Diabetes Research Review™

Making Education Easy

Issue 67 - 2014

In this issue:

Abbreviations used in this review:

BP = blood pressure; **CV** = cardiovascular;
GLP = glucagon-like peptide; **H/LDL** = high/low-density lipoprotein;
Hb_{A1c} = glycosylated haemoglobin;
SGLT = sodium glucose cotransporter

Welcome to issue 67 of Diabetes Research Review.

The papers selected for this issue include research showing that closed-loop control of an artificial pancreas using a smartphone reduced hypoglycaemia and hypoglycaemia treatments in outpatients when compared against sensor-augmented insulin pump therapy. GLP-1 agonists lowered fasting plasma and postprandial glucose excursions in patients with HNF1A (hepatocyte nuclear factor-1α) diabetes, with a greater effect with glimepiride, but at the expense of an increased risk of exclusively mild hypoglycaemia. Long-term follow-up of ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial participants reported on the retention of the benefits seen with active BP-lowering and intensive glucose-lowering therapies during the trial. This issue concludes with research showing a link between consumption of noncaloric artificial sweeteners and the induction of glucose intolerance via alterations in the gut microbiota.

We hope you find these and the other selected studies of interest, and we welcome your comments.

Kind Regards,

Associate Prof. Neale Cohen
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Effects of calcium-vitamin D co-supplementation on glycaemic control, inflammation and oxidative stress in gestational diabetes

Authors: Asemi Z et al.

Summary: Women with gestational diabetes mellitus at 24–28 weeks' gestation were randomised to receive calcium 1000 mg/day plus vitamin D 50,000U on days 0 and 21 (n=28) or matching placebo (n=28); 51 women completed the study. An intent-to-treat analysis showed that compared with placebo, calcium plus vitamin D supplementation was associated with: i) significant reductions in fasting plasma glucose level (–0.89 vs. +0.26 mmol/L [p<0.001]), serum insulin level (–13.55 vs. +9.17 pmol/L [p=0.02]), homeostatic model assessment of insulin resistance (–0.91 vs. +0.63 [p=0.001]), serum LDL cholesterol level (–0.23 vs. +0.26 mmol/L [p=0.02]), HDL cholesterol ratio (–0.49 vs. +0.18 [p=0.003]); ii) significant increases in HDL cholesterol level (+0.15 vs. –0.02 mmol/L [p=0.01]), QUICKI (quantitative insulin sensitivity check index; +0.02 vs. –0.002 [p=0.003]) and total glutathione level (+51.14 vs. –47.27 µmol/L [p=0.03]); and iii) prevention of an increase in malondialdehyde level (+0.06 vs. +0.93 µmol/L [p=0.03]).

Comment (PL): Gestational diabetes is obviously a problem of considerable importance with inherent treatment difficulties. It is a disease of insulin resistance so extremely safe treatments that address this issue are highly desirable. This simple and well-designed study of a modest number of young women over 6 weeks looked at the impact of mid/late-term joint calcium and vitamin D supplementation. Plasma calcium and vitamin D levels both increased on therapy and the treated women (versus placebo) showed a range of metabolic changes consistent with increased insulin sensitivity (decreased glucose level, decreased insulin level and increased HDL cholesterol level) and interestingly there was absolutely no change in C-reactive protein levels. There were no long-term or outcome measurements – interesting.

Reference: Diabetologia 2014;57(9):1798–806
http://link.springer.com/article/10.1007/s00125-014-3293-x/fulltext.html

Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes

Authors: Kahleova H et al.

Summary: Fifty-four patients with type 2 diabetes treated with oral hypoglycaemic agents consumed hypoenergetic diets, with the same overall macronutrient and energy content, consisting of six or two (breakfast and lunch) meals per day, each for 12 weeks in a randomised crossover design. Compared with the six-meal diet, the two-meal diet was associated with significantly greater decreases in bodyweight (–3.7 vs. –2.3kg [p<0.001]), hepatic fat content (–0.04% vs. –0.03% [p=0.009]), fasting plasma glucose level (p=0.004), C-peptide level (p=0.04) and fasting plasma glucagon level (p<0.001; a significant decrease versus a significant increase), and a significantly greater increase in oral glucose insulin sensitivity (p=0.01).

Comment (PL): There is a lot of interesting practical work going on investigating multiple aspects of the physiology of different food intake and exercise schedules and their effects on metabolic parameters in subjects with diabetes. Here, a hypoenergetic diet was given as two or six (the 'grazing' model) meals during the day (breakfast and lunch for the two-meal variant) to subjects with type 2 diabetes and a very wide range of body mass index values and Hb_{A1c} levels. The two-meal protocol gave greater improvements in metabolic parameters. There were four and three dropouts in the two respective groups. One might reflect on the personal, family and social aspects of life without an evening meal, although the authors did not turn their attention to this issue.

Reference: Diabetologia 2014;57(8):1552–60
http://tinyurl.com/np5643o

Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas

Authors: Kovatchev BP et al.

Summary: Twenty outpatients with type 1 diabetes received 40-hour closed-loop control and open-loop sensor-augmented insulin pump therapy in a randomised crossover manner. The sensor and insulin pump were connected to a smartphone artificial pancreas platform. An effect size of 0.64 (p=0.03) was seen for the reduction in risk for hypoglycaemia (primary outcome, assessed by the low blood glucose index), with significantly fewer hypoglycaemic episodes requiring carbohydrate treatment per session for the closed-loop control system versus the open-loop system (1.2 vs. 2.4 [p=0.02]), accompanied by a small decrease in percentage of time in the target blood glucose level range (3.9–10 mmol/L; 66.1% vs. 70.7%) and a higher mean blood glucose level (8.9 vs. 8.4 mmol/L [p=0.04]).

Comment (PL): Technology driven advances have been very real and substantial in the area of insulin pumps and glucose monitoring for type 1 diabetes patients. This European study compared an open- (currently most common) versus closed-loop apparatus with the latter known as an 'artificial pancreas'. The systems involved a smartphone interface for patients that could be monitored remotely by the investigators. Recalling that overall the major benefits of the systems have been in the area of reducing hypoglycaemic events, the closed-loop system gave an appreciable reduction in hypoglycaemic events versus the open-loop system, noting that numerous studies have shown the open-loop system itself can reduce hypoglycaemic events relative to a multi-injection protocol. It was noted that the operation of the 'diabetes assistant' (smartphone) system by the patient was feasible with lifelong type effects. What this points to is a promising way forward for patients with lifelong type 1 diabetes.

Reference: Diabetes Care 2014;37(7):1789–96
http://care.diabetesjournals.org/content/37/7/1789.full

Diabetes Research Review™

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

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Associate Professor Neale Cohen, a physician specialising 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, Melbourne.

Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist

Authors: Østoft SH et al.

Summary: Sixteen patients with HNF1A diabetes received 6 weeks each of liraglutide uptitrated once weekly to 1.8mg once daily and placebo, as well as glimepiride uptitrated once weekly in a treat-to-target manner and placebo injections, in a randomised crossover design. Liraglutide and glimepiride were associated with significant reductions from baseline for fasting plasma glucose levels (–1.6 and –2.8 mmol/L, respectively [p values 0.012 and 0.003]) and postprandial plasma glucose response areas under the curves (2624 and 2136, respectively, vs. 3127 min·mmol/L [p values 0.017 and 0.001]); no significant difference was seen between the two agents for either of these parameters. There were 18 hypoglycaemic episodes associated with glimepiride treatment and one with liraglutide treatment.

Comment (PL): MODY (maturity-onset diabetes of the young) is a particularly interesting form of hyperglycaemia with an interesting natural history and presenting an ongoing diagnostic and therapeutic challenge. Sulfonylureas have been the traditional therapy with their intendant risk of hypoglycaemia. This trial compared a sulfonylurea (glimepiride) with an incretin mimetic (liraglutide) looking for efficacy with reduced hypoglycaemic events. The study indeed found similar efficacy and a very large decrease in hypoglycaemic episodes for the liraglutide treatment group, noting that glucose excursions were greater for the sulfonylurea and most hypoglycaemic events were mild. MODY is particularly amenable to individualised diagnosis and therapy, and GLP-1 agonists might well be worth considering, especially in patients with troublesome hypoglycaemic episodes on sulfonylureas.

Reference: Diabetes Care 2014;37(7):1797–805
http://care.diabetesjournals.org/content/37/7/1797.full

Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes

Authors: Rosenstock J et al. on behalf of the EMPA-REG MDI Trial Investigators

Summary: Patients with type 2 diabetes inadequately controlled with multiple daily insulin injections with or without metformin were randomised to receive empagliflozin 10mg (n=186) or 25mg (n=189) or placebo (n=188) once daily for 52 weeks; the participants' insulin doses remained stable during weeks 1–18 and adjusted to meet glucose targets during weeks 19–40 and then stable during weeks 41–52. Compared with placebo, both the empagliflozin 10mg and 25mg doses were associated with significantly greater adjusted mean changes in baseline Hb_{A1c} level at week 18 (primary endpoint; –10.3 and –11.1, respectively, vs. –5.5 mmol/mol [–0.94% and –1.02% vs. –0.50%]; p<0.001 for both). Further reductions with insulin titration resulted in final changes in baseline Hb_{A1c} level at week 52 in the respective empagliflozin 10mg and 25mg and placebo arms of –12.9, –13.9 and –8.9 mmol/mol (–1.18%, –1.27% and –0.81%) and final Hb_{A1c} levels of 55, 54 and 58 mmol/mol (7.2%, 7.1% and 7.5%). Compared with placebo, empagliflozin was also associated with greater proportions of participants achieving the target Hb_{A1c} level of <53 mmol/mol (<7%; 31–42% vs. 21%), significantly lower insulin doses and a significant reduction in bodyweight at week 52 (p<0.01 for all).

Comment (PL): In type 2 diabetes, metformin is the first medical agent of choice; however, when desired glycaemic targets are not met, a second agent is added with the medium-term aim of preventing complications. There are multiple choices of second agent. The phlorizin derivatives, which are SGLT-2 inhibitors, have progressed to clinical stage. In this straightforward study, empagliflozin at two doses was added to metformin in patients with Hb_{A1c} levels 7.0–10.0% for 24 weeks. The Hb_{A1c} level fell slightly in the placebo arm (–0.13%) and the usual level of response to oral antihyperglycaemic agents occurred with the fall of –0.70% and –0.77% for empagliflozin at 10mg and 25mg, respectively. Adverse events were mostly mild, or similar, but occurred at a rate of about 50%. There were only modest urogenital infections although genital infections in females were elevated. What needs to be developed is some algorithm of patient characteristics such that the available choices for second medications increases; there can be some element of personalised medicine in matching patients to second agents.

Reference: Diabetes Care 2014;37(7):1815–23
http://care.diabetesjournals.org/content/37/7/1815.full

Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease

Authors: Yale J-F et al., on behalf of the DIA3004 Study Group

Summary: Patients with type 2 diabetes (n=269; mean estimated GFR [glomerular filtration rate] 39.4 mL/min/1.73m^2) were randomised to receive canagliflozin 100mg or 300mg or placebo once daily in this 52-week trial. The placebo-subtracted differences in Hb_{A1c} level in the canagliflozin 100mg and 300mg arms were –0.27% (95% CI –0.53 to 0.001) and –0.41% (–0.68 to –0.14). Compared with placebo, canagliflozin was also associated with lower fasting plasma glucose levels, bodyweight and BP. The overall incidences of adverse events were similar among the groups, but canagliflozin was associated with more osmotic diuresis-related events (both doses), urinary tract infections (300mg) and volume depletion-related events (300mg) than placebo. Compared with placebo, canagliflozin 100mg and 300mg recipients had greater decreases in estimated GFR (–2.1 and –4.0, respectively, vs. –1.6 mL/min/1.73m^2) and reductions in median urine albumin-to-creatinine ratio (–16.4 and –28.0 vs. +19.7%).

Comment (NC): The SGLT-2 inhibitors are now available for the treatment of type 2 diabetes, and have been shown to be effective in improving glycaemic control and achieving weight loss. Because of the renal mechanism of action, use in patients with poor renal function has been considered of little benefit; however, this long-term study with canagliflozin showed safety and modest efficacy in patients with renal impairment. Hb_{A1c} reduction with the higher canagliflozin dose was only 0.41% and bodyweight reduction around 1kg. In this setting, canagliflozin appears to be less effective compared with studies in patients with normal renal function. The BP-lowering effect was still quite impressive, and safety, particularly adverse renal effects, was not an issue. If nothing else, this is reassuring for canagliflozin use in those with borderline renal function; however, it seems unlikely that this class of drug has a major role in patients with significant renal impairment.

Reference: Diabetes Obes Metab 2014;16(10):1016–27
http://onlinelibrary.wiley.com/doi/10.1111/dom.12348/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 hazard ratios 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 hazard ratios 1.00 [95% CI 0.92–1.08]).

Comment (NC): The ADVANCE study previously demonstrated the benefits of BP lowering and intensive glucose lowering in patients with type 2 diabetes over a period of 4 years. This study looked at the follow-up of these patients 6 years after the completion of the study. The BP-lowering benefits on mortality and CV death were still present, suggesting a legacy effect of BP lowering. Disappointingly, there were no real legacy effects of glucose lowering on CV events or death, although there was a persistent reduction in end-stage renal disease. This is in contrast to the UKPDS follow-up study, which did show a glycaemic legacy effect. The reason for these differences is not clear but may relate to the small Hb_{A1c} difference in ADVANCE between conventional and intensive treatment, or perhaps the lower starting Hb_{A1c} in ADVANCE compared with the UKPDS trial. While there is little doubt that BP lowering plays an important role in preventing macrovascular disease, there remain questions around the role of tight glycaemic control.

Reference: N Engl J Med; Published online Sept 19, 2014
http://www.nejm.org/doi/full/10.1056/NEJMoa1407963

Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes

Authors: Davies MJ et al. on behalf of the BEGIN BB T1 study group

Summary: Adults with type 1 diabetes were randomised to receive once daily basal insulin degludec (n=302) or detemir (n=153) combined with mealtime bolus insulin aspart in this 26-week open-label, treat-to-target noninferiority trial. The respective Hb_{A1c} level decreases at 26 weeks in the insulin degludec and detemir arms were 8.0 and 7.1 mmol/mol (0.73% and 0.65%), with noninferiority confirmed, but the improvement in mean fasting plasma glucose level was 1.66 mmol/L lower with insulin degludec than with insulin detemir (p<0.0001). Insulin degludec and detemir were associated with similar confirmed hypoglycaemic event rates (45.83 and 45.69 episodes per patient-year of exposure [p=0.86]), but the nocturnal rate was significantly lower with insulin degludec (4.14 vs. 5.93 episodes per patient-year of exposure; rate ratio 0.66 [95% CI 0.49–0.88; p=0.0049]). The groups had similar adverse event profiles.

Comment (NC): Degludec insulin is one of the three new long-acting basal insulins currently undergoing phase 3 studies. This study compared degludec with detemir insulin in type 1 diabetes in an open-label study, and was designed to show noninferiority. It was able to show that a degludec-based basal bolus regimen was noninferior to a detemir regimen, and associated with a reduction in nocturnal hypoglycaemia. However, there was a 1kg weight differential in favour of detemir. These findings are similar to other studies with degludec in type 2 diabetes comparing with glargine insulin. Notably the most 'needy' patients were excluded from this study – i.e. patients with hypoglycaemia unawareness and severe hypoglycaemia – and these groups may benefit the most from such a stable long-acting insulin. Overall, the benefits of degludec appear significant but small compared with conventional modern basal insulins.

Reference: Diabetes Obes Metab 2014;16(10):922–30
http://onlinelibrary.wiley.com/doi/10.1111/dom.12298/full

Dietary gluten and the development of type 1 diabetes

Authors: Antvorskov JC et al.

Summary: This review described current findings and knowledge on the link between dietary gluten protein and the pathogenesis of type 1 diabetes. Studies thus far have focused mainly on describing the temporal association between introduction of dietary gluten and the incidence of type 1 diabetes, and on the effects of gluten on the intestinal flora and the immune system. The authors commented that it is important that the effect of a gluten-free diet on human type 1 diabetes is further evaluated. The balance between the innate and adaptive immune systems also needs to be clarified in future research.

Comment (NC): While it is well accepted that type 1 diabetes is due to the autoimmune destruction of ß-cells, the environmental trigger or triggers remain elusive. Many theories including early introduction of cow's milk or infection with Coxsackie viruses continue to be investigated; however, less attention has been given to gluten as an environmental trigger. It is known that coeliac disease has a strong association with type 1 diabetes and similar genetic associations; however, there is some evidence, mainly in animal models, that early exposure to gluten increases the risk of developing islet cell autoimmunity. This is an excellent review of the state of current knowledge on this interesting area. The key points are that the intestinal immune system and intestinal permeability are altered with gluten exposure and in people at risk of developing type 1 diabetes. Furthermore, exposure to gluten under 3 months of age is associated with marked increased rates of islet cell autoimmunity. We are a long way short of knowing whether providing a gluten-free diet early in childhood may prevent type 1 diabetes, but it is certainly plausible and no doubt this theory will be tested in further studies.

Reference: Diabetologia 2014;57(9):1770–80
http://tinyurl.com/mbokwxd

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Authors: Suez J et al.

Summary: These authors presented data showing a link between the consumption of commonly used noncaloric artificial sweeteners and the development of glucose intolerance via induction of compositional and functional alterations to the intestinal microbiota. Furthermore, these effects were shown to be abrogated by antibiotics, and were able to be fully transferred to germ-free mice via faecal transplantation of microbiota configurations from mice that had consumed noncaloric artificial sweeteners and of microbiota anaerobically incubated with noncaloric artificial sweeteners. The researchers identified microbial metabolic pathways linked to host susceptibility to metabolic disease that were altered by noncaloric artificial sweeteners, and showed similar dysbiosis and glucose intolerance induced by these artificial sweeteners in healthy human subjects. They concluded that their results suggest that reassessment of the widespread use of noncaloric artificial sweeteners is warranted.

Comment (NC): Artificial sweeteners are widely used in modern society, and have been previously thought to have no significant metabolic effects. This fascinating collection of studies provides evidence that these products are not metabolically inert, and remarkably, may cause glucose intolerance. The animal data displayed increased glucose intolerance with exposure to these chemicals, particularly saccharin, and this appears to be mediated through alteration in gut microbes. Faecal transplantation experiments conferred metabolic abnormalities to recipients, and short-term human studies also showed similar metabolic consequences to those seen in animals. Although the clinical significance of these findings is not clear, it is certainly a concern at both an individual level when managing our patients with diabetes, and at a population level where the impact on obesity and diabetes rates may be significant.

Reference: Nature; published online Sept 17, 2014
http://www.nature.com/nature/journal/vaop/ncurrent/full/nature13793.html

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