Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 144 – 2021

In this issue:

Abbreviations used in this issue
BP = blood pressure
CV = cardiovascular
GDM = gestational diabetes mellitus
HbA_{1c} = glycosylated haemoglobin
HR = hazard ratio
MI = myocardial infarction
OGTT = oral glucose tolerance test
RCT = randomised controlled trial

Welcome to issue 144 of Diabetes and Obesity Research Review.

We begin this issue with a randomised trial of one-step versus two-step screening (the latter being favoured in NZ) for detecting GDM (gestational diabetes mellitus) among expectant mothers. Another RCT has compared the effects of mobile versus standard management of women with GDM on *post partum* type 2 diabetes and its associated risk factors. There is also research reporting declining incidences of type 2 diabetes in many countries since 2010, which contrasts with the increasing prevalences (combination of new cases and longer survival) often cited. This issue concludes with trends in the prevalence of hypertension and dyslipidaemia in patients with incident type 2 diabetes, time to starting antihypertensive and lipid-lowering therapies, and associations with systolic BP and lipid control.

We hope you enjoy this update in diabetes and obesity research. We are always delighted to receive your comments and feedback.

Best regards,

Professor Jeremy Krebs
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A pragmatic, randomized clinical trial of gestational diabetes screening

Authors: Hillier TA et al.

Summary: Pregnant women from one of two health systems (n=23,792) were randomised to one-step screening (fasting 75g OGTT) or two-step screening (nonfasting 50g OGTT followed if positive by a fasting 100g OGTT); the adherence rates for the respective groups were 66% and 92%. The proportion of participants diagnosed with GDM (primary endpoint) was greater in the one-step screening arm than in the two-step screening arm (16.5% vs. 8.5%; unadjusted relative risk 1.94 [97.5% CI 1.79, 2.11]), with no significant between-group difference for large-for-gestational-age infants (8.9% vs. 9.2%; 0.95 [0.87, 1.05]), a perinatal composite outcome of stillbirth, neonatal death, shoulder dystocia, bone fracture, or any arm or hand nerve palsy related to birth injury (3.1% vs. 3.0%; 1.04 [0.88, 1.23]), gestational hypertension or pre-eclampsia (13.6% vs. 13.5%; 1.00 [0.93, 1.08]) or primary caesarean section (24.0% vs. 24.6%; 0.98 [0.93, 1.02]).

Comment: Screening for GDM remains controversial. There are those who feel that GDM is not a major problem and is overdiagnosed, and screening should at most be targeted and opportunistic, and those who see GDM as a major problem for mother and child and advocate for universal screening. An OGTT is unpleasant and time consuming at the best of times, but even worse when you are pregnant (I'm told). Some countries use one-step screening with an OGTT, and others, NZ included, use a two-step process with a 50g nonfasted glucose challenge followed by a formal glucose tolerance test in those above a specific threshold. Even this differs between countries, with the US using a 100g glucose OGGT (yuk), whereas most use 75g. Furthermore, the cutoff for glucose level differs as well – a real pig's breakfast. This study reports the comparison between strategies with no major differences between them for maternal and perinatal outcomes. This is interesting, but I'm not sure how it specifically relates to the NZ chosen approach. It certainly doesn't suggest a strong need to change it.

Reference: N Engl J Med 2021;384:895–904
Abstract

Pre-diabetes prevalence and associated factors in New Zealand school children

Authors: Mazahery H et al.

Summary: Relationships between selected factors and prediabetes were explored in 451 children from the cross-sectional Auckland Children's Bone Study stratified as normoglycaemic (HbA_{1c} level ≤39 mmol/mol) or prediabetic (HbA_{1c} level >39 mmol/mol). Prediabetes was present in 16% of the children overall, with higher rates in South Asian, Pacific Island and Māori children compared with European children (30%, 27% and 18%, respectively, vs. 6.0% [p<0.001]). Among children of South Asian and Pacific Island ethnicity, factors associated with prediabetes were high waist circumference, high percentage bodyfat and low physical activity.

Comment: These are really important and useful data on prediabetes in NZ children. We all know and see an increase in diabetes in young people. This is a major concern, because to date, children and young adults with type 2 diabetes do not do well. They have worse glycaemic control and earlier onset of complications compared with older adults who develop type 2 diabetes. Prediabetes is a precursor to type 2 diabetes, and whilst we debate the rate of progression and whether prediabetes defined by HbA_{1c} level carries the same risk as if diagnosed by an OGTT, the figures shown in this study remain concerning. Furthermore, they mirror the differences between ethnicities seen in adults, and once again illustrate the inequities in health in NZ. We need to better understand how we can turn this around to reduce progression to full type 2 diabetes at both individual and population levels.

Reference: N Z Med J 2021;134(1531):76–90
Abstract

This Research Review has been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for up to 1 CME credit for the General Practice Educational Programme (GPEP) and Continuing Professional Development (CPD) purposes. You can record your CME credits in your **RNZCGP Dashboard**

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THEIA™ development, and testing of artificial intelligence-based primary triage of diabetic retinopathy screening images in New Zealand

Authors: Vaghefi E et al.

Summary: These NZ authors reported on the development and evaluation of THIEA™, an artificial intelligence system for detecting diabetic retinopathy and maculopathy. Development of THEIA used routinely collected data from 32,354 consecutive individuals with diabetes who underwent 63,843 retinal screens within the Auckland and Counties Manukau DHBs. Most screening results (95–97%) were categorised as non-sight-threatening, with 0.9–2.4% and 1.1–3.1% categorised as potentially referable and sight-threatening, respectively. Using the referable/nonreferable categories, the respective sensitivity and specificity values for THEIA were 94% and 63% for the Auckland DHB dataset, and 95% and 61% for the Counties Manukau DHB dataset. It was concluded that the manual grading load associated with retinal screening of diabetics could be significantly reduced if THEIA was incorporated into NZ's diabetic screening programme.

Comment: Retinal screening for retinopathy in people with diabetes is something that lends itself to a more automated approach. A retinal screening programme is highly effective in reducing the incidence and severity of proliferative retinopathy and blindness. However, it is very user dependant and personnel heavy, and always prone to human error. Because patients have serial scans over time, with stored digital images, it is an ideal situation for artificial intelligence to be used to train a computer to read scans and identify individuals at risk. This NZ research demonstrates the effectiveness of this approach. This could make a real difference if it can be implemented across the country, and could be particularly useful in smaller and rural centres – great stuff.

Reference: Diabet Med 2021;38:e14386
Abstract

Effects of mindfulness- and acceptance-based interventions on diabetes distress and glycaemic level in people with type 2 diabetes

Authors: Ngan HY et al.

Summary: This was a systematic review and meta-analysis of nine RCTs (n=801) reporting on the effects of acceptance and commitment therapy, mindfulness-based cognitive therapy, mindfulness-based stress reduction or self-directed mindfulness practice in adults with type 2 diabetes; most of the study participants had an HbA_{1c} level of >53 mmol/mol. Compared with control groups, the interventions were associated with reductions in diabetes distress ($p<0.01$) and HbA_{1c} level ($p=0.03$) up to 1 month postintervention; however, underpowered studies may have resulted in overestimation; the interventions for both outcomes were heterogeneous.

Comment: Diabetes distress is something I think about mostly in those with type 1 diabetes, particularly in the young adult group; however, it is clear that it does occur in all groups with all forms of diabetes. It is a common reason for or contributor to sudden jumps in HbA_{1c} level or persistently elevated HbA_{1c} levels. Recognising this and acknowledging it is the first major step for both patient and clinician alike. However, reducing diabetes distress can be difficult, and requires a lot of input and time for all. This systematic review and meta-analysis looked at the effect of different interventions on distress and glycaemic control. Whilst there are positive effects, the reduction in HbA_{1c} level is modest overall, and it is hard to know what the difference in the distress score actually translates to in people's experiences and quality of life.

Reference: Diabet Med 2021;38:e14525
Abstract

Egg consumption, overall diet quality, and risk of type 2 diabetes and coronary heart disease

Authors: Djoussé L et al.

Summary: These researchers assessed the impact of egg consumption on the risks of type 2 diabetes and coronary heart disease after adjustment for overall diet using data pooled from nine prospective US cohorts (n=103,811). Most of the cohorts had median egg consumption of 1 egg per week. The risk of type 2 diabetes was not increased by consumption of ≤1 egg per week, but consumption of ≥2 eggs per week did increase the risk, with ≥7 vs. 0 eggs per week increasing the risk by 27%. Although there was no overall association between egg consumption and coronary heart disease risk, sensitivity analyses detected there was a 30% increase in risk for older adults who consumed 5–6 eggs per week.

Comment: The humble egg gets mixed reviews when it comes to whether it is a healthy choice or not. Eggs are an easy food choice for quick meals, particularly for those adopting a low-carbohydrate diet. However, concerns have been raised over the risk for CV disease, especially in those with dyslipidaemia. This study reports on pooled data from nine cohort studies on the association between egg consumption and incident diabetes or CV disease, and tries to account for confounding factors. I was surprised to see that weekly consumption of more than one egg increased the risk of diabetes but not CV disease. It was only in an exploratory analysis that it appears that older adults with a high intake of eggs may be at more risk, but in the absence of a primary effect, this must be seen with caution. It is the greater incidence of type 2 diabetes that is of concern and needs further study and understanding.

Reference: Clin Nutr; Published online March 10, 2021
Abstract

Effect of mobile health based peripartum management of gestational diabetes mellitus on postpartum diabetes

Authors: Huang F et al.

Summary: In this trial, 309 women with GDM were randomised to receive standard management or mobile management, and 75g OGTTs were performed at 6 weeks *post partum*. Compared with standard management, mobile management was associated with a higher incidence of type 2 diabetes *post partum* (12.36% vs. 3.88% [p=0.0291]). In the mobile management group, women with type 2 diabetes had significantly higher fasting, 1-hour and 2-hour OGTTs at 24–28 weeks' gestation than those without type 2 diabetes, and in the standard management group, the 1-hour and 2-hour OGTTs at 24–28 weeks' gestation were significantly higher among women with type 2 diabetes. A higher OGTT at 24–28 weeks' gestation was a risk factor for type 2 diabetes *post partum*.

Comment: The concept of using mobile technologies for improving health outcomes seems very logical and has been studied in many situations. In diabetes, the results have been very mixed, but largely underwhelming. Most studies have not shown a benefit of mobile apps, text message prompting or similar on weight, glucose control or other outcomes. This study explored mobile management for women with GDM after delivery to try to reduce the risk of developing type 2 diabetes. Once again, it seems likely to be helpful by reducing time burden on a busy new mum. However, it actually increased risk compared with standard in-person care. We must be very careful not to assume that because technology can reduce the burden of care that it will necessarily improve outcomes. This is exactly why we need well-designed RCTs.

Reference: Diabetes Res Clin Pract 2021;175:108775
Abstract

Trends in the incidence of diagnosed diabetes: a multicountry analysis of aggregate data from 22 million diagnoses in high-income and middle-income settings

Authors: Magliano DJ et al.

Summary: Changes in the incidence of clinically diagnosed diabetes (total and type 2) over time were examined using 24 population-based data sources from 19 high-income and two middle-income countries/jurisdictions. There were ~22 million diabetes diagnoses from 5 billion person-years of follow-up. Nineteen of 23 sources reporting data from 2010 onwards showed a downward or stable trend in the incidence of diabetes, with annual estimated incidence changes of –1.1% to –10.8%; the estimated changes were 0.9–5.6% for the four data sources that showed an increasing trend since 2010. The findings were robust to sensitivity analyses.

Comment: For a long time now we have been saying there is a type 2 diabetes epidemic with an ever-increasing prevalence year by year. In NZ, this has been in the order of 7% per annum over the last decade. What this paper points out is that prevalence is a combination of new cases and also longer survival. Therefore, understanding the incidence is also very important when considering whether efforts to turn this around are making any difference. This paper reports on data from multiple countries, using multiple sources over at least a decade. Whilst there are obvious confounders, such as definitions for diabetes and the increased use of HbA_{1c} level for diagnosis, the message is clear and surprising. The incidence of type 2 diabetes has plateaued and even turned downwards in many countries. If correct, this is very promising, but requires more investigation to be certain and more work to understand why and what factors have made the difference, so these can be focussed on further.

Reference: Lancet Diabetes Endocrinol 2021;9:203–11
Abstract

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Night-time heart rate variability identifies high-risk people among people with uncomplicated type 2 diabetes mellitus

Authors: Hadad R et al.

Summary: These researchers evaluated heart rate variability for predicting CV events in 653 community-dwelling individuals free of prior CV disease, including 133 with well-controlled or newly diagnosed type 2 diabetes. Over median follow-up of 14.4 years, overall there were 245 deaths and 149 CV events (36 CV-related deaths, 42 MIs, 46 revascularisation procedures and 70 strokes), including 41 CV events in the group with diabetes (13 CV-related deaths, 13 MIs, 17 revascularisation procedures and 18 strokes). In the group with type 2 diabetes, each 10 msec increment in the standard deviation for the mean value of normal-to-normal complexes in heart rate during the night was inversely associated with the risk of a CV event (adjusted HR 0.74 [95% CI 0.61, 0.89]); 24-hour heart rate variability was not associated with CV event risk, but was associated with all-cause mortality. The prediction of CV events by conventional risk factors was enhanced when night-time heart rate variability was added (p=0.037).

Comment: Autonomic neuropathy is likely under-recognised in people with diabetes. We are generally less tuned in to look for it, and tools like 24-hour heart rate monitoring have been relatively inaccessible in diabetes clinics. However, with the evolution of so many forms of personal health monitoring devices that readily capture all of these data, there is an opportunity to utilise this in clinical risk assessment. This study reports on the value of nocturnal heart rate variability in this context. It shows that the addition of this metric to traditional tools can identify individuals at high risk of CV events who would have otherwise been scored at low risk. This may become an important additional parameter to collect. It would be interesting to see how the addition of this to the PREDICT data in NZ would change the modelling.

Reference: Diabet Med; Published online March 13, 2021
Abstract

Glucose control, sulfonylureas, and insulin treatment in elderly people with type 2 diabetes and risk of severe hypoglycemia and death

Authors: Ling S et al.

Summary: The risks of severe hypoglycaemia and mortality associated with glucose level control, sulfonylurea exposure and insulin treatment were explored in this observational study of 22,857 UK patients aged ≥70 years with type 2 diabetes. Individuals with three consecutive HbA_{1c} levels <53 mmol/mol while exposed to insulin and/or sulfonylureas within 60 days prior to the third HbA_{1c} level measurement (n=6288; 5659 exposed to a sulfonylurea) were matched to nonexposed individuals. During follow-up, the mortality and severe hypoglycaemic event rates were 47.6% and 6.1%, respectively, with insulin/sulfonylurea-exposed individuals at greater risk of severe hypoglycaemia (adjusted HR 2.52 [95% CI 2.23, 2.84]), but not CV- or non-CV-related mortality (0.98 [0.91, 1.06] and 1.05 [0.99, 1.11], respectively), than the nonexposed patients. The respective 10-year severe hypoglycaemic event risks for insulin/sulfonylurea-exposed patients aged 70, 75, 80 and 85 years were 7.7%, 8.1%, 8.6% and 8.4% greater than for nonexposed patients, whereas differences for non-CV mortality ranged from 1.2% in a 70-year-old to 1.6% in an 85-year-old. Sulfonylurea and insulin use had greater relevance for predicting severe hypoglycaemia and death than glucose level.

Comment: We often talk about the risk of hypoglycaemia with sulfonylureas and insulin therapy, particularly in the elderly. This is one of the reasons for supporting the use of newer diabetes drugs, which do not in themselves cause hypoglycaemia. This study is very helpful to quantify this risk. It is important to note that the patients included had tight glycaemic control. With that in mind, the HR for severe hypoglycaemia in over 70-year-olds was 2.5 for those on a sulfonylurea or insulin. This is important and highlights the need to avoid excessively tight glucose control in the elderly. However, the risk is almost certainly a great deal lower for those with an HbA_{1c} level above 60 mmol/mol, which let's face it, most of our patients are. As there is no evidence of increased mortality, the humble sulfonylurea may be getting an overly bad rap – particularly when it is cheap and pretty damn effective in lowering glucose levels.

Reference: Diabetes Care 2021;44:915–24
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. 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. **FOR FULL BIO CLICK HERE.**

Cardiovascular and renal disease burden in type 1 compared with type 2 diabetes

Authors: Kristófi R et al.

Summary: The risks of CV and renal disease were compared between cohorts of 59,331 adults with type 1 diabetes and 484,241 with type 2 diabetes from Sweden and Norway in this observational study with a mean 2.6 years of follow-up. Type 1 and type 2 diabetics had similar prevalences of CV disease across age strata, whereas those with type 1 diabetes had more chronic kidney disease. Compared with type 2 diabetes, type 1 diabetes was associated with increased risks of heart failure in patients aged 65–79 years (1.3- to 1.4-fold), MI in those aged 55–79 years (1.3- to 1.8-fold) and stroke in those aged 40–54 years (1.4- to 1.7-fold). Among patients with type 1 diabetes, the risk of chronic kidney disease was increased 1.4- to 3.0-fold at all ages, and the risk of death from any cause was increased 1.2- to 1.5-fold in those aged ≥50 years with a similar trend seen for CV-related death.

Comment: A recent publication showed that life expectancy for people with type 1 diabetes is still about 10 years lower than for those without diabetes. It is easy to forget this, particularly when working with young people. This current paper from Scandinavia using registries of patients with diabetes clearly demonstrates that people with type 1 diabetes actually have greater risk for CV events and renal disease than those with type 2 diabetes. It is a poignant reminder that we need to aggressively manage cardiac risk factors in people with type 1 diabetes, although I still struggle with the timing of introducing statin therapy.

Reference: Diabetes Care; Published online March 2, 2021
Abstract

Fasting and postprandial plasma glucose contribution to glycated haemoglobin and time in range in people with type 2 diabetes on basal and bolus insulin therapy

Authors: Liao B et al.

Summary: Using pooled data from five insulin lispro trials, these researchers explored inter-relations between glycaemic metrics in 1572 recipients of basal-bolus or basal-plus insulin for type 2 diabetes. A 1 mmol/L change in fasting plasma glucose level was associated with a 2.7 mmol/mol change in HbA_{1c} level ($p<0.0001$), a 1 mmol/L change in postprandial glucose level was associated with a 1.8 mmol/mol change in HbA_{1c} level ($p<0.01$), and 1 mmol/L reductions in fasting plasma and postprandial glucose levels were associated with increased times in target range of 6.5% and 5.3%, respectively ($p<0.0001$). On average, an HbA_{1c} level reduction of 10.9 mmol/mol corresponded with an 8.3% increase in time in target range.

Comment: The relative contribution of fasting versus postprandial glucose level to overall glycaemic burden and HbA_{1c} level is often debated. This study adds somewhat to that question. It used pooled data from pharmaceutical company trials of people with type 2 diabetes on insulin therapy. Although useful, the main limiting feature of this study is the reliance on capillary glucose monitoring. It is clear from continuous glucose monitoring that using an isolated 2- or 3-hour postprandial measurement is relatively crude compared with the more dynamic data and ability to use the area under the curve from continuous glucose monitoring. Nevertheless, it highlights that we need to focus on both the fasting and postprandial periods to achieve a good HbA_{1c} level. What it doesn't tell us is whether postprandial hyperglycaemia has an independent and additional association with adverse outcomes.

Reference: Diabetes Obes Metab; Published online March 9, 2021
Abstract

Therapeutic inertia in the management of dyslipidaemia and hypertension in incident type 2 diabetes and the resulting risk factor burden

Authors: Ling JZJ et al.

Summary: Trends in the prevalences of hypertension and dyslipidaemia in incident type 2 diabetes, times to antihypertensive and lipid-lowering therapies and associations with systolic BP and lipid control were reported for 254,925 real-world primary-care patients from the UK with incident type 2 diabetes and existing dyslipidaemia (66%) or hypertension (66%). During 2005–2016, the prevalence of dyslipidaemia increased by 10% in patients aged <60 years while the prevalence of hypertension remained stable across all age groups. Among patients aged 18–39, 40–49 and 50–59 years who were at high risk of atherosclerotic CV disease, the respective median numbers of months to initiation of therapy were 20.4, 10.9 and 9.5 among those with dyslipidaemia, and 28.1, 19.2 and 19.9 among those with hypertension. For the respective high and low atherosclerotic CV disease risk groups, those who started lipid-lowering therapy after 1 year versus earlier had 65.3–85.3% and 65.0–85.3% higher likelihoods of failing lipid control after 2 years, and those who started antihypertensive therapy late had 46.5–57.9% and 40.0–58.7% significantly greater probabilities of failing systolic BP control.

Comment: Clinical inertia can be a major problem in the management of chronic disease. It is clearly seen in the delay to initiation of insulin therapy in type 2 diabetes prior to the expansion of our toolbox of oral agents, when people would be on maximal oral therapy with a rising HbA_{1c} level for well over 12 months before insulin initiation. Those studies highlighted the shared responsibility for this between clinicians and patients. Lipid and BP management are somewhat different issues. First the therapies are all oral medications, but second, whilst there is clear evidence for BP and lipid lowering in secondary prevention, there remain uncertainties for primary prevention. Do you look at risk factors in isolation and treat them accordingly, or do you conduct an overall risk assessment and base both interventions on that? We tend to favour the latter in NZ. Either way this paper highlights the high proportion of patients who have risk factors above recommended levels at the time of diabetes diagnosis.

Reference: Diabetes Obes Metab; Published online March 2, 2021
Abstract