisted of sitting uninterrupted for 7 hours, sitting and 3-minute simple resistance activities (half squats, calf raises, gluteal contractions and knee raises) every 30 minutes, and sitting with 6 minutes of simple resistance activities every 60 minutes. Greatest attenuation of the respective glucose and insulin 7-hour net incremental AUCs was seen with sitting with 6 minutes of activities every 60 minutes (17.0 mmol·h/L and 1229 pmol·h/L) compared with sitting only (21.4 mmol·h/L and 1411 pmol·h/L [$p<0.05$]); the difference compared with sitting and 3-minute simple resistance activities every 30 minutes was significant only for glucose (22.1 mmol·h/L [$p=0.01$]), and there were no significant differences for glucose or insulin net incremental AUCs for the comparison of sitting plus 3-minute activities every 30 minutes and sitting only. Triglyceride net incremental AUC was not significantly affected by any of the study conditions.

Comment: What a great little study. Prolonged sedentary time is a strong risk factor for type 2 diabetes and is a predictor of worse glycaemic control in established diabetes. So many jobs are now desk-based, and unless people very actively avoid or reduce sedentary time, people can spend many hours sitting. This small crossover study explored whether a simple brief activity intervention carried out every 30 or 60 minutes improves parameters of glucose metabolism in people with type 2 diabetes. Doing 6 minutes of simple resistance activities every 60 minutes resulted in significant improvements compared with a sitting control. This level of intervention is practical and could be implemented in the workplace. It further reinforces my adoption of a standing desk for consultations. I still can't get most patients to stand with me though!

Reference: Diabetes Care 2021;44:1254–63
Abstract

Strategies for overcoming therapeutic inertia in type 2 diabetes

Authors: Powell RE et al.

Summary: This was a systematic review with nonlinear random-effects meta-regression meta-analysis of 36 studies (n=22,243) examining the effects of interventions (median duration 1 year) to overcome therapeutic inertia on HbA_{1c} level control in patients with type 2 diabetes. Compared with the control arms, changes in HbA_{1c} level ranged from: i) –17.7 to –4.4 mmol/mol, or –1.62% to –0.40%, for nurse- or certified diabetes educator-based interventions; ii) –13.1 to +3.3 mmol/mol, or –1.20% to +0.30%, for care management and patient education interventions; iii) –9.8 to –6.6 mmol/mol, or –0.90% to – 0.60%, for pharmacist-based interventions; and iv) –4.4 to +2.8 mmol/mol, or –0.40% to +0.26%, for physician-based interventions. HbA_{1c} levels only declined significantly during the first year in participants with preintervention HbA_{1c} levels of >75 mmol/mol, or <9%, across all studies (–4.2 and –1.6 mmol/mol, or –0.38% and –0.15%, at 6 months and 1 year, respectively).

Comment: There is good evidence that therapeutic inertia is a common problem in the management of type 2 diabetes. Previous studies have identified both patient and practitioner factors in this inertia. This study systematically reviewed the literature of interventions designed to reduce clinical inertia. The results focus on the impact of different members of the multidisciplinary team leading the intervention. It doesn't surprise me at all that the outcomes for improved glycaemic control were better when led by nonphysician providers – nurses and pharmacists. Management of diabetes is an ideal example of where the whole of the team have very important roles and the best outcomes are achieved when the team functions as a team with a common goal and common messages. This paper supports the growing structure in primary care of prescribing nurses and pharmacists in long-term condition management.

Reference: Diabetes Obes Metab; published online June 27, 2021
Abstract

Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England

Authors: Caleyachetty R et al.

Summary: Ethnicity-specific BMI cutoffs for obesity were determined according to type 2 diabetes risk for a population-based cohort of 1,472,819 individuals in England, of whom 90.6% were White, 5.2% were south Asian, 3.4% were Black, 0.7% were Chinese and 0.2% were Arab. Type 2 diabetes was diagnosed in 6.6% of the cohort over median follow-up of 6.5 years. For the equivalent age-adjusted and sex-adjusted incidence of type 2 diabetes at a BMI of 30.0 kg/m^2 among the White individuals, the respective BMI cutoffs for the south Asian, Black, Chinese and Arab populations were 23.9, 28.1, 26.9 and 26.6 kg/m^2.

Comment: BMI is a surrogate measure of body fatness. The cutoffs we usually use for overweight and obesity are derived from Caucasian populations and relate to risk of developing CV disease. Body composition varies by ethnicity, with differences in the ratio of fat to lean body mass. Therefore, it is to be expected that the standard BMI formula might not be able to be translated to non-Caucasian ethnicities as an estimate of fat mass or the cutoffs be appropriate for identifying risk for CV or metabolic disease. This excellent study from the UK used longitudinal primary-care data to identify BMI cutoffs across different ethnicities that predict risk of type 2 diabetes compared with a cutoff of 30 kg/m^2 for Caucasians. As expected for ethnicities who have a higher incidence of type 2 diabetes, the BMI cutoff is lower. What surprised me was just how low it is for south Asian populations at 23.9 kg/m^2, which is within the healthy range for Caucasians. In NZ, we really need to know how this analysis looks for Māori and Pacific populations. The data we do have would suggest that although BMI cutoffs for estimation of fat mass are higher than Caucasians, the metabolic risk is similar at the Caucasian cutoff, and therefore shouldn't be adjusted.

Reference: Lancet Diabetes Endocrinol 2021;9:419–26
Abstract