Diabetes & Obesity Research Review™

Making Education Easy

Issue 88 – 2014

In this issue:

Abbreviations used in this issue

BMI = body mass index
BP = blood pressure
CSII = continuous subcutaneous insulin infusion
CV = cardiovascular
Hb_{A1c} = glycosylated haemoglobin
H/LDL = high/low-density lipoprotein
HR = hazard ratio
OSA = obstructive sleep apnoea
RCT = randomised controlled trial
TSH = thyroid-stimulating hormone

Welcome to issue 88 of Diabetes and Obesity Research Review.

This issue includes a report from the OpT2mise trial suggesting that insulin pump treatment can be a safe and effective option in patients with type 2 diabetes poorly controlled with multiple daily insulin injections. The importance of breakfast for protecting against type 2 diabetes in UK children has been highlighted. NZ research is represented with a study from Christchurch identifying an early pregnancy Hb_{A1c} cutoff for detecting diabetes and a significantly increased risk of adverse pregnancy outcomes. The issue concludes with a study reporting that OSA (obstructive sleep apnoea) occurred in around one-third of patients with type 2 diabetes referred to a Danish clinic.

I hope you enjoy these and the other papers selected for this issue, and I look forward to receiving your feedback and suggestions.

Best regards,

Dr Jeremy Krebs
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Effects of a patient oriented decision aid for prioritising treatment goals in diabetes

Authors: Denig P et al.

Summary: Primary-care managed patients aged ≤65 years at type 2 diabetes diagnosis were randomised to an intervention of a decision aid with individually tailored risk information and treatment options for multiple risk factors (evaluable n=199) or usual care (evaluable n=107) in this pragmatic RCT; 46% of the intervention group reported having received the basic elements of the intervention. The effect of the intervention on patient empowerment for setting and achieving goals (primary outcome) did not differ significantly to usual care. While the intervention group had a greater rate of intensified lipid-regulating drug treatment for increased cholesterol levels compared with the usual care group, the difference did not reach statistical significance (25% vs. 12%; odds ratio 2.54 [95% CI 0.89, 7.23]), although statistical significance was demonstrated in a prespecified explorative analysis for the printed version of the decision aid versus usual care (3.90 [1.29, 11.80]). There were no relevant or significant changes observed for other treatments.

Comment: There is currently a lot of interest in interventions designed to improve patient self-management of their diabetes, and indeed other chronic diseases. There are many models and programmes being developed and used with some evidence to suggest benefit. However, rigorous testing of these is limited and actually very difficult to conduct. Therefore, the focus on self-management is founded more on principles than on high-quality evidence. I have included this paper from the BMJ more as further evidence of the limitations rather than a call to arms. Whilst I support the concept of self-management, we must be careful to not sink large amounts of resource into facilitating it without careful ongoing evaluation of its real impact and a willingness to refocus if the results are not as compelling as the theory.

Reference: BMJ 2014;349:g5651
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.

CONGRATULATIONS

Dr Adrian Gane, a locum GP from Kaukapakapa.
He won a Navman In-Car GPS and Bluetooth hands-free kit for completing our GP Research Review subscriber survey.

Adherence to healthy lifestyle and risk of gestational diabetes mellitus

Authors: Zhang C et al.

Summary: The associations between combinations of healthy prepregnancy lifestyle factors and gestational diabetes risk were explored in a prospective cohort of 14,437 women enrolled in the US Nurses' Health Study II who had 20,136 singleton live births; incident first-time gestational diabetes was present in 823 pregnancies. Bodyweight, diet, exercise and smoking status were each independently, significantly associated with gestational diabetes risk. Compared with other pregnancies, the gestational diabetes risk was significantly reduced with the combination of nonsmoking, moderate-to-vigorous physical activity of ≥150 minutes per week and healthy eating (relative risk 0.59 [95% CI 0.48, 0.71]), and the addition of prepregnancy BMI <25 kg/m^2 decreased the risk further (0.48 [0.38, 0.61]); when compared with pregnancies in women who did not meet any of these low-risk lifestyle factors, the risk decreased further when all four lifestyle factors were present (0.17 [0.12, 0.25]). The combination of smoking, inactivity, overweight and poor diet was associated with a population attributable risk of 47.5%, similar to the value of 49.2% obtained when the distributions of the four low-risk factors from US National Health and Nutrition Examination Survey (2007–10) data were applied to the calculation.

Comment: Even without moving the goalposts of the diagnostic criteria for gestational diabetes, the incidence is increasing. This simply parallels the rise in obesity. The implication of this on health resources is significant. Prevention of gestational diabetes must be an important goal. This prospective cohort study gives support to the notion that prepregnancy lifestyle factors are predictive of gestational diabetes, with almost 50% of the attributable risk associated with smoking, inactivity, poor diet and BMI. The obvious question is whether interventions in women at risk of gestational diabetes before they get pregnant will have any significant effect on rates of diabetes. The evidence from this study would suggest it might and that an RCT is required to test this.

Reference: BMJ 2014;349:g5450
Abstract

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Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise)

Authors: Reznik Y et al., for the OpT2mise Study Group

Summary: Patients with poorly controlled type 2 diabetes despite insulin daily injections were randomised to continue injections (n=163) or switch to CSIIs (n=168) in this open-label trial. Compared with multiple daily injections, CSIIs were associated with a significantly greater reduction in mean baseline Hb_{A1c} level at 6 months (–12 vs. –4 mmol/mol [–1.1% vs. –0.4%; p<0.0001]) and a significantly lower mean total daily insulin dose at study end (97 vs. 122U [p<0.0001]), but no significant difference in bodyweight change (1.5 vs. 1.1kg [p=0.322]). There were two diabetes-related serious adverse events in the CSII arm and one in the daily injection arm, one severe hypoglycaemic episode (in the daily injection arm) and no ketoacidosis events in either arm.

Comment: Insulin pump therapy has been largely the domain of type 1 diabetes. However, those with type 2 diabetes are increasingly ending up on basal bolus regimens with analogue insulins. Therefore it is very reasonable to consider whether they might do as well or better with a CSII using pump technology. This very pragmatic RCT, which did not attempt to blind participants or investigators to treatment, asks this question. Lack of blinding does raise some issues, but the findings suggest that pump therapy is a valid if not better option for this group. Just as pumping is not the best option for many with type 1 diabetes, the same applies to type 2. What I think we should take from this study is that pumping is an option in type 2 diabetes, and in selected patients may provide ideal solutions to specific issues. It is not a panacea.

Reference: Lancet 2014;384(9950):1265–72
Abstract

Follow-up of blood-pressure lowering and glucose control in type 2 diabetes

Authors: Zoungas S et al., for the ADVANCE-ON Collaborative Group

Summary: This paper reported 6-year follow-up post-trial data for 8494 surviving participants from the ADVANCE trial who had previously been randomised to receive perindopril-indapamide or placebo and to intensive or standard glucose control. The between-group differences in BP and Hb_{A1c} levels seen during the trial were no longer evident at the first post-trial evaluation. The reductions in all-cause and CV-related mortality seen during the trial in participants in the active BP-lowering group were attenuated, but remained significant at the final post-trial follow-up evaluation (respective HRs 0.91 [95% CI 0.84, 0.99; p=0.03]) and 0.88 [0.77, 0.99; p=0.04]). There were no differences seen between the intensive and standard glucose control groups during follow-up for all-cause mortality or major macrovascular events (both HRs 1.00 [95% CI 0.92, 1.08]).

Comment: The long-term follow up of the UKPDS study first raised the concept of a legacy effect of a period of intensive management on CV outcomes lasting well beyond the treatment time. This paper reports a similar analysis in the ADVANCE study cohort. However, there are important differences. In ADVANCE, there is a legacy effect observed with intensive BP lowering, but not with glucose lowering. One potential reason for this may be the patient group included in the two studies. In UKPDS, the participants were newly diagnosed with diabetes and had low CV disease risk, whereas in ADVANCE, participants had diabetes for some time and higher CV disease risk. This study adds to the uncertainty over the relative importance of glucose versus BP management in CV disease risk reduction. Not that I think the answer is any clearer.

Reference: N Engl J Med 2014;371(15):1392–406
Abstract

Intensification of blood pressure treatment in Pasifika people with type 2 diabetes and renal disease

Authors: Tan J et al.

Summary: Pasifika primary-care patients with type 2 diabetes (77% male), an estimated GFR of ≥40 mL/min/1.73m^2 and urinary albumin-creatinine ratio of ≥40 mg/mmol participated in a community-based programme aimed at optimising BP; 39/47 enrolled participants completed ≥17 months of the intervention. The intervention was associated with a median BP decrease of 13/12mm Hg ($p<0.05$) and a decrease in urinary albumin-to-creatinine ratio from 126 to 51 mg/mmol ($p<0.05$). Compared with participants with no remission in albuminuria, those with albuminuria remission had faster estimated GFR loss during the first year (13.6 vs. 3.5 mL/min/1.73m^2 per year [$p=0.02$]), but the rate of loss slowed during the second year. End-stage renal failure occurred in two participants.

Comment: The virtual diabetes register shows how prevalent diabetes is in Pacific Island communities. Along with Māori, Pacific people have higher rates of microalbuminuria and diabetic nephropathy. Anecdotally, many of us would say that it is often a real challenge to facilitate good diabetes care, both glucose and BP, in pacific patients. Therefore this study is very important in the NZ context. An integrated primary care and specialist team approach is becoming the model of choice for diabetes management, and this study highlights the successes that can be achieved. Often these interventions are heavily dependent on the individuals involved and the challenge is to translate this evidence into wider practice around the country.

Reference: NZ Med J 2014;127(1404):17–26
Abstract

Regular breakfast consumption and type 2 diabetes risk markers in 9- to 10-year-old children in the Child Heart and Health Study in England (CHASE)

Authors: Donin AS et al.

Summary: This UK cross-sectional study of 4116 schoolchildren aged 9–10 years explored relationships between breakfast consumption and CV disease and type 2 diabetes; 74% of the children consumed breakfast every day, 11% most days, 9% some days and 6% not usually. Compared with children who reported eating breakfast daily, those reporting not usually having breakfast had higher fasting insulin levels (percent difference 26.4%), insulin resistance (26.7%), Hb_{A1c} level (1.2%), glucose level (1.0%) and urate level (6%), but the differences lost statistical significance after higher triglyceride levels, systolic BP and C-reactive protein levels were adjusted for adiposity. Compared with other breakfast types, a high-fibre cereal breakfast lowered insulin resistance ($p<0.01$ for heterogeneity). Differences in type 2 diabetes markers were not explained by differences in nutrient intakes between breakfast frequency groups.

Comment: It is often said that breakfast is the most important meal of the day. It is common for people trying to lose weight to skip breakfast in an attempt to reduce calorie intake, but this is often compensated for by excessive intake later in the day. This cross-sectional study in children highlights some interesting issues. Those who habitually skipped breakfast were more insulin resistant and had a higher Hb_{A1c} level than those who usually ate breakfast, although there was some confounding from lipids, BP and background inflammation. Notably, a high-fibre cereal at breakfast was protective. As the authors indicated, this calls for a well-designed RCT to test whether ensuring breakfast is consumed and actively increasing fibre intake at that time is effective in reducing the incidence of type 2 diabetes.

Reference: PLoS Med 2014;11(9):e1001703
Abstract

Metformin and low levels of thyroid-stimulating hormone in patients with type 2 diabetes mellitus

Authors: Fournier J-P et al.

Summary: These researchers assessed the risk of low TSH (thyroid-stimulating hormone) levels associated with metformin versus sulphonylurea monotherapy in patients with type 2 diabetes and treated hypothyroidism (n=5689) or euthyroidism (n=59,937). During follow-up, a TSH level of <0.4 mIU/L occurred with incidence rates of 119.7 and 4.5 per 1000 person-years among the patients with hypothyroidism and euthyroid patients, respectively. Compared with sulphonylurea monotherapy, metformin monotherapy was associated with a significantly lower incidence rate of low TSH levels in patients with treated hypothyroidism (79.5 vs. 125.2 per 1000 person-years; adjusted HR 1.55 [95% CI 1.09, 2.20]), particularly 90–180 days after starting treatment (2.30 [1.00, 5.29]), but not in euthyroid patients (0.97 [0.69, 1.36]).

Comment: This paper caught my eye from unexplained curiosity. In a relatively short longitudinal observational study, challenged by very different numbers of individuals in the four groups, metformin appears to increase the chance of altered thyroid hormone levels in those who already have hypothyroidism on replacement therapy, relative to a sulphonylurea. Specifically, metformin reduces TSH levels. The explanation for this is totally unclear, but because both type 2 diabetes and hypothyroidism are common conditions, this interaction will also be common, even if not identified. The study raises more questions than it answers. Is the reduction in TSH level clinically relevant? Should TSH level monitoring be added to the annual bloods? Should thyroxine doses be reduced in this setting? This is an interesting space to watch.

Reference: CMAJ 2014;186(15):1138–45
Abstract

An early pregnancy Hb_{A1c} ≥5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes

Authors: Hughes RCE et al.

Summary: These NZ researchers sought to determine the optimal Hb_{A1c} level threshold during early pregnancy (measured at a median of 47 days' gestation) for detecting diabetes in Christchurch women presenting during 2008–2010; of the 4201 women invited to take part, an early oral glucose tolerance test was performed in 974 at <20 weeks' gestation. All 15 cases of diabetes were detected by an Hb_{A1c} level of ≥41 mmol/mol (≥5.9%), and seven were captured by an Hb_{A1c} level of <48 mmol/mol (<6.5%). The same Hb_{A1c} threshold had specificity of 98.4% and a positive predictive value of 52.9% for detecting gestational diabetes before 20 weeks' gestation. Among women from the entire cohort, excluding those referred for management of gestational diabetes, an Hb_{A1c} level of 41–46 mmol/mol (5.9–6.4%; n=200) versus lower levels (n=8174) was associated with significantly greater likelihoods of major congenital anomalies (relative risk 2.67 [95% CI 1.28, 5.53]), pre-eclampsia (2.42 [1.34, 4.38]), shoulder dystocia (2.47 [1.05, 5.85]) and perinatal death (3.96 [1.54, 10.16]).

Comment: It is great to see NZ research in high-impact international journals. This study of early pregnancy Hb_{A1c} screening for detection of diabetes and prediction of adverse pregnancy outcomes is an important contribution to a very highly emotional and controversial area of our field. There are very strong calls to reduce the diagnostic thresholds for gestational diabetes, and equally strong rebuttal that there is no evidence that doing so, or treating the women identified, will impact on outcomes of the pregnancy or subsequent health of the offspring. There is general agreement that identifying those with unrecognised existing diabetes early in pregnancy is important, and that using Hb_{A1c} level is an acceptable tool for this. The most controversial area is the intermediate group with minimally elevated Hb_{A1c} levels. This study showed higher rates of diabetes complications in this group, and the authors called for a lower threshold to be adopted. However, the impact on the women, the cost to the health system and indeed the lack of any clear pathway for management, let alone resources to provide this in the absence of any prospective controlled data to show a clear benefit, simply do not justify this. Such a study needs to be conducted to answer this question.

Reference: Diabetes Care 2014;37(11):2953–9
Abstract

Beneficial effect of pistachio consumption on glucose metabolism, insulin resistance, inflammation, and related metabolic risk markers

Authors: Hernández-Alonso P et al.

Summary: Patients with prediabetes consumed two isocaloric diets matched for protein, fibre and saturated fatty acids, each for 4 months in a randomised crossover design with a 2-week washout period, one of which was supplemented with pistachios 57 g/day and the other a control diet. Compared with the control diet, the pistachio-supplemented diet was associated with decreases in fasting glucose level, insulin level, HOMA-IR (homeostatic model assessment of insulin resistance) and levels of other cardiometabolic risk markers such as fibrinogen, oxidised LDL and platelet factor-4, while glucagon-like peptide-1 levels increased. The pistachio-supplemented diet was also associated with significant decreases in interleukin-6 mRNA and resistin gene expression in lymphocytes of 9% and 6%, respectively, and lymphocyte cellular glucose uptake was reduced significantly by 78.78%, while SLC2A4 expression increased by 69% with the control diet.

Comment: There are many claims for the glucose-lowering benefits of various micronutrients or food items such as honey, cinnamon, chromium or magnesium for example. Effects are often quite variable and may depend on the underlying status of these nutrients in any individual. This study reports on the benefit of pistachio nuts in a short crossover study in participants with prediabetes. There were benefits in glucose metabolism and markers of CV disease risk with pistachio supplementation. Larger and longer studies are required to test this further, but it is an interesting and potentially simple nutritional intervention if subsequent studies support the current data.

Reference: Diabetes Care 2014;37(11):3098–105
Abstract

At least one in three people with type 2 diabetes mellitus referred to a diabetes centre has symptomatic obstructive sleep apnoea

Authors: Storgaard H et al.

Summary: Two hundred newly referred patients with type 2 diabetes received stepwise screening for OSA with the Berlin questionnaire and then, if indicative, overnight monitoring with a home sleep testing device (ApneaLink™); those with an apnoea-hypopnea index ≥5/h were offered referral for diagnosis and treatment. A high risk of OSA was reported for 106 Berlin questionnaire respondents, 72 of who were referred for diagnosis based on overnight monitoring, giving a symptomatic OSA prevalence of 39%. Compared with participants unlikely to have OSA, those with symptomatic OSA had significantly higher BMI, worse glycaemic control and lower plasma HDL cholesterol levels, with age, BMI and HDL cholesterol level all significant, independent predictors of OSA in a multivariate analysis.

Comment: OSA is a common accompaniment of obesity. Therefore one might predict that many patients with type 2 diabetes may have sleep apnoea. Sleep apnoea can be an important contributor to hypertension and poor glycaemic control, and therefore it is important to identify those affected. Identification of sleep apnoea strengthens the call for weight management, and also, if appropriate, other treatments such as CPAP (continuous positive airway pressure), which can have dramatic benefits not only on quality of life, but also on BP and glycaemic control. This study shocked me. I frequently think about OSA in clinic, but would not have predicted that a third of patients were affected. This calls for clear cost-effective pathways for screening.

Reference: Diabetic Med 2014;31(11):1460–7
Abstract