Diabetes & Obesity Research Review™

Making Education Easy

Issue 85 – 2014

In this issue:

Abbreviations used in this issue
BMI = body mass index
CV = cardiovascular
Hb_{A1c} = glycosylated haemoglobin
RCT = randomised controlled trial
RR = relative risk

CONGRATULATIONS

Dr Bart Vangronsvelt,
a GP at the Wakatipu Medical Centre in Frankton, who won an iPad Mini at GPCME South by subscribing to www.researchreview.co.nz

Welcome to issue 85 of Diabetes and Obesity Research Review.

This issue begins with data from an observational study suggesting a link between statin potency and risk of developing new diabetes. Still on the topic of statins, the second paper presents research describing increases in caloric and fat intake among statin users since 1999. I have also included a fascinating RCT from the US reporting on use of a 'bionic' pancreas for managing glycaemia in patients with type 1 diabetes. This issue concludes with NZ research reporting safe, high-quality and appropriate outcomes of a diabetes nurse specialist prescribing project.

I hope this issue provides interesting reading for you and, as always, I invite you to send your comments, feedback or suggestions.

Best regards,

Dr Jeremy Krebs
jeremykrebs@researchreview.co.nz

Higher potency statins and the risk of new diabetes

Authors: Dormuth CR et al., for the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators

Summary: Eight population-based cohort studies and a meta-analysis were used to explore the impact of higher versus lower potency statins, prescribed for secondary prevention after hospitalisation for a major CV event or procedure, on the risk of developing new-onset diabetes in 136,966 recipients of these agents. It was found that during the first 2 years of regular statin use, higher potency statin recipients were more likely to have been hospitalised with new-onset diabetes or receive a prescription for insulin or an oral antidiabetic agent than recipients of lower potency statins (rate ratio 1.15 [95% CI 1.05, 1.26]), and the likelihood was even greater during the first 4 months of statin use (1.26 [1.07, 1.47]).

Comment: The question of whether statins may increase the risk of developing type 2 diabetes has been raised in previous observational studies. This present study takes this a step further to ask whether the more potent statins confer a greater risk. In those who have had a major CV event, new prescription of a potent statin was associated with a 15% greater risk of developing type 2 diabetes over the subsequent 2 years. However, we must be very careful in the assessment of this result. Firstly and most importantly, this was not an RCT. There may be many plausible reasons why those who were given a more potent statin were already at greater risk. In addition, we don't know how many of these people may have already had prediabetes. These issues aside, it is perhaps relevant to ask whether there is greater benefit in a more potent statin for CV disease risk reduction, and if not that choosing a weaker agent as first-line therapy is more appropriate.

Reference: BMJ 2014;348:g3244
Abstract

Different time trends of caloric and fat intake between statin users and nonusers among US adults: gluttony in the time of statins?

Authors: Sugiyama T et al.

Summary: Differences in the temporal trends of caloric and fat intake between statin recipients and nonrecipients were explored in 27,886 US NHANES survey respondents in this cross-sectional analysis. During 1999–2000, statin recipients had a significantly lower caloric intake overall than statin nonrecipients (2000 vs. 2179 kcal/day [p=0.007]), but the gap between the groups closed as time progressed with the statin recipients' caloric intake increasing by 9.6% by the 2009–2010 period (p=0.02); no significant change was seen among statin nonrecipients. Similarly, statin recipients consumed significantly less fat than nonrecipients in the 1999–2000 period (71.7 vs. 81.2 g/day [p=0.003]), but increased by 14.4% among statin recipients (p=0.007) and did not change significantly among statin nonrecipients. Statin recipients also experienced a significantly greater BMI increase than nonrecipients (p=0.02).

Comment: This is an interesting look at the effect of the introduction of statins for cholesterol lowering on dietary restraint and subsequent effect on bodyweight. Prior to statin prescription, people are strongly advised to reduce saturated fat intake and lose weight to control their lipid profile and reduce CV disease risk. However, unfortunately such strategies have limited impact in most individuals, and with a strong evidence base for the benefits of statins, there is a low threshold for introducing these agents. A consequence of this may be for people to ease off their dietary efforts and resume greater intake of fat. This is supported by this longitudinal observational study where statin users were more likely to increase weight than statin nonusers. This highlights the need to remind people when starting a statin that maintaining dietary efforts remains important.

Reference: JAMA 2014;174(7):1038–45
Abstract

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.

Physical activity and sedentary behaviors associated with risk of progression from gestational diabetes mellitus to type 2 diabetes mellitus

Authors: Bao W et al.

Summary: Data were analysed from a prospective cohort of 4554 participants in the Nurses' Health Study II with a history of gestational diabetes. During follow-up from 1991 to 2007 (59,287 person-years), 635 women were diagnosed with type 2 diabetes. Each 5-MET (metabolic equivalent)-h/wk increment of total physical activity was associated with a significant reduction in the risk of progressing to type 2 diabetes (adjusted RR 0.91 [95% CI 0.88, 0.94]); this inverse association remained significant after adjustment for BMI. Compared with women who maintained their total physical activity levels, those who increased their total physical activity levels by ≥7.5 MET-h/wk almost halved their risk of developing type 2 diabetes (RR 0.53 [95% CI 0.38, 0.75]); the association remained significant after adjusting for BMI. Watching television for 6–10, 11–20 and ≥20 h/wk significantly increased the risk of progressing to type 2 diabetes compared with 0–5 h/wk (respective adjusted RRs 1.28 [95% CI 1.04, 1.59], 1.41 [1.11, 1.79] and 1.77 [1.28, 2.45]; p<0.001 for trend); adjusting for BMI attenuated these associations.

Comment: Along with a rise in obesity, there is a rise in rates of gestational diabetes. It is well known that gestational diabetes is associated with a high lifetime risk of developing type 2 diabetes. Therefore women with gestational diabetes are an ideal group to target interventions to reduce this risk. This observational study demonstrates the potential for increases in physical activity to be effective in this. Although it is an observational study, the negative effects of sedentary behaviour and benefits of activity are consistent and compelling. The real question though is how do we facilitate women to achieve increased physical activity in the *post partum* period, particularly at a time when they are under considerable added stress and often not focused on their own health and wellbeing.

Reference: JAMA Intern Med 2014;174(7):1047–55
Abstract

Outpatient glycemic control with a bionic pancreas in type 1 diabetes

Authors: Russell SJ et al.

Summary: This research compared glycaemic control between a wearable, bihormonal, automated, 'bionic' pancreas and insulin pump, each for 5 days in a randomised crossover design, in 20 adults and 32 adolescents with type 1 diabetes. Compared with the insulin pump, the bionic pancreas was associated with a significantly lower mean glucose level on continuous monitoring after 1 day of automation adaptation in the adult participants (133 vs. 159 mg/dL [p<0.001]) and a significantly lower proportion of time with a low glucose level (4.1% vs. 7.3% [p=0.01]). Among the adolescent participants, the mean plasma glucose level after 1 day of automation adaptation was significantly lower with the bionic pancreas (138 vs. 157 mg/dL [p=0.004]) and their mean frequency of interventions for hypoglycaemia was significantly lower (one per 1.6 days vs. one per 0.8 days [p<0.001]), but the proportions of time with a low plasma glucose level were similar (6.1% vs. 7.6% [p=0.23]).

Comment: This is extremely exciting. It takes me back to my childhood awe of the 6 million dollar man and his bionic eye and arm. Wow! Is this the holy grail that people with type 1 diabetes have been waiting for – the artificial pancreas? It would seem to have many features that make it very close, such as closed loop, intelligence, tight control with pretty low rates of hypoglycaemia. The combined use of insulin and glucagon makes physiological sense. This study was testing the device in a real-world setting, but only over a very short period. The next step is of course to establish whether this can be replicated with ongoing use over a longer time period and under more varied and extreme conditions. Cost aside, this is an exciting development in the management of type 1 diabetes.

Reference: N Engl J Med 2014;371(4):313–25
Abstract

AUTONOMY: the first randomized trial comparing two patient-driven approaches to initiate and titrate prandial insulin lispro in type 2 diabetes

Authors: Edelman SV et al.

Summary: Patients aged 18–85 years with type 2 diabetes inadequately controlled with basal insulin (n=1106) were enrolled into two independent, parallel, open-label studies that were identical in design to compare insulin self-titration algorithms that adjusted lispro either every day or every 3 days for 24 weeks. No significant differences were seen between the two algorithms for reductions in Hb_{A1c} from baseline in both studies (between 10.06 and 10.93 mmol/mol) or the incidences and rates of hypoglycaemia. Furthermore, no clinically relevant differences were seen between the two algorithms in participants aged ≥65 years in either study.

Comment: Introducing prandial insulin and titrating to effective doses is a challenge to achieve efficiently. There is an increasing need for insulin therapy as the prevalence of type 2 diabetes increases, but also the age at diagnosis decreases, meaning that more individuals are exhausting the effectiveness of oral therapy. Introduction of prandial insulin can be very time consuming for health professionals, and therefore systems that can facilitate this effectively whilst minimising nurse or doctor input are needed. In addition, systems that empower those with diabetes to have greater control of their own management are preferable for long-term success. Therefore this study is a very useful demonstration of how this can be achieved with important reductions in Hb_{A1c} level and minimal hypoglycaemia. Such a system can be effectively and safely deployed in both primary- and secondary-care settings. I have no doubt that these findings can be extrapolated to any of the prandial insulins available in NZ.

Reference: Diabetes Care 2014;37(8):2132–40
Abstract

Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes

Authors: Hirakawa Y et al.

Summary: The impact of visit-to-visit Hb_{A1c} and fasting glucose level variability on major outcomes was investigated in 4399 ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial participants with type 2 diabetes randomised to intensive glucose control and blood pressure lowering. Greater visit-to-visit Hb_{A1c} level variability (assessed using the standard deviations of five readings taken 3–24 months after randomisation) was associated with significantly increased risks of vascular events and death from any cause after 24 months (respective adjusted highest versus lowest tenth hazard ratios 1.64 [95% CI 1.05, 2.55] and 3.31 [1.57, 6.98]), while greater visit-to-visit fasting glucose level variability significantly increased only the risk of vascular events (2.70 [1.65, 4.42]). Hb_{A1c} level variability significantly increased the risk of only macrovascular events (p=0.02 for trend), while glucose level variability increased the risks of both macro- and microvascular events (respective p values 0.005 and <0.001 for trend). Consistent findings were seen in sensitivity analyses using other indices and in ADVANCE participants randomised to standard treatment.

Comment: The findings of the ADVANCE and ACCORD studies are challenging the dogma of striving to achieve tight glycaemic control as the mainstay of good diabetes management. In this analysis of ADVANCE data, the impact of fluctuations in glycaemic control over time was examined. Greater visit-to-visit variability was associated with worse outcomes. One analysis from the ACCORD study has also shown that those attempting to achieve tight control, but not achieving this, also do worse. So whilst the evidence that achieving a good Hb_{A1c} level in those newly diagnosed with diabetes is a good thing (UKPDS), we are often dealing with patients more like those in ADVANCE and ACCORD who have had diabetes for several years and are already at high risk of CV events. I think it is becoming increasingly unclear what the best approach to glucose targets is for these individuals.

Reference: Diabetes Care 2014;37(8):2359–65
Abstract

Aging is associated with increased HbA_{1c} levels, independently of glucose levels and insulin resistance, and also with decreased HbA_{1c} diagnostic specificity

Authors: Dubowitz N et al.

Summary: This cross-sectional analysis of 1573 adults without known diabetes from the SIGT (Screening for Impaired Glucose Tolerance) study and 1184 NHANES (National Health and Nutrition Examination Survey) respondents sought to examine the effects of age on Hb_{A1c} screening. Each 10-year increase in age was associated with statistically significant increases in Hb_{A1c} level of 0.87 and 0.76 mmol/mol for individuals with diabetes and normal glucose tolerance, respectively; glucose intolerance also increased with age. Multivariate analyses of patients with normal glucose tolerance revealed a significant relationship between age and Hb_{A1c} level after adjusting for a number of relevant covariates including glucose levels. The difference in Hb_{A1c} level between individuals with normal glucose tolerance aged 30 and 80 years would be clinically significant at 3.82 mmol/mol. Moreover, a statistically significant decrease was seen in the specificity of Hb_{A1c}-based diagnostic criteria for prediabetes as age increased (p<0.0001).

Comment: This study raises an interesting issue. Does Hb_{A1c} level increase with age independent of factors associated with increased risk of diabetes? If so, does this have an important impact on the utility of Hb_{A1c} as a diagnostic test for diabetes? The study reports on data from two cross-sectional studies, and suggests that there may be an important independent effect of age on Hb_{A1c}. However, we must remember that Hb_{A1c} is a continuous biological variable, and our criteria for prediabetes and diabetes are somewhat arbitrary cutoff points in this continuum. I am not convinced that a 3.82-mmol/mol drift from age 30–80 years constitutes an important variable in the utility of Hb_{A1c} as our chosen diagnostic test. The convenience and simplicity of Hb_{A1c} compared with the oral glucose tolerance test makes it so much more useful on a population basis for capturing those at greatest risk.

Reference: Diabet Med 2014;31(8):927–35
Abstract

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Prevention of type 2 diabetes: a systematic review and meta-analysis of different intervention strategies

Authors: Merlotti C et al.

Summary: This systematic review and meta-analysis of 71 studies (n=490,813) sought to evaluate the effectiveness of different intervention strategies for preventing type 2 diabetes, including diet plus physical activity, physical activity alone, antidiabetic drugs, CV drugs, dietary factors, lipid-affecting drugs and bariatric surgery. Bariatric surgery in morbidly obese subjects has been the most effective reported means of preventing the risk of developing type 2 diabetes (odds ratio 0.16 [95% CI 0.11, 0.24]). With the exceptions of ß-cell-stimulating drugs, oestrogens and vitamins, most nonsurgical strategies have also been associated with reduced risks of developing type 2 diabetes (odds ratios 0.37–0.85). A meta-regression analysis revealed that patient age and amount of bodyweight lost were associated with intervention effectiveness.

Comment: All is not lost. With increasing enthusiasm to focus on prevention of diabetes, particularly in the growing group with prediabetes, finding effective strategies and implementing these is a key objective over coming years. This study is a very useful analysis of the evidence for a wide variety of interventions ranging from lifestyle interventions, through pharmaceuticals to bariatric surgery. It is encouraging that many of these were effective in preventing progression to diabetes, with bariatric surgery not surprisingly the most effective. However, bariatric surgery is obviously not appropriate, nor affordable, for all those at risk, and individualising treatment informed by this evidence base is the best approach. We desperately need to implement all options in an integrated way throughout the health system in NZ.

Reference: Diabetes Obes Metab 2014;16(8):719–27
Abstract

The prognostic value of metformin for cancer patients with concurrent diabetes

Authors: Zhang Z-J & Li S

Summary: This systematic review and meta-analysis of 28 studies showed that cancer patients with concurrent diabetes had a lower risk of death from any cause if they were receiving metformin, particularly if they had breast, colorectal, ovarian or endometrial cancer (respective RRs 0.70 [95% CI 0.55, 0.88; p=0.003], 0.70 [0.59, 0.84; p<0.001], 0.44 [0.30, 0.64; p<0.001] and 0.49 [0.32, 0.73; p=0.001]). Furthermore, metformin use was also associated with lower likelihoods of cancer-specific mortality.

Comment: There continues to be interest in the effect of metformin on risk of cancer, and in this study the effect on survival in those with cancer. Here a meta-analysis again supports a beneficial effect of metformin in common cancers. Whilst the RR reduction is impressive, these are still observational associations. We really need an RCT to truly test this hypothesis. Sadly I can't see this being conducted as there is very little commercial opportunity to drive funding. I still think metformin should be put in the drinking water along with fluoride!

Reference: Diabetes Obes Metab 2014;16(8):707–10
Abstract

Evaluation of a diabetes nurse specialist prescribing project

Authors: Wilkinson J et al.

Summary: This paper reported on an NZ project that examined the safety and effectiveness of diabetes nurse specialist prescribing. Data for this analysis were obtained from: i) twelve specialist diabetes nurses involved in the project (who saw 1274 patients and wrote 3402 prescriptions); ii) surveys with 30 general practitioners, 19 team members and 89 patients; iii) audits from 117 patient notes and 227 prescriptions; and iv) interviews with 18 project participants and 19 patients. Prescribing by the diabetes nurse specialists was deemed to be safe, of high quality and appropriate, afforded important benefits to specialist diabetes services, was accepted by patients and supported by the wider healthcare team.

Comment: As the prevalence of diabetes increases, it impacts on the health system, and the ability of the traditional model of care to meet demands becomes increasingly stretched. Nurses trained in diabetes are highly skilled, and in NZ have delivered a high-quality service to those with diabetes for many years. Often, nurses are utilised to initiate and titrate insulin therapy, frequently with equal or greater confidence than many doctors prescribing it. Therefore it makes a lot of sense to enable appropriately trained and experienced nurses to step up to prescribing diabetes-related medications. This study reports on qualitative aspects of the NZ nurse prescribing project with highly favourable results. It must be acknowledged that those taking part in this were highly experienced, enthusiastic trailblazers. It is now essential that the success of this project is replicated in a broader rollout to a wider pool of nurses. This must be carefully managed with adequate supervision and oversight.

Reference: J Clin Nurs 2014;23(15–16):2355–66
Abstract