Diabetes Research Review™

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Issue 53 - 2013

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Abbreviations used in this issue

BMI = body mass index
BP = blood pressure
CIMT = carotid intima-media thickness
CV = cardiovascular
Hb_{A1c} = glycosylated haemoglobin
HR = hazard ratio
LDL = low-density lipoprotein
MI = myocardial infarction
SMBG = self-monitoring of blood glucose

Welcome to issue 53 of Diabetes Research Review.

In this issue's selection, we learn that including CIMT does not add any useful information to the Framingham CV disease risk score. Research out of the UK has reported on the association between sugar-sweetened beverage consumption and type 2 diabetes, while another UK-based group analysed glucose monitoring data from patients with type 1 diabetes, and determined that the Somogyi effect is rare in clinical practice. We conclude with evidence that more SMBG measures are associated with lower Hb_{A1c} values.

We trust you enjoy the selections for this month, and we look forward to your comments and feedback.

Kind Regards,

Associate Prof. Neale Cohen

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Reduction of circulating neutrophils precedes and accompanies type 1 diabetes

Authors: Valle A et al

Summary: These researchers monitored peripheral immune cells in patients with early stage type 1 diabetes (healthy autoantibody-positive patients) and more advanced disease (at disease onset and years after diagnosis). Mild, yet significant and reproducible, peripheral neutropenia, which was not due to peripheral cell death, impaired differentiation or the presence of antineutrophil antibodies, was seen to precede and accompany type 1 diabetes onset. Electron microscopy and immunohistochemical analysis revealed neutrophils in the exocrine pancreas of multiorgan donors with type 1 diabetes at onset and at later disease stages, but not in multiorgan donors with type 2 diabetes or nondiabetic donors. These pancreas-infiltrating neutrophils mainly localised in very small blood vessels.

Comment (PL): The innate immune system is comprised of cytokines and white blood cells, and it provides acute, nonspecific defence usually against bacterial pathogens, but it has recently been drawn into the area of chronic nonresolving diseases. As a brief overview, there would appear to be a slight but significant movement in the concepts surrounding the aetiology of type 1 diabetes, and this may have arisen as a result of the massive increase in research in the areas of inflammation and immunology. This study found lower levels of circulating neutrophils in subjects with type 1 diabetes, but not type 2 diabetes, plus the presence of neutrophils in the exocrine pancreas of subjects with type 1 diabetes, but not in type 2 diabetes. These data allow for a previously un- or under-recognised clinical phenotype and a role for the innate immune system in the pathogenesis of type 1 diabetes.

Reference: Diabetes 2013;62(6):2072–7
http://diabetes.diabetesjournals.org/content/62/6/2072.abstract

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Common carotid intima-media thickness does not add to Framingham risk score in individuals with diabetes mellitus

Authors: den Ruijter HM et al

Summary: The USE-IMT initiative explored whether mean common CIMT added to the Framingham score improves CV risk prediction in 4220 participants with diabetes from a large ongoing meta-analysis of 56,194 individuals from 17 international population-based cohorts. The absolute 10-year MI or stroke risk was estimated using the Framingham assessment on its own and with the inclusion of mean common CIMT. There were 684 first-time CV events among patients with diabetes over median follow-up of 8.7 years. The respective C statistics for the Framingham and CIMT models were 0.67 and 0.68, and the absolute 10-year risk for MI or stroke was 16% in both models. No net reclassification improvement was seen when mean common CIMT was included, and the results did not differ between genders.

Comment (PL): Assessment of carotid artery wall thickness is one of the most accessible measures of vascular disease or subclinical atherosclerosis; one might expect that it would be very useful in assessing or monitoring CV disease risk and progression. In this study of several thousand people with diabetes, the classic Framingham model predicting CV disease was compared with the model with the addition of the baseline measurement of mean CIMT. The addition of the CIMT measurement added no predictive value to the model. There is possibly a dilemma in this study that whereas a parameter such as cholesterol is static, the CIMT is actually advancing and a part of the disease process itself. It can be noted that people with diabetes have higher CV disease risk than those without diabetes, and within the diabetes population there is stratification of risk. In conclusion, or perhaps confusion(!), the CV risk profile of people with diabetes is very high, so full-scale medical intervention is probably warranted whatever.

Reference: Diabetologia 2013;56(7):1494–502
http://link.springer.com/article/10.1007/s00125-013-2898-9

Independent commentary by Professor Peter Little and Associate Professor Neale Cohen.

Professor Peter Little is Head of Pharmacy and Leader, Diabetes Complications Group, Health Innovations Research Institute at RMIT University, Bundoora, Victoria. Peter is a past national President of Diabetes Australia.

Associate Professor Neale Cohen is a physician specializing in Diabetes and Endocrinology, and is the General Manager of Diabetes Services at the Baker IDI Heart and Diabetes Institute. He is an Adjunct Associate Professor of RMIT University.

Consumption of sweet beverages and type 2 diabetes incidence in European adults

Authors: The InterAct consortium

Summary: This case-control study explored the relationship between sugar-sweetened beverage consumption and type 2 diabetes incidence in European adults. The analysis included 11,684 cases of incident type 2 diabetes and a stratified subcohort of 15,374 EPIC (European Prospective Investigation into Cancer and Nutrition) study participants. Each 336g daily increment in both sugar-sweetened and artificially sweetened soft-drink consumption was associated with an increased incidence of type 2 diabetes (respective adjusted HRs 1.22 [95% CI 1.09–1.38] and 1.52 [1.26–1.83]); additional adjustment for energy intake and BMI resulted in a persistently significant relationship for sugar-sweetened soft-drinks (1.18 [1.06–1.32]), but not artificially sweetened soft-drinks (1.11 [0.95–1.31]). No significant association was seen between consumption of juice or nectar and incident type 2 diabetes.

Comment (PL): A while ago it was traditional dogma in diabetes circles to say that 'sugar does not cause diabetes', presumably not to oversimplify the complexity of diabetes; however, more recently this statement has been brought into some doubt – those massive bottles of high sugar-containing beverages must surely do something negative to health! For reference, the largest available drink in a convenience store contains almost 200g of sugar. This was a European study where sugary drink consumption is lower than in the US, but is rising. One daily increment of a large soft-drink was associated with a 22% increased risk for type 2 diabetes for sugar-sweetened drinks and, intriguingly, a 52% increased risk for artificially sweetened soft-drinks. Consumers of artificially sweetened soft-drinks had higher BMIs, and the association was lost when adjusted for BMI. It appears that high-sugar soft-drink consumption can drive type 2 diabetes with a mechanism likely associated with acute glycaemic effects (on insulin resistance) and chronic effects on bodyweight.

Reference: Diabetologia 2013;56(7):1520–30
http://tinyurl.com/n9xohuy

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Cardiovascular safety of the dipetidyl [*sic*] peptidase-4 inhibitor alogliptin in type 2 diabetes mellitus

Authors: White WB et al

Summary: These researchers compared CV event risks in 4168 individuals exposed to alogliptin 12.5mg or 25mg daily (2023 person-years) for type 2 diabetes versus 691 placebo recipients (263 person-years) and 1169 patients exposed to metformin, sulfonylureas or thiazolidinediones (703 person-years). Compared with placebo or the other antidiabetic agents, alogliptin was not associated with an increased risk of major adverse cardiac events (HR 0.635 [95% CI 0.0–1.41]) or other types of serious CV events.

Comment (PL): Various classes of drugs target CV disease risk factors, such as lipids, BP, glycaemia, etc., but the big question is always the impact on reducing CV events *per se*. This is particularly relevant in relation to glycaemia, noting especially recent experiences with thiazolidinediones. With some agents, some companies may have strategically skirted around this question. This desk research looked at the dipeptidyl peptidase-4 (DPP-4) inhibitor, alogliptin (Nesina, Takeda). Base data for this new agent were understandably a relatively modest 2000 patient-years of treatment with alogliptin. There was no sign of increased CV risk associated with alogliptin use in patients with type 2 diabetes. A coming trial, EXAMINE, will provide specific data on alogliptin. It is noted that it was necessary to treat 65,000 subjects to find one death associated with the use of troglitazone, so careful postmarketing surveillance is required for all new clinical entities. The manufacturers of alogliptin have made applications for both registration as a therapeutic good and PBS subsidy in Australia.

Reference: Diabetes Obes Metab 2013;15(7):668–73
http://onlinelibrary.wiley.com/doi/10.1111/dom.12093/abstract

Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia

Authors: Ikramuddin S et al

Summary: The Diabetes Surgery Study RCT enrolled patients with Hb_{A1c} ≥8.0%, BMI 30.0–39.9 kg/m², C-peptide level >1.0 ng/mL and type 2 diabetes for ≥6 months to receive lifestyle and intensive medical management with or without Roux-en-Y gastric bypass; the participants were prescribed medications for hyperglycaemia, hypertension and dyslipidaemia according to protocol. Compared with the control group, at 12 months the gastric bypass group had a significantly higher rate of the composite primary outcome (Hb_{A1c} <7.0%, LDL cholesterol level <100 mg/dL, systolic BP <130mm Hg; 49% vs. 19%; odds ratio 4.8 [95% CI 1.9–11.7]), required fewer medications (mean 1.7 vs. 4.8) and lost a greater proportion of their baseline bodyweight (26.1% vs. 7.9%). Regression analyses showed that bodyweight loss was the main reason for achieving the composite primary endpoint. Serious adverse events occurred in 22 (including one CV event) and 15 participants from the gastric bypass and control groups, respectively. Gastric bypass was associated with four and six perioperative and late postoperative complications, respectively, and greater nutritional deficiency.

Comment (PL): Roux-en-Y gastric bypass named after Swiss surgeon Cesar Roux is a surgical procedure which greatly reduces the volume of the stomach and directs food directly to the small intestine. This study in centres in the US and Taiwan examined 120 subjects, only moderately obese, with relatively recent (six months) type 2 diabetes comparing surgery with lifestyle changes with intensive medications. In an interesting design, all subjects received the lifestyle and medical intervention then 60 were randomly assigned to surgery. After 12 months 50% of the surgery group compared with 20% of the medical group achieved the primary endpoint (mostly Hb_{A1c} <7%). Somewhat frighteningly, only 50% reached target with surgery and intensive medical management (noting that the triple target included BP and LDL cholesterol). Surgical adverse effects were substantial despite a comment that all surgeons were experts. These results are less than some spectacular results for some surgery studies and support an ongoing careful risk benefit and cost analysis in this area.

Reference: JAMA 2013;309(21):2240–9
http://jama.jamanetwork.com/article.aspx?articleid=1693889

Do high fasting glucose levels suggest nocturnal hypoglycaemia? The Somogyi effect – more fiction than fact?

Authors: Choudhary P et al

Summary: This research explored the prevalence of the Somogyi effect (i.e. that nocturnal hypoglycaemia causes fasting hyperglycaemia secondary to counter-regulatory hormone release) in 89 participants with type 1 diabetes from the UK Hypoglycaemia study. The fasting capillary blood glucose level was significantly lower following nights during which a hypoglycaemic episode (sensor blood glucose <3.5 mmol/L) occurred (5.5 vs. 14.5 mmol/L; p<0.0001), and after nights with a glucose level nadir of <2.2 vs. 3.5 mmol/L (5.5 vs. 8.2 mmol/L; p=0.018). A fasting capillary blood glucose level >10 mmol/L following nocturnal hypoglycaemia only occurred twice, both times occurring after likely treatment of the episode. Evidence of nocturnal hypoglycaemia was seen in 94% of nights with a subsequent fasting capillary blood glucose level of <5 mmol/L.

Comment (NC): The phenomenon of fasting hyperglycaemia remains a difficult management problem in patients with type 1 diabetes. The Somogyi effect has traditionally been considered as a possible cause with nocturnal hypoglycaemia leading to rebound and fasting hyperglycaemia. This study, which used continuous glucose monitoring sensors, does not support this theory. High fasting glucose levels were not associated with nocturnal hypoglycaemia, but rather nocturnal hyperglycaemia. Furthermore, nocturnal hypoglycaemia was associated with fasting hypoglycaemia, and a fasting glucose level of <5.0 mmol/L was associated with nocturnal hypoglycaemia in 94% of cases. The suggestion here is that fasting hyperglycaemia is most likely due to under-insulinisation rather than over-insulinisation. This should give some sense of comfort to doctors and patients increasing nocturnal insulin doses in patients with persistently high morning readings. The problem often is that fasting readings can be highly variable.

Reference: Diabet Med 2013;30(8):914–7
http://onlinelibrary.wiley.com/doi/10.1111/dme.12175/full

Glucose-independent ethnic differences in HbA_{1c} in people without known diabetes

Authors: Hare MJL et al

Summary: This research out of Mauritius looked at glucose-independent ethnic differences in Hb_{A1c} levels among individuals without diabetes of African (n=1219 from the main island; n=1505 from Rodrigues), South Asian (n=3820) and Chinese (n=157) descent. After adjustments, Africans from Rodrigues had significantly higher mean Hb_{A1c} values than Africans from the main island of Mauritius, South Asians or Chinese (6.1% vs. 5.7% for each; p<0.001). The age-standardised prevalence of diabetes among Africans from Rodrigues was lower when diagnosed by oral glucose tolerance test compared with Hb_{A1c} (7.9% vs. 17.3%), but no such difference was evident in the other ethnic groups.

Comment (NC): Hb_{A1c} is currently the most reliable measure of long-term glycaemic control in patients with diabetes; however, it has limitations that have been well described. As it is haemoglobin dependent, conditions associated with anaemia, altered red cell turnover or haemoglobinopathies will alter Hb_{A1c} independent of blood glucose. There are reports of age and ethnicity also altering Hb_{A1c} levels, and this study conducted in Mauritius confirms ethnic differences in a subgroup of African people. This is important both from a diagnostic point of view and when assessing glycaemic control in patients with diabetes from different ethnic groups. Further work needs to be done in this area, as nonglycaemic Hb_{A1c} differences in some ethnic groups may result in errors in diagnosis and management of diabetes.

Reference: Diabetes Care 2013;36(6):1534–40
http://care.diabetesjournals.org/content/36/6/1534.abstract

Clinical inertia in people with type 2 diabetes

Authors: Khunti K et al

Summary: A retrospective analysis of data from a cohort of 81,573 patients with type 2 diabetes assessed time to treatment intensification with one, two or three oral antidiabetic drugs and the associated degrees of glycaemic control. Hb_{A1c} values of ≥7.0%, ≥7.5% and ≥8.0% (≥53, ≥58 and ≥64 mmol/mol) were associated with respective median times from exceeding Hb_{A1c} cutoff to intensification with an additional oral antidiabetic agent of: i) 2.9, 1.9 and 1.6 years for those taking one oral antidiabetic agent; and ii) >7.2, >7.2, and >6.9 years for those taking two oral antidiabetic agents. The median times to intensification with insulin were >7.1, >6.1 and 6.0 years for recipients of one, two and three oral antidiabetic agents, respectively. Mean Hb_{A1c} values at intensification (with an oral antidiabetic agent or insulin) were 8.7%, 9.1% and 9.7% for recipients of one, two and three oral antidiabetic agents, respectively, and the median time from start of treatment to intensification was >7.2 years (maximum follow-up). Treatment intensification with an oral antidiabetic agent at the end of follow-up was associated with a greater likelihood of poor glycaemic control than intensification with insulin (21.1–43.6% vs. 5.1–12.0%).

Comment (NC): Intensifying therapy in the management of type 2 diabetes is surprisingly difficult in clinical practice. The reasons for this are not entirely clear, but are collectively called 'clinical inertia'. In the largest of its kind, this UK primary-care study confirms this inertia. While the median Hb_{A1c} for adding insulin was >9.0%, even more worrying was the median duration to intensification with insulin therapy of >6 years. Although inertia with oral agents was less, there were still considerable delays in adding extra agents. There are similar published results from Australian primary care. The blame for this phenomenon is not completely with the treating clinicians; however, it is clear that we must do a better job of educating doctors and patients on the importance of intensification of treatment in type 2 diabetes.

Reference: Diabetes Care; Published online July 22, 2013
http://care.diabetesjournals.org/content/early/2013/07/18/dc13-0331.abstract

Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes

Authors: The Look AHEAD Research Group

Summary: Overweight or obese patients with type 2 diabetes (n=5145) were randomly assigned to an intensive lifestyle intervention (promotion of weight loss through decreased caloric intake and increased physical activity) or to a control group of usual diabetes support and education. A futility analysis at median follow-up of 9.6 years resulted in early termination of the trial – the intervention group had experienced a similar number of primary endpoint events (CV-related death, nonfatal MI, nonfatal stroke or hospitalisation for angina) as the control group (1.83 vs. 1.92 events per 100 person-years; HR 0.95 [95% CI 0.83–1.09; p=0.51]). However, compared with the control group, the intervention was associated with greater bodyweight loss at 1 year and at study end (8.6% vs. 0.7% and 6.0% vs. 3.5%), greater reductions in Hb_{A1c} and greater initial improvements in fitness and all CV risk factors, with the exception of LDL cholesterol level.

Comment (NC): The LOOKAHEAD trial will no doubt be the subject of much debate in the coming years. It is a study designed to assess the CV effects of an intensive lifestyle intervention compared with standard treatment in patients with type 2 diabetes. Although the intensive lifestyle intervention achieved improved glycaemic control and sustained weight loss compared with the control group, there were no CV benefits seen over 10 years. Notably, the control group had greater statin use, which may have influenced outcomes. Perhaps, like the UKPDS trial, there may be some longer term benefits in years to come in those in the intensive lifestyle group. There were some microvascular and quality of life benefits in the intensive lifestyle group; however, overall this is a disappointing outcome for those advocating for intensive lifestyle measures in the management of type 2 diabetes.

Reference: N Engl J Med 2013;369(2):145–54
http://www.nejm.org/doi/full/10.1056/NEJMoa1212914

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RESEARCH REVIEW the Australian perspective

Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A_{1c} levels in T1D exchange clinic registry participants

Authors: Miller KM et al, for the T1D Exchange Clinic Network

Summary: The association between the number of SMBG measurements and Hb_{A1c} level was explored in 20,555 registry patients with type 1 diabetes of ≥1 year duration who did not use a continuous glucose monitor. After adjusting for other factors significantly associated with higher numbers of daily SMBG measurements (non-Hispanic white race, insurance coverage, higher household income, insulin pump use), a strong association was seen between more daily SMBG measurements and lower Hb_{A1c} values ($p<0.001$), and this association was seen across all age groups and in both insulin pump and injection users.

Comment (NC): Although SMBG has revolutionised the treatment of type 1 diabetes, it is costly and there is much debate around the optimal frequency for SMBG and its cost effectiveness. This large US study in over 20,000 patients with type 1 diabetes showed an inverse relationship between self-reported SMBG frequency and Hb_{A1c} across all age ranges, and in pump and multiple daily injection users. There are many potential confounders in this study, and it is likely that the increased frequency of SMBG was accompanied by greater patient motivation and education. These factors could equally account for lower Hb_{A1c} levels associated with the increased SMBG frequency. Nevertheless, SMBG is an integral part of a management approach for the patient with type 1 diabetes. Although it does not resolve the issue of optimal frequency, this paper is supportive of an approach that includes frequent SMBG.

Reference: Diabetes Care 2013;36(7):2009–14
http://care.diabetesjournals.org/content/36/7/2009.abstract

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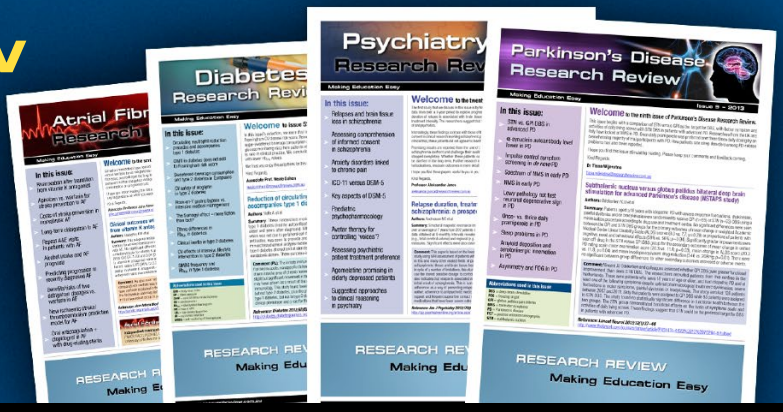

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