Diabetes & Obesity Research Review™

Making Education Easy

Issue 79 – 2014

In this issue:

Abbreviations used in this issue
BMI = body mass index
CV = cardiovascular
Hb_{A1c} = glycosylated haemoglobin
HR = hazard ratio
ICU = intensive care unit
RCT = randomised controlled trial

Welcome to issue 79 of Diabetes and Obesity Research Review.

This issue begins with an analysis of data from the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial reporting an increased risk of new-onset diabetes with diuretic or statin use. There is also research from Spain reporting a reduced risk of developing diabetes associated with consumption of a Mediterranean diet supplemented with extra-virgin olive oil, while US research found that coffee consumption also reduced the risk of type 2 diabetes in a dose-dependent fashion. The final paper in this issue takes a look at how obesity differs between Pacific Island adolescents in NZ who attend church and those who do not.

I hope you enjoy the selection and commentary for this issue. As always, your thoughts and comments are appreciated.

Best regards,

Dr Jeremy Krebs
jeremykrebs@researchreview.co.nz

Role of diuretics, β blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance

Authors: Shen L et al.

Summary: This re-analysis of NAVIGATOR trial data, including 915, 1316, 1353 and 1171 participants who started β-blockers, diuretics, statins and calcium channel antagonists, respectively, during a median 5 years of follow-up, found that diuretic and statin use was associated with an increased risk of developing diabetes, while β-blockers and calcium-channel antagonists were not (respective adjusted HRs 1.23 [95% CI 1.06, 1.44], 1.32 [1.14, 1.48], 1.10 [0.92, 1.31] and 0.95 [0.79, 1.13]).

Comment: With the systematic screening of individuals in primary care in NZ for CV risk, which includes Hb_{A1c}, there is a group of people being identified who are at increased CV risk and also have prediabetes. Current management algorithms include the use of statins for lipids and diuretics for blood pressure for these people. Therefore it is a very relevant question whether these agents may increase the risk of those with prediabetes progressing on to diabetes. This analysis from the NAVIGATOR trial suggests a significant negative effect of statins and diuretics on this. The trial was not designed to test this question and is an observational study rather than an RCT, but nevertheless the effect is consistent with other similar evidence. The clinical question though is whether we would not prescribe statins or diuretics to those with prediabetes and elevated CV disease risk? I would suggest that alternative antihypertensives are an option, but that the benefits of statins outweigh the risk – particularly if people follow the diabetes prevention study and adopt an intensive change to diet and lifestyle!

Reference: BMJ 2013;347:f6745
Abstract

Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia

Authors: Steele AM et al.

Summary: This cross-sectional study assessed micro- and macrovascular complications in 99 glucokinase mutation carriers aged ≥35 years, 91 related controls without the mutation or diabetes and 83 individuals with type 2 diabetes diagnosed at age ≤45 years. Compared with controls, participants with glucokinase mutations had similar (low) rates of microvascular complications, clinically significant macrovascular complications, neuropathy and microalbuminuria, and a significantly higher rate of retinopathy (30% vs. 14% [p=0.007]); the proteinuria rate was 0% in both groups. In comparison with the diabetes group, the glucokinase mutation group had lower rates of microvascular complications (1% vs. 36% [p<0.001]), clinically significant macrovascular complications (4% vs. 30% [p<0.001]), neuropathy (2% vs. 29% [p<0.001]), microalbuminuria (1% vs. 21% [p<0.001]), proteinuria (0% vs. 10%) and retinopathy (30% vs. 63% [p<0.001]).

Comment: There is increasing understanding of a range of monogenic causes of diabetes, which have been formally known as MODY. Defects in the glucose kinase enzyme result in lifelong mild hyperglycaemia. These patients are often picked up serendipitously, such as women during pregnancy being screened for gestational diabetes, but many may go undetected. This study confirms previous reports that this form of diabetes is 'mild' in terms of risk for developing complications. It is notable that the mean Hb_{A1c} in this group was 6.9% (52 mmol/mol), which is very similar to the goal of treatment in those with type 1 and 2 diabetes. Although there was a reasonably high rate of background retinopathy, this did not progress to more severe retinopathy and there was no increase in rates of other micro- or macrovascular complications compared with controls. This evidence again underpins the importance of identifying those with this form of diabetes because they do not require intensive management.

Reference: JAMA 2014;311(3):279–86
Abstract

A randomized trial of hyperglycemic control in pediatric intensive care

Authors: Macrae D et al., for the CHiP Investigators

Summary: Patients admitted to a paediatric ICU who were expected to require mechanical ventilation and vasoactive drugs for ≥12 hours were randomised to tight (target blood glucose level 72–126 mg/dL [4.0–7.0 mmol/L]; n=694) or conventional (<216 mg/dL [12.0 mmol/L]; n=675) glycaemic control; 60% of the enrolled participants underwent surgery. There was no significant between-group difference for number of days alive and free from mechanical ventilation at 30 days, and no differences according to subgroup. Compared with conventional glycaemic control, tight glycaemic control was associated with a significantly higher severe hypoglycaemia rate (7.3% vs. 1.5%; p<0.001) and lower 12-month costs, but the latter appeared to apply only to the subgroup who had not undergone cardiac surgery.

Comment: There is ample evidence that having hyperglycaemia whilst an inpatient in hospital is generally associated with worse outcomes. The question of whether aiming for tight glycaemic control in these patients is beneficial has been controversial, with some studies supporting this and others showing no benefit or even harm. The strongest evidence for benefit has been for adult patients in a surgical ICU setting. This study assessed the benefits in children in ICU of whom most had undergone cardiac surgery. There was no benefit and higher rates of hypoglycaemia with tight glycaemic control. So this does not support moves to intensify glucose management in inpatients.

Reference: N Engl J Med 2014;370(2):107–18
Abstract

Diabetes & Obesity Research Review

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

Body-mass index and mortality among adults with incident type 2 diabetes

Authors: Tobias DK et al.

Summary: These researchers analysed data from 8970 and 2457 participants with incident diabetes from the Nurses' Health Study and Health Professionals Follow-up Study, respectively, who had no CV disease or cancer when diabetes was diagnosed; 3083 participants died during mean follow-up of 15.8 years. The relationship between all-cause mortality and BMI formed a J-shaped curve (respective HRs, using BMI 22.5–24.9 kg/m^2 as reference, 1.29 [95% CI 1.05, 1.59], 1.12 [0.98, 1.29], 1.09 [0.94, 1.26], 1.24 [1.08, 1.42] and 1.33 [1.14, 1.55] for BMI ranges of 18.5–22.4, 25.0–27.4, 27.5–29.9, 30.0–34.9 and ≥35.0 kg/m^2, respectively); this relationship was linear among never smokers (respective HRs 1.12, 1.00, 1.16, 1.21, 1.36 and 1.56), but nonlinear among ever smokers (1.32, 1.00, 1.09, 1.04, 1.14 and 1.21; p=0.04 for interaction). A linear trend was also seen between BMI and all-cause mortality among participants aged <65 years but not older when diabetes was diagnosed (p<0.001 for interaction).

Comment: Much of the focus on increased bodyweight related to adverse health outcomes is predicated on the use of BMI as a measure of total body fatness and epidemiological evidence of an association between increased BMI and various outcomes such as CV disease, diabetes, etc. However, the importance of this relationship has been challenged, with some proposing a healthy obese group, arguing against fatness *per se* being the important factor. That argument is not supported by this analysis of the Nurses' Health study and Physicians Study, which shows a clear relationship between increasing BMI and mortality.

Reference: N Engl J Med 2014;370(3):233–44
Abstract

Prevention of diabetes with Mediterranean diets

Authors: Salas-Salvadó J et al.

Summary: These authors performed a subgroup analysis of an RCT in which 3541 individuals aged 55–80 years with high CV disease risk but without diabetes were randomised to consume a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with nuts or a control diet with advice on low-fat intake; diabetes was newly diagnosed in 80, 92 and 101 participants (16.0, 18.7 and 23.6 per 1000 person-years) from the respective study arms during median follow-up of 4.1 years. A multivariate analysis revealed that compared with the control diet, the risk of developing diabetes was significantly reduced with the Mediterranean diet supplemented with extra-virgin olive oil, but not the one supplemented with nuts (respective adjusted HRs 0.60 [95% CI 0.43, 0.85] and 0.82 [0.61, 1.10]).

Comment: Finding the optimal diet to prevent type 2 diabetes in those at risk is an important question, but one that has been elusive. Many studies have focused on manipulating macronutrients with variable success. The results are often confounded by the effects of bodyweight loss and difficulties determining whether the dietary composition itself has important effects independent of this. Recently there have been a number of studies supporting beneficial effects of a dietary pattern, a Mediterranean diet, rather than a focus on macronutrients or calories *per se*. The present report is an analysis of a subgroup from one of these studies showing a reduced rate of development of diabetes in those randomised to a Mediterranean diet supplemented with olive oil, without any specific focus on weight loss. The results must be interpreted with caution due to the subgroup analysis and potential for baseline differences to have influenced the results, but the study does add further support for this dietary approach.

Reference: Ann Intern Med 2014;160(1):1–10
Abstract

Obesity and late-age survival without major disease or disability in older women

Authors: Rillamas-Sun E et al.

Summary: This analysis of data from 36,611 women aged 66–81 years from the Women's Health Initiative observational study and clinical trial programmes investigated the effects of BMI and waist circumference on survival to age 85 years without a major chronic disease or mobility disorder. Healthy, prevalent diseased, incident diseased, disabled and deceased classifications were applied to 19.0%, 14.7%, 23.2%, 18.3% and 24.8% of the women, respectively. Compared with women classified as a healthy bodyweight, underweight and obese women were more likely to die before reaching 85 years of age, while the incident disease risk and mobility disability risks were increased in overweight and obese women – the risk of mobility disability was particularly increased (adjusted odds ratios 1.6 [95% CI 1.5, 1.8], 3.2 [2.9, 3.6], 6.6 [5.4, 8.1] and 6.7 [4.8, 9.2] for overweight and class I, II and III obesity, respectively). An association was also seen between waist circumference >88cm and increased risks of early death, incident disease and mobility disability.

Comment: This study is another way of looking at the same question of the relationship between bodyweight and risk of disease and mortality. It is a particular focus on the effects of obesity in the elderly. This takes out a group of women who have died earlier and therefore represents a so-called healthy cohort. Once again, increasing obesity is strongly predictive of incident disease and disability and of premature mortality. This study also supports the notion that weight loss in obese elderly may still have health benefits, although of course this hypothesis needs to be specifically tested in a prospective RCT.

Reference: JAMA Intern Med 2014;174(1):98–106
Abstract

Earlier onset of complications in youth with type 2 diabetes

Authors: Dart AB et al.

Summary: These researchers examined population-based cohorts of 1011, 342 and 1170 patients aged 1–18 with prevalent types 1 and 2 diabetes and no diabetes, respectively. The risk of any complication was increased in the cohort with type 2 diabetes (HR 1.47 [95% CI 1.02, 2.12]). Significant predictors associated with the increased risk were age at diagnosis (HR 1.08 [95% CI 1.02, 1.12]), Hb_{A1c} (1.06 [1.01, 1.12]) and renin-angiotensin-aldosterone system inhibitor use (1.75 [1.27, 2.41]), while HNF-1α G319S polymorphism was protective (0.58 [0.34, 0.99]). Patients from the type 2 diabetes cohort also had diagnoses of renal and neurological complications, manifesting within 5 years of diagnosis. Retinopathy did not differ among the cohorts. While CV and cerebrovascular diseases were rare, major complications (dialysis, blindness, amputation) began to manifest 10 years postdiagnosis among those with type 2 diabetes. Higher rates of all outcomes were seen in the type 2 diabetes cohort compared with the nondiabetic cohort, with the risk of any vascular disease increased by a factor of 6.15.

Comment: With the obesity epidemic, we are seeing type 2 diabetes diagnosed at younger and younger ages. I'm sure others would agree that some of the most difficult patients to help manage their diabetes are those with type 2 diabetes aged in their teens and 20s. This clinical observation is echoed in this study, with concerning evidence that this is the very group who have the worst outcomes and complications. I have no doubt that prevention is the preferable approach to averting this situation, but the same challenges are likely to apply to achieving the necessary lifestyle changes and self-awareness and wellness focus required.

Reference: Diabetes Care 2014;37(2):436–43
Abstract

Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes

Authors: Ding M et al.

Summary: This was a systematic review and dose-response meta-analysis of 28 prospective studies (n=1109,272; 45,335 cases of type 2 diabetes) with follow-up duration of 10 months to 20 years. Compared with nil or rare coffee consumption, the risk of developing diabetes decreased as daily coffee consumption increased (respective relative risks for 1–6 cups 0.92 [95% CI 0.90, 0.94], 0.85 [0.82, 0.88], 0.79 [0.75, 0.83], 0.75 [0.71, 0.80], 0.71 [0.65, 0.76] and 0.67 [0.61, 0.74]). The decreased diabetes risk associated with each daily cup of caffeinated coffee consumption did not differ significantly from that for decaffeinated coffee consumption (relative risk 0.91 vs. 0.94; p=0.17).

Comment: Previous observational studies have suggested a protective effect of regular coffee consumption on the risk of developing type 2 diabetes. However, experimental studies using capsules of caffeine have shown opposite effects on insulin sensitivity. Coffee beans contain a number of other compounds that might have beneficial effects on glucose metabolism. This meta-analysis of epidemiological studies further supports a protective effect of coffee, with a dose-response effect up to 6 cups per day. Furthermore the benefits are also seen for decaffeinated coffee, which suggests that any caffeine effect is minimal. This may all be good news with New Zealanders obsession with espresso coffees.

Reference: Diabetes Care 2014;37(2):569–86
Abstract

The prevalence of diabetes complications and associated risk factors in Pacific Islands countries

Authors: Tin STW et al.

Summary: This cross-sectional study of 459 patients with type 2 diabetes in Nauru, Solomon Islands and Vanuatu found that patients on Nauru had significantly higher prevalences of microalbuminuria, retinopathy and abnormal foot sensation than their respective counterparts on the Solomon Islands and Vanuatu (71% vs. 36% and 51% [p<0.001], 69% vs. 40% and 42% [p<0.001] and 30% vs. 23% and 19% [p=0.036], respectively). High prevalences of hypertension, overweight/obesity and poor glycaemic control were consistent across these Pacific Islands, while the proportions of patients achieving recommended clinical targets were low. Significant associations were seen between: i) microalbuminuria and diabetes duration, hypertension and glycaemic control; ii) diabetic retinopathy and diabetes duration; and iii) abnormal foot sensation and diabetes duration and glycaemic control.

Comment: It is well known that rates of type 2 diabetes are much higher in Pacific populations living in NZ than Europeans. In fact the highest rate of diabetes is in middle-aged Pacific people, where it is up to 45%. Pacific people also have a greater risk of diabetes complications, and with less access to healthcare in the Pacific Islands, this may be even higher in those countries. This study compared rates of diabetes complications in three Pacific Islands. Microvascular complications were extremely high in Nauru – up to 71% with microalbuminuria. There will be many factors contributing to this, but it is likely that with relatively small interventions and access to antihypertensives and adequate glucose-lowering drugs (including insulin), based on UKPDS evidence, these complication rates could be dropped dramatically. I guess it comes down to funding and systems.

Reference: Diabetes Res Clin Pract 2014;103(1):114–8
Abstract

The association between church attendance and obesity-related lifestyle behaviours among New Zealand adolescents from different Pacific Island ethnic groups

Authors: Dewes O et al.

Summary: This research looked at factors associated with obesity among 2495 Pacific Island adolescents from six secondary schools in Auckland, comparing those who attended a church or other place of worship (77%) with nonattendees. Structured individual interviews and anthropometric measurements revealed that BMI was significantly higher among church attendees than nonattendees (27.4 vs. 26.6 kg/m^2; p=0.01). Significant associations were seen among church attendees between bodyweight status and less healthy breakfast and lunch sources, reduced physical activity levels and limited knowledge of obesity risk factors (p<0.05).

Comment: Obesity and diabetes are major health problems for the Pacific community, and unhealthy lifestyle factors are major contributors to this. It is of major concern that obesity and diabetes have become so prevalent in the younger age group, and it is essential that a way to modify this is found. There is a very high rate of church attendance in the Pacific community, as highlighted by this study, which compared lifestyle factors and bodyweight between church attendees and nonattendees. To my surprise, the attendees actually had higher BMIs and several less healthy lifestyle behaviours. This is an opportunity for the Pacific community to utilise the church setting to capture a group who are at high risk of adverse health outcomes and make a difference. Any such intervention needs to be generated and driven from within the community to have a chance of success.

Reference: J Prim Health Care 2013;5(4):290–300
Abstract