Diabetes & Obesity Research Review™

Making Education Easy

Issue 91 – 2015

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Abbreviations used in this issue

BMI = body mass index
CHF = congestive heart failure
CV = cardiovascular
GFR = glomerular filtration rate
HR = hazard ratio
RCT = randomised controlled trial
RR = risk ratio

Welcome to issue 91 of Diabetes and Obesity Research Review.

I have started this issue with an editorial published in the BMJ, which criticises the extent to which public health experts are involved with the food industry, and the impact this has on the obesity epidemic. One of several systematic review and meta-analyses included this month found that metformin and insulin for gestational diabetes mellitus were superior in terms of safety to mother and foetus than glibenclamide. A study of Scottish patients documented life expectancy reductions among patients with type 1 diabetes mellitus, while an analysis of data from DCCT (Diabetes Control and Complications Trial) participants who received intensive therapy during the trial had a modest reduction in all-cause mortality over long-term follow-up than those who received conventional treatment.

I hope you find this month's selection useful in your clinical practice, and I look forward to your questions and feedback.

Best regards,

Associate Professor Jeremy Krebs
jeremykrebs@researchreview.co.nz

Sugar: spinning a web of influence

Author: Gornall J

Summary: This editorial discussed an investigation by the BMJ that claimed to have *"uncovered evidence of the extraordinary extent to which key public health experts are involved with the sugar industry and related companies"* that produce products that receive much of the blame for the obesity epidemic, via research grants, consultancy fees and other funding. The paper outlined the role of industry money, commercial considerations, funding pressures and what it described as the 'illusion of self-regulation'.

Comment: I have included this editorial from the BMJ as I believe it is a piece of poor journalism published in a journal from which I would expect higher standards. The writer makes accusations of lack of independence of scientific evaluation and influence over government policy around nutrition and obesity when funding for the research is derived from the food industry. It implies that Prof Jebb, a highly respected and influential nutritionist in the UK, has been bought out by the food industry. Prof Jebb is a colleague and a friend, but this aside, this editorial is an unjustified personal attack. Readers who attended the NZSSD conference in Queenstown in 2014 may have heard Prof Jebb's evidence-based, balanced review of the existing literature around obesity and public health measures that could be employed to address this. It is true that some industry-funded research has limited utility because of restrictions on study design, patient selection, undue influence over data analysis or reporting, but none of these factors have been at play here. Prof Jebb receives a very small minority of her research funding from the food industry and is rigorous in maintaining scientific independence over study design, conduct interpretation and reporting. A more relevant point raised by the editorial relates to the decline of government funding of research, which is a worldwide phenomenon. Indeed governments are actively encouraging and promoting partnerships with industry. We cannot have our cake and eat it too. If this public-private model of research funding is to become the norm, then rather than be seen as a villain, Prof Jebb should be held up as a model of how to achieve this effectively whilst maintaining scientific rigour and integrity.

Reference: BMJ 2015;350:h231
Abstract

The effect of rate of weight loss on long-term weight management

Authors: Purcell K et al.

Summary: For phase 1 of this RCT, adults with BMI 30–45 kg/m^2 were randomised to a rapid (12-week; n=97) or gradual (36-week; n=103) bodyweight loss programme aimed at 15% bodyweight loss. Seventy-six and 51 participants from the respective rapid and gradual weight loss arms, who lost ≥12.5% of their bodyweight during phase 1, entered a bodyweight maintenance diet for 144 weeks in phase 2. Bodyweight regain at the end of phase 2 (primary outcome) was 70.5% and 71.2% in the (phase 1) rapid and gradual weight loss participants, respectively, among study completers, with similar percentages seen in the intent-to-treat population (76.3% in each group).

Comment: Most current weight loss recommendations focus on a 10% reduction over 6–12 months as a healthy approach. This is based on some evidence of greater loss of lean body mass with rapid weight loss and a belief that rapid weight loss has greater risk of subsequent weight regain. This well-conducted RCT refutes this latter belief. In those who achieved a minimum loss of 12.5% bodyweight, there was no difference in weight regain between rapid initial weight loss over 12 weeks and slower loss over 36 weeks. What is disappointing is the extent of weight regain in both groups over the almost 3-year follow-up, despite a maintenance programme and the involvement in a clinical trial. This highlights again that it is less about the initial weight loss method itself and more about finding effective ways to help people maintain the weight they have lost. Nonetheless, this useful study debunks a commonly held misbelief.

Reference: Lancet Diabetes Endocrinol 2014;2(12):954–62
Abstract

Type 2 diabetes and cancer

Authors: Tsilidis KK et al.

Summary: The risk of cancer associated with type 2 diabetes mellitus was explored in this umbrella review of meta-analyses of observational studies. All 27 eligible meta-analyses reported that patients with versus without diabetes had a higher risk of developing cancer, with the summary random effects estimates reaching statistical significance (p=0.05) in 20 meta-analyses. Seven meta-analyses including >1000 cases, reported a statistical significance for summary associations of p≤0.001 for both random and fixed effects calculations, and had neither evidence of small study effects nor evidence for excess significance. Furthermore, only six of these had an I^2 value >75% for heterogeneity, which pertained to associations between type 2 diabetes and risk of developing breast, colorectal, endometrial and gallbladder cancers and cholangiocarcinoma (intrahepatic and extrahepatic); the 95% prediction intervals excluded the null value for associations with breast, colorectal and endometrial cancers and intrahepatic cholangiocarcinoma.

Comment: The association between type 2 diabetes and various cancers has been topical in the last few years. There are biologically plausible reasons why obesity and type 2 diabetes may be related to cancer, including dietary composition and circulating hormonal and cytokine factors. However, this meta-analysis of observational studies points out the risks of over-interpreting these types of data and making assumptions of causality. Here the strength of some of the reported associations is questioned. Nevertheless there are still robust associations between diabetes and common and important cancers such as breast and bowel. The key question now is to establish the direction and mechanism for this and then interventions to modify this.

Reference: BMJ 2015;350:g7607
Abstract

Glibenclamide, metformin, and insulin for the treatment of gestational diabetes

Authors: Balsells M et al.

Summary: This was a systematic review and meta-analysis of 15 RCTs comparing glibenclamide or metformin with insulin or each other in a total of 2509 women with gestational diabetes. Compared with insulin, glibenclamide was associated with higher birthweight (mean difference 109g [95% CI 35.9, 181]) and higher risks of macrosomia (RR 2.62 [1.35, 5.08]) and neonatal hypoglycaemia (2.04 [1.30, 3.20]), and metformin was associated with less maternal bodyweight gain (mean difference –1.14kg [–2.22, –0.06]), earlier gestational age at delivery (–0.16 weeks [–0.30, –0.02]), an increased risk of preterm birth (RR 1.50 [1.04, 2.16]) and a trend for lower risk of neonatal hypoglycaemia (0.78 [0.60, 1.01]). Compared with glibenclamide, metformin was associated with less maternal weight gain (mean difference –2.06kg [95% CI –3.98, –0.14]) and birthweight (–209g [–314, –104]) and reduced risks of macrosomia (RR 0.33 [0.13, 0.81]) and a large-for-gestational-age neonate (0.44 [0.21, 0.92]). Metformin was associated with a higher treatment failure rate than glibenclamide.

Comment: Historically, the only option for the management of gestational diabetes if glucose levels were not adequately controlled by diet was insulin. As with so many treatments in pregnancy, this was predominantly due to lack of safety data for other agents. However, there is now a body of evidence for both sulphonylureas and metformin. NZ researchers have been at the forefront of trials with metformin. This meta-analysis of studies has shown a clear benefit of metformin and/or insulin over glibenclamide and reinforces current practice in NZ. With the increasing incidence of gestational diabetes creating a significant burden on health services, an effective and safe oral therapy is very important. This study provides further support for the use of metformin in gestational diabetes.

Reference: BMJ 2015;350:h102
Abstract

Metformin in patients with type 2 diabetes and kidney disease

Authors: Inzucchi SE et al.

Summary: These researchers systematically reviewed the evidence from 65 pharmacokinetic/metabolic studies, large case series, retrospective studies, meta-analyses or clinical trials pertaining to metformin, kidney disease and lactic acidosis. In patients with mild-to-moderate chronic kidney disease (estimated GFR 30–60 mL/min/1.73m^2), metformin concentrations generally remain within the therapeutic range and lactate levels are not substantially increased. The overall lactic acidosis incidence in metformin recipients varied across studies at ~3–10 per 100,000 person-years, which is generally indistinguishable from the background rate among all diabetics. There were limited data suggesting that metformin increases the risk of lactic acidosis in patients with chronic kidney disease, and no RCT has investigated the safety of metformin in patients with significantly impaired kidney function. Population-based studies have shown that metformin may be prescribed contrary to prevailing guidelines, which suggest renal risk in ≤25% of patients with type 2 diabetes; in the majority of reports, metformin did not increase lactic acidosis rates. Data from observational studies indicated that metformin had a potential benefit on macrovascular outcomes, even in patients with prevalent renal contraindications for its use.

Comment: Don't you love it when the Americans catch up to the rest of the world! Metformin has long been tainted by the experience of previous biguanides and risk of lactic acidosis. This delayed the approval for use of metformin in the US for many years and underpinned much tighter regulations for use in renal impairment. Consequently, many people with type 2 diabetes with mild degrees of renal impairment have been denied the benefits of metformin when guidelines were strictly followed. However, most of us in NZ have taken a more relaxed approach due to lack of compelling evidence of harm. This systematic review further supports this position. From these data it is reassuring to see that there is no significant increase in the risk of lactic acidosis purely related to renal function down to an estimated GFR of 30 mL/min/1.73m^2.

Reference: JAMA 2014;312(24):2668–75
Abstract

Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010

Authors: Livingstone SJ et al., for the Scottish Diabetes Research Network epidemiology group and the Scottish Renal Registry

Summary: Life expectancy associated with type 1 diabetes was prospectively investigated in all 24,691 individuals in Scotland aged ≥20 years registered as having the condition, providing a total of 67,712 person-years of follow-up during which 1043 deaths were recorded. Compared with nondiabetics, men and women with diabetes had estimated life expectancy losses of 11.1 and 12.9 years, respectively, and the respective values for patients with type 1 diabetes and an estimated GFR rate of ≥90 mL/min/1.73m^2 were 8.3 and 7.9 years. Ischaemic heart disease accounted for 36% and 31% of deaths in men and women, respectively, but death from diabetic coma or ketoacidosis was the greatest contributor in patients dying before age 50 years, accounting for 29.4% of male deaths and 21.7% of female deaths.

Comment: This is an important and rather alarming study. Historically type 1 diabetes has been associated with reduced life expectancy from multiple causes. However, post-DCCT evidence that tight glycaemic control reduces the risk of complications (see next study), and progressive improvement of insulin therapy, delivery devices including pumps and glucose monitoring systems all enabling tight glycaemic control, we would hope and expect that life expectancy would have improved. The results of this Scottish cohort study are therefore disappointing, demonstrating a persistent gulf between those with and without type 1 diabetes. The predominant cause of this is ischaemic heart disease, which raises an issue for which there remains a dearth of good evidence in this population. Most CV disease risk calculators are strongly weighted for age, yet most with type 1 diabetes are exposed to hyperglycaemia from a very young age and often have low-risk lipid profiles. More work is required to establish the best approach to CV disease risk reduction in this group.

Reference: JAMA 2015;313(1):37–44
Abstract

Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality

Authors: Writing Group for the DCCT/EDIC Research Group

Summary: These researchers compared mortality differences between recipients of intensive (n=711) versus conventional (n=730) treatment in the DCCT trial and EDIC follow-up study (during which intensive therapy was recommended for all participants). Among 1429 evaluable participants, 43 deaths were recorded in the intensive therapy arm, compared with 64 in the conventional therapy arm (HR 0.67 [95% CI 0.46, 0.99; p=0.045]). The main causes of death were CV disease (22.4%), cancer (19.6%), acute diabetes complications (17.8%) and accidents/suicides (16.8%). The risk of death from any cause was significantly increased by each 10% relative increase in Hb_{A1c} (glycosylated haemoglobin) level (HR 1.56 [95% CI 1.35, 1.81; p≤0.001]) and the development of albuminuria (2.20 [1.46, 3.31; p<0.001]).

Comment: The results of this study should be reviewed in parallel with those of the previous Scottish cohort study, which showed an important difference in life expectancy between those with type 1 diabetes and those without diabetes. In the present analysis of the long-term outcomes of an initial difference between groups in intensification of glycaemic control from the DCCT study, there is a persistent benefit of this tight control on all-cause mortality after almost 30 years. Most of the people included in the Scottish study would have benefitted from the findings of the DCCT trial and had advice and assistance to improve their glucose control. Therefore whilst the findings of the present analysis of DCCT patients further supports tight glycaemic control in type 1 diabetes, there is still an important gap in long-term outcomes compared with those without diabetes.

Reference: JAMA 2015;313(1):45–53
Abstract

Association between bariatric surgery and long-term survival

Authors: Arterburn DE et al.

Summary: These authors reported long-term survival outcomes for a retrospective cohort of 2500 patients who had undergone bariatric surgery (74% gastric bypass; 15% sleeve gastrectomy; 10% adjustable gastric banding; 1% other) compared with 7462 matched controls. The respective Kaplan-Meier estimated 1-, 5- and 10-year mortality rates were 2.4%, 6.4% and 13.8% among the surgical patients, and 1.7%, 10.4% and 23.9% among the control patients. Bariatric surgery did not decrease the risk of death from any cause during the first year (adjusted HR 1.28 [95% CI 0.98, 1.68]), but did at 1–5 years and 5–14 years (0.45 [0.36, 0.56] and 0.47 [0.39, 0.58], respectively), with no significant differences seen across diabetes diagnosis, sex and period of surgery subgroups.

Comment: There is increasing evidence to support the long-term benefits of bariatric surgery for those with obesity. The Swedish Obesity Study has provided the most compelling long-term data on mortality. This present study adds to these data from a retrospective cohort study. Allowing for the potential selection bias of retrospective matched controls, the difference in mortality with bariatric surgery, which becomes apparent after the first year, is very impressive with an almost 50% reduction out to 14 years postsurgery. Compared with many studies in the field, this study included predominantly men, further broadening the evidence base for the benefits of bariatric surgery. It is notable though that the mean BMI was 47 kg/m^2, and whether the same benefits are observed in those with lower BMIs who are increasingly getting surgery is unclear.

Reference: JAMA 2015;313(1):62–70
Abstract

Independent commentary by Associate Professor Jeremy Krebs, an endocrinologist with a particular interest in obesity and diabetes. He is an Associate Professor with the University of Otago, and Director of the Clinical Research Diploma at Victoria University. As well as clinical and teaching activities, Assoc Prof Krebs maintains active research interests in the area of obesity and diabetes, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery.

For full bio CLICK HERE.

Healthcare professional requirements for the care of adult diabetes patients managed with insulin pumps in Australia

Authors: Xu S et al., and the Australian National Adult Insulin Pump Therapy Working Group

Summary: This research sought to prospectively determine healthcare professional time spent caring for 895 patients (99% with type 1 diabetes) receiving insulin pump therapy at 24 Australian insulin pump therapy-experienced institutions. Data on 2577 healthcare professional-adult patient interactions (62% face-to-face, 29% remote and 9% administrative) collected over 12.2 ±6.4 weeks were evaluated. Nurses, dieticians and doctors respectively spent 5.4, 0.4 and 1.0 hours per week on insulin pump therapy interactions, with 20.4%, 4.6% and 2.7% of diabetes clinic time spent. Insulin pump therapy initiations accounted for 48% of the interaction time. Data from a subgroup of patients tracked from prepump to stabilisation over 11.8 ±4.5 weeks (n=15) showed that the required median times needed by nurses, dieticians and doctors were 9.2, 2.4 and 1.8 hours per patient, respectively.

Comment: There is no question that insulin pumps provide an excellent tool for many with type 1 diabetes to facilitate good glycaemic control and quality of life. However, the time investment for both the individual and healthcare professionals at the initiation of pump therapy is significant. This Australian study quantified this time for nurses, dieticians and doctors. In NZ, the number of people benefiting from pump therapy expanded rapidly after PHARMAC put in place funding for pumps and consumables for selected patients. However, this does not cover the time for health professionals. The increase in time required for pump initiation and stabilisation has become an increasing stress on specialist diabetes services to deliver within already tight budgets. This study provides a useful reference point for the staff hours required.

Reference: Intern Med J 2015;45(1):86–93
Abstract

Incretin-based drugs and the risk of congestive heart failure

Authors: Yu OHY et al.

Summary: These researchers used data from the UK Clinical Practice Research Datalink linked to the Hospital Episode Statistics database to examine the impact of incretin-based drugs (GLP [glucagon-like peptide]-1 analogues and DPP [dipeptidyl peptidase]-4 inhibitors) on the risk of CHF in a cohort of 57,373 patients with type 2 diabetes. There were 1118 incident cases of hospitalisation for CHF recorded over a mean 2.4 years of follow-up among the participants, with each case matched to ≤20 controls. No association was seen between current incretin-based drug use and increased CHF risk (adjusted odds ratio 0.85 [95% CI 0.62, 1.16]), and secondary analyses showed no duration-response relationship (p=0.39 for trend).

Comment: It is important that any new class of antidiabetes medication not only effectively reduces blood glucose levels, but that they also have a safe CV risk profile, and ideally additional CV risk reduction. The US FDA requires long-term CV outcome studies for full approval, but even with such requirements in place, it is often not until drugs are widely used in a clinical setting, rather than a highly selected clinical trial setting, that the full spectrum of the side effect profile becomes apparent. This study is 'real-world' experience of GLP-1 and DPP-4 antagonist agents in those with type 2 diabetes in the UK. Compared with multiple matched control patients, the incretin therapies were not associated with increased risks of CHF. This is reassuring, but we also need more extensive data on myocardial infarction, stroke and revascularisation procedures.

Reference: Diabetes Care 2015;38(2):277–84
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.