Diabetes & Obesity Research Review™

Making Education Easy

Issue 90 – 2015

In this issue:

Abbreviations used in this issue
CAD = coronary artery disease
CCTA = coronary CT angiography
CT = computed tomography
CV = cardiovascular
GI = glycaemic index
GLP = glucagon-like peptide
Hb_{A1c} = glycosylated haemoglobin
RCT = randomised controlled trial
RR = relative risk
SMBG = self-monitoring of blood glucose

Welcome to issue 90 of Diabetes and Obesity Research Review.

2015 begins with an extended edition, including research showing that robust glycaemic control with no increased hypoglycaemia or bodyweight gain can be achieved using a GLP-1 agonist combined with basal insulin. Other research has explored the impact of diabetes/hyperglycaemia on cognitive function and muscle weakness. NZ research is included, with a report on SMBG test strip use in relation to antidiabetic medication type (as a proxy for diabetes severity), and a study in Otago adolescents looking at the impact of proximity of food outlets to schools on dietary quality.

Thank you for your feedback and comments last year, and I hope you continue to find Diabetes and Obesity Research Review helpful in everyday practice.

Best regards,

Dr Jeremy Krebs
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Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes

Authors: Muhlestein JB et al.

Summary: The FACTOR-64 RCT investigated whether routine screening of patients with diabetes at high risk for CAD using CCTA followed by CCTA-directed therapy reduces the risk of death and nonfatal coronary outcomes. Patients with type 1 or type 2 diabetes of at least 3–5 years' duration and without symptoms of CAD (n=900) were randomised 1:1 to CAD screening with CCTA (followed by CCTA-directed therapy) or to standard national guidelines-based optimal diabetes care. After a mean follow-up of 4 years, primary outcome event rates (all-cause mortality, nonfatal myocardial infarction or unstable angina requiring hospitalisation) did not differ significantly between groups (6.2% vs 7.6%).

Comment: This is a very useful study that answers an area of uncertainty. The main cause of premature death in those with diabetes remains CV disease. This is despite the use of well-validated screening tools and treatment algorithms for selecting those for primary prevention. The anxiety remains that we are missing an opportunity to intervene in some who would benefit. Use of widespread coronary angiography would be inappropriate, but the role for CT angiography is unclear. This well-conducted RCT demonstrates that in asymptomatic individuals with diabetes there is no benefit in a CT angiography screening strategy. Case closed.

Reference: JAMA 2014;312(21):2234–43
Abstract

Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity

Authors: Sacks FM et al.

Summary: Overweight adults with systolic blood pressure 120–159mm Hg were each assigned to two or more of the following four complete diets, each for 5 weeks, in the OmniCarb RCT: i) high-GI (glycaemic index; 65% on the glucose scale), high-carbohydrate (58% energy); ii) low-GI (40%), high-carbohydrate; iii) high-GI, low-carbohydrate (40% energy); iv) low-GI, low-carbohydrate. There were 135–150 evaluable participants for all diet comparison pairs. With a high carbohydrate content, the low- versus high-GI diet was associated with a 20% decrease in insulin sensitivity (from 8.9 to 7.1 units [p=0.002]) and a 6% increase in low-density lipoprotein cholesterol level (from 139 to 147 mg/dL [p≤0.001]), with no significant change in high-density lipoprotein cholesterol level, triglyceride level or blood pressure. With a low carbohydrate content, the low- versus high-GI diet was associated with a 5% decrease in triglyceride level (from 91 to 86 mg/dL [p=0.02]), but no effect on the other parameters measured. Similarly, the low-GI, low-carbohydrate versus high-GI, high-carbohydrate diet was associated with a 23% reduction in triglyceride level (from 111 to 86 mg/dL [p≤0.001]), but no significant change in the other parameters.

Comment: The effect of type and amount of carbohydrate in the diet on metabolic and CV risk factors has received a lot of attention over the last 20 years. The idea of GI has become particularly popular to conceptualise the response to different foods on insulin and glucose metabolism, the notion being that low-GI foods induce a lower insulin demand and glucose rise. However, not all data have been consistent, particularly when foods are incorporated into meals rather than studied in isolation. This study adds to that uncertainty. The strength of the study is the randomised crossover design, and the provision of all foods makes compliance more likely. Although the duration of the study was short, previous research has shown effects in this time. The relative deterioration in insulin sensitivity with a low-GI, high-carbohydrate diet is difficult to explain, and as the authors concluded, this study does not support using GI to inform food choices.

Reference: JAMA 2014;312(23):2531–41
Abstract

Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes

Authors: Eng C et al.

Summary: This systematic review and meta-analysis of 15 RCTs (n=4348) found that compared with antidiabetic agents, a GLP-1 agonist combined with basal insulin was associated with a greater mean reduction in Hb_{A1c} level of –0.44%, a greater probability of achieving an Hb_{A1c} level of ≤7.0% (RR 1.92 [95% CI 1.43, 2.56]), no increased risk of hypoglycaemia (0.99 [0.76, 1.29]) and a mean 3.22kg decrease in bodyweight. Such combinations were also associated with a mean Hb_{A1c} level reduction of –0.1%, a lower hypoglycaemia risk (RR 0.67 [95% CI 0.56, 0.80]) and a mean 5.66kg bodyweight decrease when compared with basal-bolus insulin regimens.

Comment: Until recently, managing type 2 diabetes has been a fine balance between trying to improve glycaemic control without causing hypoglycaemia or exacerbating obesity. With the exception of metformin, all other pharmaceutical agents commonly used (at least in NZ) have either or both of these side effects. Therefore the newer classes of agents that do not themselves cause hypoglycaemia or promote weight gain are attractive options. This meta-analysis of combined basal insulin and GLP-1 analogue therapy demonstrates how this combination stacks up well, with good glycaemic control, low risk of hypoglycaemia and weight loss rather than gain. Let's hope we get funded access to this class of drugs soon – just saying PHARMAC.

Reference: Lancet 2014;384(9961):2228–34
Abstract

Diabetes in midlife and cognitive change over 20 years

Authors: Rawlings AM et al.

Summary: The impact of midlife diabetes on cognitive decline over 20 years, assessed using delayed word recall, digit symbol substitution and word fluency tests, was prospectively assessed in a cohort of 13,351 ARIC (Atherosclerosis Risk in Communities) study participants aged 48–67 years at baseline. Cognitive decline over 20 years was greater in: i) participants with diabetes (Hb_{A1c} level ≥6.5%) versus nondiabetics (adjusted global Z-score difference –0.15 [95% CI –0.22, –0.08]); ii) participants with prediabetes (Hb_{A1c} level 5.7–6.4%) versus those with an Hb_{A1c} level <5.7%; iii) participants with poorly controlled diabetes (Hb_{A1c} level ≥7.0%) versus those whose diabetes was controlled (adjusted global Z-score difference –0.16 [p=0.071]); and iv) participants with a longer diabetes duration (p<0.001 for trend).

Comment: We frequently think about microvascular and macrovascular complications of diabetes confined to retinopathy, nephropathy, neuropathy, stroke and CAD. However, there are numerous other complications of poorly controlled diabetes. This longitudinal observational study highlights an interesting and important area that has not been well described or studied. Limitations of a single baseline measure of Hb_{A1c} level as the predictor aside, there is a clear and progressive trend of greater cognitive decline with increasing Hb_{A1c} level from within the normal range through to poorly controlled diabetes. The authors tempt us to think that preventing diabetes or maintaining tight control will protect against this, which it may, but an intervention trial is required to show this. This is obviously an area ripe for further research.

Reference: Ann Intern Med 2014;161(11):785–93
Abstract

Hyperglycemia predicts persistently lower muscle strength with aging

Authors: Kalyani RR et al.

Summary: The relationship between hyperglycaemia and declining muscle function was explored in 984 participants from the Baltimore Longitudinal Study of Aging with ≤7.5 years of available relevant data. Compared with the lowest Hb_{A1c} level quartile, participants in the highest quartile had significantly lower muscle strength after adjusting for demographics, height and weight (–4.7 N·m [p=0.02 for trend]) and after additional adjustment for physical activity (p=0.045 for trend); statistical significance was borderline after further adjustment for peripheral neuropathy (p=0.05 for trend). Muscle quality was also significantly reduced in the highest versus lowest Hb_{A1c} level quartile after adjusting for demographics (–0.32 N·m/kg [p=0.02 for trend]), but statistical significance was lost after further adjusting for weight and height (–0.25 N·m/kg [p=0.07 for trend]). There were no significant differences in muscle mass measures across Hb_{A1c} level quartiles.

Comment: As with cognitive function, another issue less well studied is the effect of diabetes and specifically glycaemic control on muscle strength. These data from a longitudinal cohort study on aging showed that muscle strength declined more in those with diabetes and poor control. The observation that peripheral neuropathy mediated some of this effect points to the possibility that other health factors not adjusted for may have been an important component of this observation, with poor glycaemic control simply being a marker for poorer general health. However, there are plausible explanations for a direct effect on muscle function, and once again these observational data tempt a prospective randomised interventional trial to test this further.

Reference: Diabetes Care 2015;38(1):82–90
Abstract

Initial choice of oral glucose-lowering medication for diabetes mellitus

Authors: Berkowitz SA et al.

Summary: In this patient-centred comparative effectiveness study, the effects of initial oral glucose-lowering agent class were evaluated in a retrospective cohort of 15,516 patients registered with a large US health insurer who had received a new prescription for an oral glucose-lowering agent, and ≤90 days of the end-of-day's supply, filled a second prescription for a medication in the same class at a dosage greater than or equal to the WHO-defined daily dose. The likelihoods of adding a second oral agent only, insulin only and a second agent or insulin were significantly increased among users of a medication other than metformin (p<0001 for all). Propensity score and Cox proportional hazards models revealed that the likelihood of treatment intensification was increased by therapy with a sulphonylurea (adjusted hazard ratio 1.68 [95% CI 1.57, 1.79]), thiazolidinedione (1.61 [1.43, 1.80]) or DPP (dipeptidyl peptidase)-4 inhibitor (1.62 [1.47, 1.79]). Metformin alternatives did not reduce the risk of hypoglycaemia, emergency department visits or CV events.

Comment: This is an interesting report, but probably of limited value. International guidelines are consistent that unless contraindicated, the first-line pharmaceutical agent for type 2 diabetes should be metformin. The most striking finding from this study is that in the US population studied, only 60% of initial prescriptions were for metformin. In a real-world retrospective observational study like this, it is impossible to tease out what factors influenced the clinician's decisions to use other agents, and therefore what confounding factors affect the other outcome measures. The bottom line is that unless there is a very good reason not to, metformin should be the first-line agent.

Reference: JAMA Intern Med 2014;174(12):1955–63
Abstract

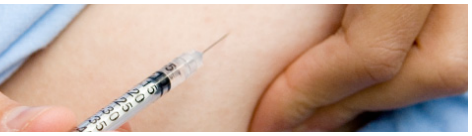
diabetes new zealand

PHARMACY GUILD OF NEW ZEALAND

NZMA New Zealand Medical Association

Independent commentary by Dr Jeremy Krebs, Endocrinologist & Clinical Leader at Wellington Hospital. He is also a Senior Clinical Lecturer with the University of Otago, and Director of the Clinical Research Diploma at Victoria University.

For full bio CLICK HERE.



Self-monitoring blood glucose test strip use with diabetes medicines in people with types 1 and 2 diabetes in New Zealand

Authors: Metcalfe S et al.

Summary: These NZ researchers related the use of blood glucose test strips dispensed to patients in 2011 to antidiabetic agent type as a proxy of disease severity; data from 122,000 patients assumed to be stabilised on the same medication regimen for ≥1 year were analysed. There was wide variability in patient numbers and ages across treatment groups and by gender and ethnicity. When compared with published guidelines, there was evidence of both over- and under-dispensing blood glucose test strips in some treatment groups, particularly for under-dispensing in patients receiving insulin aged 25–44 years or of Māori/Pacific ethnicity, and over-dispensing among those receiving metformin monotherapy or no antidiabetic agent.

Comment: SMBG is a contentious area. Patients and funders generally hate it, and clinicians love it! The ability to have a real-time accurate measure of blood glucose level to guide therapy is one of the quantum leaps in diabetes care that occurred in the latter part of last century. However, there is still great uncertainty about how it is best used, with international guidelines based more on consensus opinion rather than high-quality studies. These NZ data highlight a clinical reality, that those using insulin probably don't test as much as they would benefit from, and there may be many not on insulin who test frequently for whom it doesn't change management at all. SMBG needs to be individualised and my standard mantra to patients is 'don't test unless you will do something with the information'. That is the critical step that often gets lost when trying to analyse data on SMBG use.

Reference: NZ Med J 2014;127(1406):48–62
Abstract

Dairy consumption and risk of type 2 diabetes

Authors: Chen M et al.

Summary: This follow-up of 41,436 men in the US Health Professionals Follow-Up Study and 153,022 women in the Nurses' Health Study I and II explored the relationship between dairy consumption and incident type 2 diabetes. There were 15,156 incident cases of type 2 diabetes during 3984,203 person-years of follow-up. A meta-analysis showed no significant increased risk of type 2 diabetes for each daily serving increase of total dairy (adjusted hazard ratio 0.99 [95% CI 0.98, 1.01]), low-fat dairy or high-fat dairy, but there was a consistent, inverse association for yoghurt (0.83 [0.75, 0.92]; p<0.001 for trend). A meta-analysis of 14 prospective cohorts (n=459,790; 35,863 incident cases of type 2 diabetes) revealed consistent findings for each daily serving of total dairy and yoghurt (respective RRs 0.98 [95% CI 0.96, 1.01] and 0.82 [0.70, 0.96]).

Comment: Global consumption of dairy products is critical to NZ's economy. Therefore the last thing we need is evidence of harm to health from dairy products. This meta-analysis of long-term prospective cohort data from the three very large American population studies looked at dairy consumption and risk for type 2 diabetes. Reassuringly, once other known lifestyle risk factors were taken into account, overall dairy consumption had no effect on risk. Curiously though, yoghurt appeared to be protective. Whether this was due to a specific property of yoghurt itself or due to the absence of another food that yoghurt was being substituted for is impossible to say from these data, but the effect size is robust and worthy of more study.

Reference: BMC Med 2014;12:215
Abstract

Is the food environment surrounding schools associated with the diet quality of adolescents in Otago, New Zealand?

Authors: Clark EM et al.

Summary: Relationships between food outlets in an 800m buffer around Otago schools and dietary quality were investigated in adolescent subjects. A multivariate regression analysis showed that while distance to cafés, restaurants, supermarkets and takeaways was associated with a higher Diet Quality Index scores in boys, the distance to the nearest convenience store, café, restaurant or supermarket was associated with lower scores in girls. The effect sizes were small, suggesting a minor role of the food environment around schools in the quality of adolescents' diets.

Comment: It is a real bugbear of mine seeing kids arriving at school eating hot chips at times like 8am. Intuitively I suspected that the proximity and availability of fast food at schools or in outlets very close to schools was a key determinant in this behaviour. This NZ study therefore interested me. Although there was a small negative effect in girls, in fact for boys proximity and availability of food close to school improved dietary choice. Neither effect was large, and contrary to my belief, controlling this aspect of the built environment may have very little effect on rates of childhood obesity.

Reference: Health Place 2014;30:78–85
Abstract

Hb_{A1c} as a predictor of diabetes and as an outcome in the Diabetes Prevention Program

Authors: Diabetes Prevention Program Research Group

Summary: Adults without but at high risk for diabetes were randomised to receive metformin, an intensive lifestyle intervention or placebo in this RCT; this report includes 2765/3234 randomised participants who were nondiabetic according to fasting plasma and 2-hour postload glucose and Hb_{A1c} levels. The risk of incident diabetes was predicted by baseline Hb_{A1c} level in all study groups. The incidences of diabetes defined as an Hb_{A1c} level ≥6.5% in the respective metformin and lifestyle intervention arms were reduced by 44% and 49% during the initial 3.2-year trial and by 38% and 29% during the 10-year follow-up study. Metformin and the lifestyle intervention had similar effects for preventing diabetes defined by Hb_{A1c} level, unlike glucose level criteria used in the early findings of the study.

Comment: What is type 2 diabetes? The recent changes to the diagnostic criteria to include Hb_{A1c} level have again ignited this debate. We have seen from other studies that for the large part, using glucose level-based criteria or using Hb_{A1c} level will detect the same proportion if not exactly the same individuals with diabetes. This is particularly true at higher levels, but towards the lower threshold or into the upper 'normal range' there is much more discrepancy. This highlights the issues of creating an arbitrary 'cutoff' in a biological continuum. The Diabetes Prevention Program study is one I frequently quote to highlight the benefits of diet and lifestyle modification in preventing diabetes in those at high risk. In the original study there was a very clear superior effect of lifestyle change over metformin. Therefore these present data from the same study, but analysed using Hb_{A1c} level as the entry and subsequent diagnostic criteria, are of great interest. First the overall benefit was lower and the difference between metformin and lifestyle is lost. Second the effect of lifestyle is more attenuated over time. As Hb_{A1c} level is a more global measure of glycaemic burden than either fasting glucose or an oral glucose tolerance test, this perhaps tells us something about the effects of a dietary/physical activity intervention compared with metformin. As the authors concluded, the long-term health outcomes will be of great interest when reflecting on the most appropriate diagnostic criteria.

Reference: Diabetes Care 2015;38(1):51–8
Abstract

A randomised controlled trial of high dose vitamin D in recent-onset type 2 diabetes

Authors: Elkassaby S et al.

Summary: Fifty adults diagnosed with type 2 diabetes within the prior 12 months and a normal baseline serum 25-hydroxyvitamin D (25-OH-D) level were randomised to receive vitamin D3 6000 IU/day (n=26) or placebo (n=24) for 6 months. Among vitamin D3 recipients, median serum 25-OH-D levels increased from 59 to 150 and 128 nmol/L at 3 and 6 months, respectively, and 1,25-OH-D levels increased from 135 to 200 and 190 pmol/L. No significant difference was seen between the vitamin D3 and placebo groups for β-cell function at 3 months as assessed by change in delta C-peptide (glucagon-stimulated serum C-peptide; p=0.112) or change in Hb_{A1c} level (p=0.459), but vitamin D3 recipients had significant decreases in fasting plasma glucose level (–0.40 vs. +0.1 mmol/L [p=0.007]) and postprandial blood glucose level (–0.30 vs. +0.8 mmol/L [p=0.005]); no significant between-group difference was seen for any of these measures at 6 months.

Comment: Many a crime has been ascribed to vitamin D deficiency, and many more solutions to vitamin D supplementation. Roles for vitamin D in the aetiology of both type 1 and type 2 diabetes have been proposed. This prospective RCT of vitamin D supplementation in those with recently diagnosed type 2 diabetes helps to answer some of these questions. Importantly, all participants had normal levels of vitamin D at baseline. Although the study was for only a short duration, there was no benefit of vitamin D supplementation in this population. This does not exclude a benefit in those who have low levels of vitamin D, but does not support widespread prescription of vitamin D to all with type 2 diabetes.

Reference: Diabetes Res Clin Pract 2014;106(3):576–82
Abstract

Reversal of type 2 diabetes after bariatric surgery is determined by the degree of achieved weight loss in both short- and long-duration diabetes

Authors: Steven S et al.

Summary: The impact of diabetes duration and extent of weight loss on the reversibility of type 2 diabetes after bariatric surgery was investigated using data from 89 patients with type 2 diabetes who had undergone any bariatric surgical procedure. Hb_{A1c} levels <43 mmol/mol (<6.1%) were achieved by 62% and 26% of patients with diabetes for <4 and >8 years, respectively. It was rare for patients with diabetes duration >8 years to achieve normoglycaemia if bodyweight loss was <25kg. A clear, significant relationship was seen between greater weight loss and lower Hb_{A1c} levels across the entire cohort (R_S=–0.53 [p<0.0001]).

Comment: It is interesting that in the early days of bariatric surgery, people with diabetes were excluded as too high-risk. Now diabetes is often a specific indication for surgery and the long-term effects of bariatric surgery on diabetes are becoming clearer with better data. I include this present study this month, not because it is particularly novel, but it highlights the natural history of diabetes and the critical balance between insulin sensitivity and pancreatic β-cell mass/function. The principal effect of bariatric surgery is weight loss and consequent improvement in insulin sensitivity. Although there is some evidence that it may also impact on β-cells, there is still the inevitable decline in pancreatic function. Therefore in this study, duration of diabetes is simply a surrogate measure of insulin production. The balance between this and degree of weight loss is the great physiological battle playing out.

Reference: Diabet Med 2015;32(1):47–53
Abstract