Diabetes & Obesity Research Review™

Making Education Easy

Issue 83 – 2014

In this issue:

Abbreviations used in this issue
BMI = body mass index
DPP = dipeptidyl peptidase
ED = emergency department
GLP = glucagon-like peptide
Hb_{A1c} = glycosylated haemoglobin
RCT = randomised controlled trial

Welcome to issue 83 of Diabetes and Obesity Research Review.

This winter issue starts with two papers reassuring us that any fears surrounding an increased risk of pancreatitis with incretin-based drugs appear to be unfounded. Research out of the US reports a disturbing increase in the prevalences of both type 1 and type 2 diabetes among children over the 2001–2009 period. This issue concludes with a report from the DIRECT (Diabetes Research on Patient Stratification) consortium detailing the rationale and design of two prospective cohort epidemiological studies in patients with prediabetes and type 2 diabetes that will yield an unprecedented array of biomaterials and data.

I hope you have been enjoying Diabetes Research Review, and I continue to look forward to receiving your comments, feedback and suggestions.

Best regards,

Dr Jeremy Krebs
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Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus

Authors: Li L et al.

Summary: This systematic review and meta-analysis of 55 RCTs (n=33,350) and five observational studies (n=320,289) comparing GLP-1 receptor agonists or DPP-4 inhibitors with placebo, lifestyle modification or active antidiabetic agents for type 2 diabetes examined the impact of the incretin-based therapies on pancreatitis risk. Data pooled from the RCTs showed no increased risk of pancreatitis associated with either GLP-1 agonists or DPP-4 inhibitors compared with controls (respective odds ratios 1.05 [95% CI 0.37, 2.94] and 1.06 [0.46, 2.45]). No differential effects were seen by subgroups assessed or by sensitivity analyses using alternative statistical modelling and effect measures. While no signal for an increased pancreatitis risk with incretin use was seen in three retrospective cohort studies and one case-control study, another case-control study at moderate risk of bias suggested an increased risk of acute pancreatitis with ≤2 years use of exenatide or sitagliptin versus no use (adjusted odds ratio 2.07 [95% CI 1.36, 3.13]).

Comment: Although we don't have funded access to either GLP-1 analogues or DPP-4 antagonists in NZ, they are available for prescription, and are likely to become more commonly prescribed over time. One issue that has been hanging over these classes of agents is the suggestion that they might increase the risk of pancreatitis. This is biologically plausible given the mode of action. It is therefore encouraging and reassuring to see the results of this extensive systematic review and meta-analysis of trials using these agents. Not only was the incidence of pancreatitis low in the studies overall, but there was no evidence that either class increases the risk of pancreatitis. However, the authors encourage caution because of the low overall incidence, and it will be important to continue to collect long-term data in very large population sets to truly be reassuring.

Reference: BMJ 2014;348:g2366
Abstract

Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes

Authors: Faillie J-L et al.

Summary: This cohort study involving 680 UK general practices compared acute pancreatitis risks in 20,748 new users of incretin-based drugs with 51,712 sulphonylurea users. The acute pancreatitis incidences were 1.45 and 1.47 per 1000 patients per year for users of incretin-based drugs and sulphonylureas, respectively (adjusted hazard ratio 1.00 [95% CI 0.59, 1.70]).

Comment: This is the second paper on this topic that I have included in this issue. These data were taken from real-world primary-care patients who were exposed to incretin therapy for at least 12 months, and compared with sulphonylureas. Once again the rate of pancreatitis was low, and there was no observed increased risk with incretin therapy. Together these studies are reassuring, and whilst the authors of both make cautionary statements about not being able to exclude some increased risk, it would appear that any such risk is very small, and in the setting of effective glycaemic lowering would not seem to be a significant issue for most patients.

Reference: BMJ 2014;348:g2780
Abstract

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Long term maintenance of weight loss with non-surgical interventions in obese adults

Authors: Dombrowski SU et al.

Summary: This was a systematic review and meta-analysis of 45 RCTs investigating interventions designed to maintain weight loss in 7788 initially obese participants who had lost ≥5% of bodyweight, and with ≥12 months of follow-up bodyweight data. Compared with controls, average differences in weight regain at 12 months were –1.56kg for behavioural interventions focusing on both food intake and physical activity (n=2949) and –1.80kg for orlistat plus behavioural interventions (n=1738). The effect with orlistat was dose dependent, with significantly greater weight loss maintenance seen with 120mg three times daily compared with 30–60mg three times daily (–2.34 vs. –0.70kg [p=0.02]). Higher frequencies of adverse gastrointestinal events were seen with orlistat compared with placebo.

Comment: After the recent release of data showing alarming rates of overweight and obesity in NZ, it is timely to include this paper. Dietary and physical activity interventions are the mainstay of weight management, although are frequently criticised for having low primary efficacy and/or high relapse rates. This systematic review and meta-analysis looked specifically at weight maintenance following at least 5% loss of bodyweight. The main findings were that a combined approach of dietary and activity intervention improved the maintenance of weight loss at 12 months. Unfortunately, the effect size was small and the evidence beyond 12 months limited. It must be remembered that in such studies, this is a group effect and hides considerable individual variation. It is also important to consider that the health benefits of modest sustained weight loss maintenance are perhaps greater than the degree of weight lost might suggest. At a population level it is worth it!

Reference: BMJ 2014;348:g2646
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.

Effect of intervention aimed at increasing physical activity, reducing sedentary behaviour, and increasing fruit and vegetable consumption in children

Authors: Kipping RR et al.

Summary: Primary school children aged 9–10 years were randomised by school to receive an intervention, designed to increase physical activity, reduce sedentary behaviour and increase fruit and vegetable consumption, or standard teaching in the AFLY5 (Active for Life Year 5) trial. No difference was seen between the intervention and control schools for any of the three primary outcomes of accelerometer-assessed minutes of moderate-to-vigorous physical activity and sedentary behaviour per day and reported daily consumption of fruit and vegetable servings. After multiple testing was taken into account, the intervention was found to reduce the following three of the nine secondary outcomes assessed: self-reported time spent in weekend screen viewing, self-reported daily snack servings and daily servings of high energy drinks. Similar results were seen in sensitivity analyses.

Comment: Childhood obesity is well recognised as a critical area to address, and many studies have assessed interventions in this field. This present study in UK primary schools targeted increases in physical activity, reductions in sedentary time and increased fruit and vegetable consumption as simple measures to target. However, the results are disappointing, and do not show any convincing benefits of this programme. This is in contrast to the NZ APPLE project, which had similar goals, but was delivered in a different fashion. This highlights just how important this aspect of a programme can be, and therefore just how carefully we must consider translation of evidence into practice to ensure that we have the best chance of success in the real world.

Reference: BMJ 2014;348:g3256
Abstract

Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009

Authors: Dabelea D et al., for the SEARCH for Diabetes in Youth Study

Summary: These researchers estimated changes in the prevalences of type 1 and type 2 diabetes among patients aged <20 years in the US. They reported increases in the respective incidences of type 1 (ages 0–19 years) and type 2 (ages 10–19 years) diabetes from 1.48 and 0.34 per 1000 in 2001 to 1.93 and 0.46 per 1000 in 2009. The incidences of type 1 diabetes increased over this time for both sexes and all ages and ethnicities, except for American Indians and children aged 0–4 years, and white youth had the greatest incidence in 2009 of all ethnicities at 2.55 per 1000. Significant increases were also seen over the assessment period for type 2 diabetes for both sexes, all age-groups and all ethnicities except Asian Pacific Islanders and American Indians. After adjustment for completeness of ascertainment, the overall increases in type 1 and type 2 diabetes were 21.1% and 30.5%, respectively.

Comment: In NZ, the prevalence of diabetes in adults has increased at a rate of approximately 8% per annum over the last 8 years, as seen in the virtual diabetes register. We do not have good data on this in children and adolescents, but an anecdotal feeling is that rates are also increasing. This current study from the US shows truly alarming increases in the rates of both type 1 and type 2 diabetes in young Americans. The increase in type 2 diabetes might be predicted by the obesity epidemic, and is really just bearing out all our predictions from 10 years ago. However, the rise in type 1 diabetes is less readily explained. Whilst the absolute risk of diabetes remains low, the observed increases are of concern.

Reference: JAMA 2014;311(17):1778–86
Abstract

Bariatric surgery versus intensive medical therapy for diabetes – 3-year outcomes

Authors: Schauer PR et al., for the STAMPEDE Investigators

Summary: Three-year results from the STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) trial are presented in this paper. STAMPEDE recruited 150 obese patients with uncontrolled type 2 diabetes and randomised them to receive intensive medical therapy plus Roux-en-Y gastric bypass (n=50) or sleeve gastrectomy (n=50), or to intensive medical therapy alone (n=50). At 3 years, the primary endpoint (Hb_{A1c} level ≤42 mmol/mol [≤6.0%]) was achieved by 5% of patients in the medical therapy group compared with 38% of those in the gastric bypass group (p<0.001) and 24% in the sleeve gastrectomy group (p=0.01). The use of glucose-lowering medications, including insulin, was lower in the surgical groups than in the medical-therapy group. Surgery was associated with greater mean percentage reductions in bodyweight from baseline of 24.5% in the gastric bypass group and 21.1% in the sleeve gastrectomy group, compared with just 4.2% in the medical therapy group (p<0.001 for both). Quality-of-life measures were significantly better in the two surgical groups than in the medical therapy group.

Comment: This is an important study. There has been a groundswell of opinion that bariatric surgery 'resolves' or 'cures' type 2 diabetes. Case series report this in up to 85% of individuals at 12 months. However, what is resolution of diabetes? There are many and varied definitions. Relatively subtle differences in these criteria can make a major difference to the supposed outcomes. Furthermore, case series are highly susceptible to selection bias, which usually overestimates an effect size. Therefore it is great to see some RCT data beyond 1–2 years emerging, and specifically in those with established diabetes preoperatively. There is no doubt that bariatric surgery has impressive benefits on weight and glycaemic control, but in this study it is clear that this is not the universal 'cure' that some would claim.

Reference: N Engl J Med 2014;370(21):2002–13
Abstract

National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations

Authors: Geller AI et al.

Summary: These researchers obtained nationwide data from EDs in US-based hospitals and a national household survey of insulin use to assess rates of ED visits and emergency hospitalisations among insulin-treated patients between 1 January 2007 and 31 December 2011. An estimated 97,648 ED visits occurred annually for insulin-related hypoglycaemia and errors, of which 60.6% documented severe neurological sequelae such as altered mental status and falls, 53.4% of cases recorded blood glucose levels of ≤50 mg/dL, and 29.3% of ED visits resulted in hospitalisation. Compared with insulin-treated patients aged 45–64 years, those aged ≥80 years were significantly more likely to require an ED visit (rate ratio 2.5 [95% CI 1.5, 4.3]) and be subsequently hospitalised (4.9 [2.6, 9.1]) for insulin-related hypoglycaemia and errors. Reduced food intake and administration of the wrong insulin product were the most commonly identified precipitating factors for ED visits.

Comment: Insulin safety is currently topical in NZ. We will all have horror stories of incidents in which an error in insulin prescription or administration has resulted in a significant hypoglycaemic event, or less commonly in hyperglycaemia or ketoacidosis. This study has attempted to quantify this in the US, although is likely to have underestimated the rates. Perhaps most notably, those at greatest risk of an error leading to an ED visit or hospitalisation were the elderly. There are multiple factors contributing to this, and it highlights the importance of careful consideration to appropriate Hb_{A1c} targets and safe insulin regimens in this age group. We are hoping that the Ministry of Health will support efforts to target insulin safety in NZ over the coming year.

Reference: JAMA Intern Med 2014;174(5):678–86
Abstract

Depression in adults in the T1D Exchange Clinic registry

Authors: Trief PM et al., for the T1D Exchange Clinic Network

Summary: Depression was explored in 6172 adults with type 1 diabetes who completed the eight-item PHQ-8 (Patient Health Questionnaire). The four definitions of probable major depression (PHQ-8 ≥10, PHQ-8 ≥12, per diagnostic algorithm and as a continuous variable) used returned rates of 4.6–10.3% of participants. Participants with depression were more likely to be female, nonwhite ethnicity, to have lower household income and education level, to exercise less often, to miss insulin doses and to have ≥1 complication ($p<0.01$ for all). Compared with participants without depression, those with depression had a significantly higher Hb_{A1c} level (68 vs. 62 mmol/mol [8.4% vs. 7.8%; $p<0.001$]) and higher rates of ≥1 diabetic ketoacidosis event (11% vs. 4% [$p<0.001$]) and ≥1 severe hypoglycaemic event (18% vs. 9% [$p<0.001$]) in the prior 3 months.

Comment: Depression is common in people with type 2 diabetes, but there are less data in those with type 1 diabetes. This observational study in adults with type 1 diabetes of long duration has confirmed a similar relationship. Furthermore, it showed that depression is also associated with worse outcomes. Rates of diabetes complications were higher, as were presentations with ketoacidosis and hypoglycaemia. As always, it is not possible to determine direction of causality in such observational studies, but it does remind us of the importance of considering depression in our patients – particularly if they are struggling to achieve their management goals.

Reference: Diabetes Care 2014;37(6):1563–72
Abstract

Evaluating the feasibility and impact of an internet-based lifestyle management program in a diabetes care setting

Authors: Sherifali D et al.

Summary: Patients with type 2 diabetes and BMI ≥30 kg/m² participated in an online lifestyle management programme for 1 year added to routine care in this single-arm cohort study; 49/78 enrolees contributed 1-year data. Mean reductions from baseline at 12 months were seen for Hb_{A1c} level (–0.3% [3 mmol/mol; $p<0.05$]), total/high-density lipoprotein cholesterol ratio (–0.2 [$p<0.05$]), bodyweight (–8.6lb [3.9kg; $p<0.05$]), BMI (–1.5 kg/m² [$p<0.05$]) and bodyfat (–1.8% [$p<0.05$]); changes for BMI, bodyfat percentage and self-reported daily steps were statistically significant after adjusting for programme use, age and sex.

Comment: Delivering interventions to promote healthier diet and exercise activities can be a challenge in the real world. There is no shortage of evidence-based interventions to choose from; however, engagement from consumers and cost-effective structures are often limiting factors. Therefore utilising an internet-based programme is an attractive option. Although this is not an RCT and the final data are only derived from two-thirds of the group, both of which raise significant design questions, the study shows that a virtual programme can work for some individuals to assist in improving diabetes care.

Reference: Diabetes Technol Ther 2014;16(6):358–62
Abstract

Discovery of biomarkers for glycaemic deterioration before and after the onset of type 2 diabetes

Authors: Koivula RW et al.

Summary: This paper reported the rationale and design of two prospective cohort epidemiological studies within the IMI DIRECT consortium. The study populations will be 2200–2700 patients with prediabetes and ~1000 with newly diagnosed type 2 diabetes who will undergo detailed metabolic phenotyping at baseline, 18 months and 36 months. Magnetic resonance imaging will be used to assess abdominal, pancreatic and liver fat levels, while frequently sampled oral glucose tolerance tests and mixed meal tolerance tests will be used to assess insulin secretion and action in participants without diabetes and those with type 2 diabetes, respectively. Venous blood, faecal urine and nail clippings will be sampled and characterised at genetic, transcriptomic, metabolomic, proteomic and metagenomic levels. High-resolution triaxial accelerometry, 24-hour diet records and food habit questionnaires will also be utilised to evaluate lifestyle factors.

Comment: Although we use one label, type 2 diabetes is clearly not one disorder. There are a range of phenotypes and probably an even greater range of pathogenic pathways to these phenotypes. Understanding these is critical to the future ability to really design and tailor our therapies to individuals. This bold project will help move us forward to that level of understanding. I look forward to seeing the outcomes from this project over the coming years. In NZ as part of the National Science Challenge, a similar project has been proposed, which if it goes ahead will align extremely well with this project and has the potential to contribute to the global understanding of diabetes. We have much to learn from the diverse ethnic differences in body composition and in associated insulin sensitivity and ß-cell function. This is an exciting area.

Reference: Diabetologia 2014;57(6):1132–42
Abstract