Diabetes & Obesity Research Review™

Making Education Easy

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Abbreviations used in this issue
BMI = body mass index
BP = blood pressure
CV = cardiovascular
Hb_{A1c} = glycosylated haemoglobin
HDL = high-density lipoprotein
RCT = randomised controlled trial

Welcome to the eightieth issue of Diabetes and Obesity Research Review.

This issue begins with two papers from the new Lancet Diabetes & Endocrinology journal, one of which found no useful role for metformin in patients with coronary heart disease without diabetes, and the other reporting *"some evidence"* supporting carbohydrate counting over alternatives or usual care in adult patients with type 1 diabetes. Studies looking at progression from prediabetes to type 2 diabetes are also included, including Australian research reporting that the risk is reduced by around three-quarters by gastric banding, and research from China reporting that a combination of ten Chinese herbal medicines (Tianqi) reduced the risk by a degree comparable with metformin (i.e. around one-third).

I hope you enjoy the selection for this issue, and I look forward to any feedback and discussion.

Best regards,

Dr Jeremy Krebs
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Metformin for non-diabetic patients with coronary heart disease (the CAMERA study)

Authors: Preiss D et al.

Summary: Statin recipients with coronary heart disease and large waist circumferences, but without type 2 diabetes, received metformin 850mg twice daily (n=86) or placebo (n=87) in this RCT. No significant difference was seen between the metformin and placebo arms for the primary endpoint of mean distal carotid intima-media thickness progression between baseline and 18 months in a modified intent-to-treat analysis (p=0.29), nor was there any significant between-group difference for carotid plaque score change (p=0.92). Secondary endpoints of Hb_{A1c}, insulin, homeostasis model assessment of insulin resistance and tissue plasminogen activator levels were significantly lower with metformin than placebo, while high-sensitivity C-reactive protein, fasting glucose, triglyceride and total, HDL and non-HDL cholesterol levels did not differ significantly. Metformin was associated with more diarrhoea and nausea/vomiting events than placebo (28 vs. 5).

Comment: Is it possible that there is something that metformin isn't good for? This study tested whether metformin reduced progression of established CV disease in those who do not have diabetes over 18 months. The conclusion was that metformin has little effect. It must be noted that studies where metformin has been shown to have a benefit on CV disease, such as the UKPDS, tend to be longer in duration and have been in participants with established diabetes. Therefore I am not surprised by this result and agree that metformin should not be recommended in this population.

Reference: Lancet Diabetes Endocrinol 2014;2(2):116–24

Abstract

Efficacy of carbohydrate counting in type 1 diabetes

Authors: Bell KJ et al.

Summary: This was a systematic review and meta-analysis of seven RCTs comparing carbohydrate counting with general/alternative dietary advice in 599 adults and 104 children with type 1 diabetes. The average quality score of the trials was 7.6/13, and significant heterogeneity, potentially related to study design, was identified. Overall, no significant improvement was seen for Hb_{A1c} levels with carbohydrate counting versus controls (p=0.096), although when five studies in adults with a parallel design were analysed, a significant 7.0 mmol/mol (0.64 percentage point) difference was seen in favour of carbohydrate counting (p<0.0001).

Comment: There have been many different approaches to enable people with type 1 diabetes to match insulin to their food to achieve good glycaemic control. One popular current approach is carbohydrate counting. Like many things in healthcare, a treatment or approach can become dogma without always having a sound evidence base. This study reported a systematic review and meta-analysis of RCTs testing carbohydrate counting. It may surprise some that from this, the evidence to support its benefits was unconvincing. However, the authors showed that with a pure RCT study design, there was a statistically significant improvement in Hb_{A1c} level. So whilst it is a valid tool and can be very helpful for some patients, the benefit is not overwhelming and other approaches should also be considered to tailor the management to the person.

Reference: Lancet Diabetes Endocrinol 2014;2(2):133–40
Abstract

Independent commentary by Dr Jeremy Krebs,
Endocrinologist & Clinical Leader at Wellington Hospital.
For full bio CLICK HERE.

Rates of complications and mortality in older patients with diabetes mellitus

Authors: Huang ES et al.

Summary: These researchers analysed data from 72,310 patients aged ≥60 years with type 2 diabetes enrolled in the Diabetes and Aging Study to compare diabetes complication and mortality rates across age (60–69, 70–79 and ≥80 years) and diabetes duration (0–9 and ≥10 years) categories. CV complications and hypoglycaemia were the most common nonfatal complications with increasing age and shorter diabetes duration. For example, age 70–79 years with short diabetes duration was associated with higher rates of coronary artery disease and hypoglycaemia (11.47 and 5.03 per 1000 person-years, respectively) compared with end-stage renal disease, lower limb amputation and acute hyperglycaemic events (2.60, 1.28 and 0.82 per 1000 person-years). A similar pattern was seen for the same age group with long diabetes duration, with higher rates of coronary artery disease and hypoglycaemia (18.98 and 15.88 per 1000 person-years, respectively) than end-stage renal disease, lower limb amputation and acute hyperglycaemic events (7.64, 4.26 and 1.76 per 1000 person-years). Each outcome's rate, particularly hypoglycaemia and microvascular complications, increased dramatically with longer diabetes duration for each age group; however, for a given diabetes duration, the hypoglycaemia, CV complication and mortality rates increased with advancing age, and microvascular complication rates remained stable or decreased.

Comment: With an increasing prevalence of type 2 diabetes and an aging population, it is important that we understand the predictors of morbidity and mortality in this group. Whilst the evidence for intensive glycaemic control to prevent microvascular complications is convincing, debate continues for macrovascular complications. Furthermore, intensive glycaemic control is associated with an increased risk of hypoglycaemia. The results of this cohort study in adults aged ≥60 years suggest that hypoglycaemia and CV events become more common in older adults with diabetes, and that microvascular complications are relatively less important. This would suggest that a management strategy based more on interventions with good evidence for reduced CV events and a less intensive glycaemic strategy may be more appropriate for this age group.

Reference: JAMA Intern Med 2014;174(2):251–8
Abstract

Patterns of obesity development before the diagnosis of type 2 diabetes

Authors: Vistisen D et al.

Summary: These authors analysed data from 645/6705 Whitehall II Cohort Study participants followed with 5-yearly clinical examinations who developed type 2 diabetes over a median of 14.1 years. The following three patterns of BMI changes were identified: i) 'stable overweight' (n=604; i.e. those in the overweight category with a relatively constant BMI during follow-up; ii) 'progressive weight gainers' (n=15; i.e. those who consistently gain weight up to diagnosis); and iii) 'persistently obese' (n=26). Patients from the stable overweight group experienced slight β-cell function and insulin sensitivity worsening from 5 years prior to diagnosis. The progressive weight gain group experienced linear BP increases and exponential insulin resistance increases, which accompanied their weight increase, a few years prior to diagnosis. Patients from the persistently obese group experienced an initial β-cell compensation followed by loss of β-cell function, while insulin sensitivity remained relatively stable.

Comment: It is clear that type 2 diabetes is a heterogeneous group of disorders with a common phenotype of hyperglycaemia. For any one individual, diabetes ensues when there is an imbalance between insulin production and insulin sensitivity. However, there is enormous variability between individuals in where this line sits and what the temporal progression of its components is. This analysis of the Whitehall II study suggests that for the majority of those who develop diabetes, the shift in weight prior to diagnosis is relatively small and accompanied by small reductions in β-cell function. As the authors suggested, this may imply that similarly small weight losses may prevent or delay diabetes, as seen in the diabetes prevention study. If this can be achieved at a population level, it may be able to achieve meaningful reversal of the burgeoning diabetes epidemic.

Reference: PLoS Med 2014;11(2):e1001602
Abstract

Antihypertensive treatment and resistant hypertension in patients with type 1 diabetes by stages of diabetic nephropathy

Authors: Lithovius R et al., on behalf of the FinnDiane Study Group

Summary: This cross-sectional analysis of data from 3678 participants with type 1 diabetes from FinnDiane (Finnish Diabetic Nephropathy Study) assessed their BP control, antihypertensive treatment and prevalence of resistant hypertension. The respective rates of antihypertensive use and uncontrolled BP despite treatment were: i) 14.1% and 74.6% for participants with a normal albumin excretion rate; ii) 60.5% and 71.2% for those with microalbuminuria; iii) 90.3% and 80.0% for those with macroalbuminuria; iv) 88.6% and 88.1% for those requiring dialysis; and v) 91.2% and 90.4% for those who had undergone renal transplantation. The prevalences of resistant hypertension were 1.2%, 4.7%, 28.1%, 36.6% and 26.3% in the normoalbuminuric, microalbuminuric, macroalbuminuric, dialysis and kidney transplant groups, respectively. Factors independently associated with resistant hypertension were age (odds ratio 1.04 [95% CI 1.02, 1.05]), estimated glomerular filtration rate (0.97 [0.96, 0.97]), waist-to-hip ratio (1.44 [1.15, 1.80]), triglyceride level (1.19 [1.01, 1.40]), microalbuminuria (2.58 [1.43, 4.67]) and macroalbuminuria (5.61 [3.20, 9.84]).

Comment: There is a well-established association between hypertension and diabetic nephropathy, and a solid evidence base for BP lowering and prevention of nephropathy. This cross-sectional study demonstrated that in those who have advanced nephropathy, despite antihypertensive therapy, BP is frequently poorly controlled. In such a cross-sectional analysis, it is not possible to determine whether the lack of BP control is a cause or consequence of nephropathy, but other studies would support the conclusion that greater effort is required in those with early nephropathy to prevent progression.

Reference: Diabetes Care 2014;37(3):709–17
Abstract

Laparoscopic adjustable gastric banding and progression from impaired fasting glucose to diabetes

Authors: Wentworth JM et al.

Summary: The risk of progression from impaired fasting glucose to diabetes was retrospectively compared between 281 obese individuals who had undergone laparoscopic adjustable gastric banding and adults with impaired fasting glucose from the AusDiab study. Among the patients who had undergone gastric banding, the respective diabetes incidences for the lowest, middle and highest weight loss tertiles were 19.1, 3.4 and 1.8 per 1000 person-years, compared with 12.5 per 1000 person-years among AusDiab participants who had a BMI of ≥28 kg/m^2. Compared with AusDiab participants classified as obese (n=322), the diabetes incidence was significantly lower among the patients who had undergone gastric banding (20.5 vs. 8.2 per 1000 person-years; p=0.02). A multivariable analysis of data from the gastric banding and AusDiab cohorts combined showed that gastric banding significantly lowered the risk of developing diabetes (odds ratio 0.24 [95% CI 0.10, 0.57; p=0.004]).

Comment: With an ever-increasing number of individuals being identified with prediabetes, particularly now that screening is simple with a nonfasting Hb_{A1c} level test, it is important that we identify effective interventions to reduce progression to diabetes. There is good evidence that even modest weight loss can achieve this, as seen with intensive lifestyle interventions in the diabetes prevention programme and study. However, not all individuals respond to this, and there may be some who require a more aggressive approach. This study reports on the impact of laparoscopic gastric bands on this issue. The study design is not ideal, using a completely different cohort as controls, and a retrospective analysis of the banding data opening the study up to multiple potential selection biases. That aside, the results were as we might expect – that weight loss significantly reduces the rate of progression to diabetes. Once again though, those who didn't achieve weight loss despite the surgery did not get the metabolic benefit. This again supports the notion that it's weight loss that counts rather than how you achieve it.

Reference: Diabetologia 2014;57(3):463–8
Abstract

Longitudinal association between dairy consumption and changes of body weight and waist circumference

Authors: Wang H et al.

Summary: These researchers included 3440 Framingham Heart Study Offspring Cohort participants in their investigation into the relationship between dairy intake and bodyweight gain. The participants' bodyweight and waist circumferences increased during follow-up. Compared with total daily dairy consumption of <1 serving, ≥3 servings was associated with a 0.10kg smaller annualised increment of bodyweight increase and a marginally smaller increase in waist circumference after adjustments for demographic and lifestyle factors (respective p values 0.04 and 0.05 for trend), and 0.10kg and 0.13cm smaller annualised increments for bodyweight and waist circumference were seen for ≥3 versus <1 serving per week of yogurt (0.03 and 0.008). Consumption of skim/low-fat milk, cheese, total high-fat or total low-fat dairy did not significantly impact on long-term bodyweight or waist circumference changes.

Comment: Many people report consciously avoiding dairy products in their diet either to avoid bodyweight gain or for CV reasons. This paper from the Framingham Offspring Study looked at the relationship between dairy intake and weight change over a 17-year interval. Contrary to popular thought, intake of ≥3 servings of total dairy per day was associated with less weight gain than low intakes. The difference was only 100g per year, so hardly stunning, but perhaps most importantly when considering other health issues, such as calcium intake and osteoporosis, there is no evidence of harm in greater dairy intake. Fonterra will be happy!

Reference: Int J Obes 2014;38(2):299–305
Abstract

Chinese herbal medicine Tianqi reduces progression from impaired glucose tolerance to diabetes

Authors: Lian F et al.

Summary: Patients with impaired glucose tolerance were randomised to receive Tianqi capsules (containing ten Chinese herbal medicines; evaluable n=198) or placebo (evaluable n=191) for 12 months in this RCT. Compared with placebo, Tianqi was associated with a significantly lower rate of progression to diabetes at 12 months (18.18% vs. 29.32%; p=0.01), and a greater proportion of participants with normal glucose tolerance (63.13% vs. 46.60%; p=0.001), but no significant difference for change in bodyweight or BMI. No severe adverse events were reported.

Comment: Once again we're on the theme of prediabetes – this seems to be occupying a lot of my thoughts at the moment. This Chinese RCT compared a capsule containing ten herbal medicines used for the treatment of type 2 diabetes with placebo on the rate of progression from impaired glucose tolerance to diabetes. The results are impressive, with a 32% relative reduction in progression with the herbal capsule. The capsule was well tolerated, and retention in the trial was excellent. This compares favourably with the metformin arm of the diabetes prevention study, where the relative reduction was also 33%, but significantly less than the 68% reduction with an intensive lifestyle intervention. This could provide a useful adjunct for the management of those with prediabetes.

Reference: J Clin Endocrinol Metab 2014;99(2):648–55
Abstract

A comparison of functional brain changes associated with surgical versus behavioral weight loss

Authors: Bruce AS et al.

Summary: This research examined brain responses to food cues in 15 obese individuals who lost bodyweight after adjustable gastric banding surgery and another 16 obese individuals who did so with a behavioural dietary intervention. Compared with participants who underwent surgery, those in the behavioural diet group exhibited increased premeal activation to food images in the right medial prefrontal cortex (a region associated with valuation and processing of self-referent information) and left precuneus following weight loss. The surgery group also exhibited increased bilateral activation in regions of the brain associated with higher level perception in response to food cues following weight loss compared with the diet intervention group.

Comment: OK, I confess that I haven't quite got my head around this one, but I have included it anyway as it is interesting. It is observed that those who lose bodyweight through bariatric surgery tend to have a different appetite and approach to food following surgery than those who lose weight through diet and exercise alone. In particular, they tend to complain less of hunger, which is often the driving force for weight regain. Therefore, the concept that there may be differences in brain activity after these two interventions is intriguing. Using functional magnetic resonance imaging scanning, this study has demonstrated differences in areas of the brain that are activated by food images. Whether this raises the potential to target these areas pharmaceutically is a tempting thought, but beyond my small brain!

Reference: Obesity 2014;22(2):337–43
Abstract

Implementation of the HbA1c IFCC unit – from the laboratory to the consumer: the New Zealand experience

Authors: Florkowski C et al.

Summary: This paper described the successful implementation in NZ of measuring and reporting Hb_{A1c} levels in IFCC (International Federation of Clinical Chemistry) units (mmol/mol). Consultation for this process, which began in 2003, involved close co-operation between the clinical and laboratory organisations, particularly the NZSSD (New Zealand Society for the Study of Diabetes). A phased process of consultation was designed to increase familiarity and comfort with replacing percentages with mmol/mol for Hb_{A1c} measurements, culminating in the coupling of the adoption of Hb_{A1c} as a diagnostic test, with some evidence-based pragmatism around using the rounded cutoff value of ≥50 mmol/mol for diagnosis. Following a 2-year period of reporting both units, the IFCC units came into exclusive use in our healthcare systems on Oct 3, 2011 for diagnosing diabetes and patient monitoring. The authors highlighted the importance of genuine clinical engagement in the successful transition to the IFCC units.

Comment: Isn't it amazing how time flies by? It only seems like yesterday that we changed over from reporting Hb_{A1c} as percentage units to mmol/mol. Like me, I'm sure most of you struggled initially, but the new units have now become second nature. I have included this paper for interest, as it covers the process and rationale for change and the choice of the cutoff values we have adopted in NZ.

Reference: Clin Chim Acta; Published online Oct 19, 2013
Abstract