Diabetes & Obesity Research Review™

Making Education Easy

Issue 127 – 2019

In this issue:

Abbreviations used in this issue

BMI = body mass index
CGM = continuous glucose monitoring
CSII = continuous subcutaneous insulin infusion
CV = cardiovascular
HbA_{1c} = glycosylated haemoglobin
LGA = large for gestational age
MDI = multiple daily injection
SGLT = sodium glucose cotransporter

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Welcome to issue 127 of Diabetes and Obesity Research Review.

A study from the BMJ focussing on the effects of varying dietary carbohydrate content on total energy expenditure during weight loss begins this issue. This issue also includes helpful papers on: i) the interconnectivity of various biomarkers associated with the aetiology of diabetes; ii) the role of cognitive skills like executive functioning during the transition from parental- and healthcare provider-guided type 1 diabetes management to self-management in young patients; iii) ways to improve attendance at structured diabetes education programmes for type 2 diabetes; and iv) the prevalences of a range of autoimmune diseases among patients with type 1 diabetes.

I hope you enjoy this issue and, as always, I invite you to send me your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance

Authors: Ebbeling CB et al.

Summary: Adults with a BMI of ≥25 kg/m^2 were randomised to an energy-adjusted diet with a high (60%; n=54), moderate (40%; n=53) or low (20%; n=57) carbohydrate content for 20 weeks in this trial. A significant difference was seen for total energy expenditure according to diet (p=0.002), with a linear trend of 52 kcal/day for every 10% decrease in total energy intake due to carbohydrates. Compared with the high carbohydrate diet, consumption of the low and moderate carbohydrate diets was associated with increases in total energy expenditure of 91 and 209 kcal/day, respectively, in an intent-to-treat analysis; the respective values in a per-protocol analysis were 131 and 278 kcal/day. For the third of participants with the greatest insulin secretion before weight loss, the differences between those from the low and high carbohydrate diet groups were 308 and 478 kcal/day in the intent-to-treat and per-protocol analyses, respectively. Compared with the high carbohydrate group, the low carbohydrate group had significantly lower ghrelin levels in both analyses and a significantly lower leptin level in the per-protocol analysis.

Comment: We are in a phase of a focus on proportion of carbohydrate in the diet again. There seems to be a cycle of popular and scientific interest in dietary macronutrient composition. Deciphering the literature is difficult because any restriction in the proportion of one macronutrient necessarily must be accompanied by a reciprocal increase in the proportion of another, and often by the reduction in total energy intake. Therefore, determining which manipulation is responsible for any measured changes in weight or metabolic factors is extremely hard. This weight maintenance study seeks to test whether reduced carbohydrate intake contributes to differences in energy expenditure. The findings suggest that compared with a diet of 60% carbohydrate, consuming 20% carbohydrate is associated with an increase in energy expenditure and an almost 500 kcal difference in total energy per day in some people. This may be a useful strategy for some obese insulin-resistant individuals, but only if they can stick with it. As always with restriction to carbohydrate, caution needs to be expressed for reduction in fibre and some micronutrients.

Reference: BMJ 2018;363:k4583
Abstract

Independent commentary by Professor Jeremy Krebs.

Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He trained in Endocrinology at Wellington Hospital in New Zealand and then did his doctorate with the Medical Research Council - Human Nutrition Research unit in Cambridge England. His thesis was on the impact of dietary factors on obesity and insulin resistance. Professor Krebs returned to New Zealand in 2002 to take up a consultant Endocrinology post at Wellington Hospital, where he was Clinical Leader of Endocrinology and Diabetes. He heads the research group and is Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established.

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Effect of lorcaserin on prevention and remission of type 2 diabetes in overweight and obese patients (CAMELLIA-TIMI 61)

Authors: Bohula EA et al., for the CAMELLIA-TIMI 61 Steering Committee Investigators

Summary: Individuals with a BMI of ≥27 kg/m^2 who had, or were at high risk for, atherosclerotic vascular disease, and who had access to a standardised weight management programme based on lifestyle modification, were randomised to receive lorcaserin 10mg (n=6000) or placebo (n=6000) twice daily. The numbers of participants with diabetes, prediabetes and normoglycaemia at baseline were 6816, 3991 and 1193. There were significant net losses in bodyweight at 1 year for lorcaserin recipients with diabetes, prediabetes and normoglycaemia of 2.6, 2.8 and 3.3kg, respectively. Among participants with prediabetes and those without diabetes, lorcaserin was associated with significantly lower incident diabetes rates (8.5% vs. 10.3%; hazard ratio 0.81 [95% CI 0.66, 0.99] and 6.7% vs. 8.4%; 0.77 [0.63, 0.94], respectively), and among participants with prediabetes, lorcaserin was associated with a nonsignificant increase in the rate achieving normoglycaemia (9.2% vs. 7.6%; 1.20 [0.97, 1.49]). Compared with placebo, lorcaserin was also associated with a 0.33% reduction in HbA_{1c} level at 1 year in participants with diabetes, but a higher rate of severe hypoglycaemic events with serious complications (0.4% vs. 0.1% [p=0.054]).

Comment: I really only have one comment for this study – please see the Diabetes Prevention Study and Diabetes Prevention Program. In both of these studies, intensive diet and lifestyle modification reduced the progression of prediabetes to diabetes by 67%. Compare this with the 19% reduction in this study with the use of an expensive medication, or with the 33% risk reduction observed with metformin in the DPP study. This was a very large study in 12,000 people, so we can be confident that we have a pretty accurate effect size. Yes lorcaserin is effective, and yes it could be a useful addition to the treatment toolbox, but diet and lifestyle remain more effective in prediabetes. The Direct study has also shown efficacy in reversing diabetes with diet in established type 2 diabetes.

Reference: Lancet 2018;392:2269–79
Abstract

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes

Authors: Zelniker TA et al.

Summary: This systematic review and meta-analysis examined the effect of SGLT-2 inhibitors on CV and renal outcomes in patients with type 2 diabetes. Three randomised, placebo-controlled trials of SGLT-2 inhibitors in patients with type 2 diabetes (n=34,322) were included. SGLT-2 inhibitors were found to reduce major adverse CV events by 11% (p=0.0014), with benefit only seen in patients with atherosclerotic CV disease and not in those without it. SGLT-2 inhibitors also reduced the risk of CV-related death or hospitalisation for heart failure by 23% (p<0.0001), with similar benefits in patients with and without atherosclerotic CV disease as well as those with and without a history of heart failure. The risk of progression of renal disease was also reduced with SGLT-2 inhibitor use by 45% (p<0.0001), with similar benefits in those with and without atherosclerotic CV disease.

Comment: The new consensus guideline from the ADA and EASD released in October last year has brought a focus of discussion about the place of the SGLT-2 inhibitor class in the management of type 2 diabetes in NZ. PHARMAC, quite rightly, have an evidence-based approach to assessing whether to fund new medicines. This new meta-analysis of data from over 30,000 people in combined CV outcome trials provides plenty of evidence to underpin an urgent call to review funding of this class of drugs. Along with the consensus guideline, it is clear that there are very significant benefits on CV events, hospitalisation for heart failure and progression of renal disease in subgroups of patients, who could all be selected for with special authority criteria. Surely it is time to act.

Reference: Lancet 2019;393:31–9
Abstract

High diabetes prevalence and insulin medication errors in hospital patients

Authors: Taylor JE et al.

Summary: Three surveys of inpatient clinical records undertaken for single days in November in 2013, 2014 and 2016 found diabetes prevalences of 19.7–25.3%. Among inpatients with diabetes, 63.4–76% had type 2 diabetes. The respective rates of diabetes diagnoses during hospital admission in 2013, 2014 and 2016 were 21%, 12% and 22.6%, with 41.8%, 46.7% and 51.6% requiring insulin. Based on their data, the authors recommend active detection and specialist management of diabetes during hospital admission.

Comment: As the prevalence of diabetes increases in the population, it is not surprising that the proportion of people admitted to hospital with diabetes as one of their conditions increases too. Diabetes is an important comorbidity that has been shown to influence length of stay and outcome in numerous studies. This study presents data from Australia, which is useful for us here in NZ as our health system is similar enough to be able to make some inference to what is happening here also. One important observation was the high rate of those requiring insulin therapy during admission. This is particularly important, since there are significant risks associated with insulin use in hospital, with frequent errors in prescription and administration. These data underpin the importance of a review of inpatient diabetes management in NZ and call for a standardised approach and specific resources allocated to specialist teams.

Reference: Intern Med J 2018;48:1529–32
Abstract

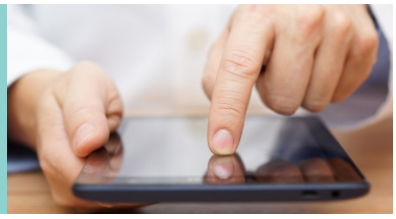
A network analysis of biomarkers for type 2 diabetes

Authors: Huang T et al.

Summary: Data from 1303 women with incident diabetes and 1627 healthy controls from an existing study nested in the Nurses' Health Study were used for this network analysis of 27 plasma biomarkers representing glucose metabolism, inflammation, adipokines, endothelial dysfunction, insulin-like growth factor axis and iron stores. A correlation network constructed on pairwise correlations of factors that differed significantly between case and control subjects revealed that although there was a tendency towards similar directions comparing case and control subjects, most correlations were stronger in controls than in case subjects, particularly insulin/HbA_{1c} and leptin/adiponectin level correlations. Two hubs in the network were leptin and soluble leptin receptor, with large numbers of different correlations with other biomarkers in case versus control subjects. When the correlation network was analysed according to timing of diabetes onset, more perturbations were seen for case subjects diagnosed >10 vs. <5 years after blood collection, with consistent differential correlations of insulin and HbA_{1c} levels. The most highly connected node in the early-stage network was C-peptide level, whereas leptin level was the hub for mid- and late-stage networks.

Comment: The more we learn, the less we know. I have recently been teaching medical students and pointed out that the fundamental problem in type 2 diabetes is a mismatch between insulin production and insulin sensitivity or demand. However, understanding the complexities underlying the development of this mismatch remains elusive. We continue to learn more about some of the pathways leading to the development of insulin resistance and about disturbances in β-cell response, with an ever-increasing realisation that type 2 diabetes is very heterogeneous, with similar shared common expression of hyperglycaemia. This is an interesting paper that tries to connect the associations of all the inter-related markers of the disease, reinforcing the slow evolution over many years. It also presents the adipose-derived hormone leptin as a key player in linking aetiological parameters. This is very interesting from an academic perspective, if not directly influencing clinical practice.

Reference: Diabetes 2019;68:281–90
Abstract



Youth with type 1 diabetes taking responsibility for self-management: the importance of executive functioning in achieving glycemic control

Authors: Vloemans AF et al.

Summary: This paper reported results from the longitudinal DINO study, in which parents of 174 youth with type 1 diabetes completed yearly assessments over a 4-year period. HbA_{1c} levels were extracted from hospital charts, and the youths' executive functioning and diabetes responsibility were evaluated with parent-reported Behaviour Rating Inventory of Executive Functioning and Diabetes Family Responsibility Questionnaire scores. A significant association was seen between more executive functioning problems and higher HbA_{1c} levels over time, and more executive functioning problems combined with less youth responsibility or with more parental responsibility were significantly associated with better glycaemic control over time. The only significant moderator of the relationships among executive functioning problems, shared responsibility and glycaemic control was age.

Comment: Transition of care for young people with type 1 diabetes from intensive parental input and healthcare professional oversight to the young person themselves taking responsibility for their own care and outcomes is a difficult period, with many challenges for all concerned. This study highlights that executive function, the ability to concentrate on a task, flexibility of thought, reasoning and problem solving, have a significant impact on the success of this transition. The good news is that to some extent these functions develop and mature over time. Whilst this is intuitive, it is helpful to remember that the timing for encouraging and facilitating transition needs to be flexible and individualised to achieve the best outcome. This is something my paediatric colleagues are experts in doing. Unfortunately, despite this there are still some, usually males in my experience, who never quite get there until much later!

Reference: Diabetes Care 2019;42:225–31
Abstract

Glycemic outcomes with early initiation of continuous glucose monitoring system in recently diagnosed patients with type 1 diabetes

Authors: Mulinacci G et al.

Summary: These researchers reported differences in mean HbA_{1c} level and diabetes-related emergency visits over a 2.5-year period for early CGM users versus non-CGM users among 396 patients with newly diagnosed type 1 diabetes (94% aged <18 years). Compared with non-CGM users, CGM users had significantly better glycaemic control at 1, 1.5, 2 and 2.5 years, irrespective of insulin delivery methods. At 2.5 years, HbA_{1c} levels were significantly lower for: i) patients using both CGM and MDIs compared with MDIs only (7.7% vs. 9.2% [p<0.0001]); ii) patients using both CGM and CSIIs compared with CSIIs only (8.0% vs. 8.7% [p<0.0001]); and iii) patients using both CGM and MDIs compared with CSIIs only (7.7% vs. 8.7% [p<0.0001]). Early CGM users had significantly fewer emergency department visits for severe hypoglycaemia or hyperglycaemia than non-CGM users.

Comment: We are in the age of technology with devices touching all aspects of our lives. In diabetes, the greatest advances for type 1 diabetes in the last 10 years have been in technologies to support insulin therapy and self-management. Although finger-prick capillary glucose monitoring is a quantum ahead of urine dipstick testing, there are still significant barriers to its use and limitations of its impact on management, even when done frequently. CGM of interstitial fluid with subcutaneous devices has now become reliable and more affordable. They remove barriers to testing and provide data at times that are difficult to monitor, such as overnight. Together these benefits increase information for people with diabetes to base insulin dosing decisions on and translate to better glycaemic outcomes. This is seen in this study of the use of CGM in people within the first year of diagnosis, with around 11 mmol/mol differences in HbA_{1c} level to standard monitoring. Let's hope that this evidence can be used to persuade PHARMAC to fund CGM for people with type 1 diabetes.

Reference: Diabetes Technol Ther 2019;21:6–10
Abstract

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Barriers and facilitators to attendance at type 2 diabetes structured education programmes

Authors: Mc Sharry J et al.

Summary: The experiences of structured type 2 diabetes education programme attendees in Ireland were reported, along with barriers and facilitators to attendance, in this qualitative study. Data were obtained from semi-structured telephone interviews. Responses from 12 programme attendees and 14 educators identified two themes related to experiences of programme attendance and delivery, namely 'structured education: addressing an unmet need' and 'the problem of non-attendance'. A third theme 'Barriers to attendance: can't go, won't go, don't know and poor system flow' outlined the impact on attendance of practicalities of attending, lack of knowledge of existence and benefits, and limited resources and support for education within the diabetes care pathway. A fourth theme 'supporting attendance: healthcare professionals and the diabetes care pathway' described facilitators of participant attendance and strategies that educators perceived to be important for improving attendance.

Comment: Structured diabetes self-management education is widely accepted as an important part of diabetes care. There are many programmes, some with a good evidence base and others rather *ad hoc* and developed locally out of perceived need. The evidence from randomised controlled trials is for benefit across a range of domains including glycaemic control, but also diabetes-related behaviours such as foot checks, lifestyle choices, etc. However, despite this, it is common for locally delivered programmes to be poorly attended. This qualitative study looks at some of the potential reasons for this. It identifies barriers to attendance and potential enablers, including the role of the healthcare professional in promoting the programme, which I suspect we all feel we do already. Therefore, new ways to achieve this are required.

Reference: Diabet Med 2019;36:70–9
Abstract

Association between maternal diabetes, being large for gestational age and breast-feeding on being overweight or obese in childhood

Authors: Kaul P et al.

Summary: This research analysed data from 5926 children who were LGA (large for gestational age) and born to mothers without diabetes, 4563 who were appropriate size for gestational age and born to mothers with gestational diabetes, 573 who were LGA and born to mothers with gestational diabetes, 480 who were appropriate size for gestational age and born to mothers with pre-existing diabetes, 178 who were LGA and born to mothers with pre-existing diabetes and 69,506 control children who were appropriate size for gestational age and born to mothers without diabetes. Compared with controls, a greater proportion of children in the LGA/gestational diabetes group were overweight or obese by preschool age (42.9% vs. 20.5%). The adjusted attributable risk percentage for being LGA alone was higher than for maternal gestational diabetes and pre-existing diabetes alone (39.4% vs. 16.0% and 15.1%, respectively), and the respective risks associated with the combinations of gestational diabetes/LGA and pre-existing diabetes/LGA were 50.1% and 39.1%. Stratification by pre-existing diabetes type found that the respective prevalences of being overweight or obese in the type 1 diabetes group who were of appropriate size and LGA were 21.2% and 31.4%, and these values were 26.7% and 42.5% for these two respective size for gestational age groups born to mothers with type 2 diabetes. The likelihood of being overweight or obese in childhood was lowered by breastfeeding across all groups with the exception of LGA children born to mothers with gestational diabetes or pre-existing type 1 or 2 diabetes.

Comment: The association between maternal weight, pregnancies affected by diabetes, birthweight and subsequent risk of obesity or diabetes in the offspring is a hot topic and remains controversial – at least which of these parameters has the dominant effect, and then whether modification of them prior to or during pregnancy makes a difference. This large observational cohort study provides some useful insights. Being LGA trumped diabetes during pregnancy, either pre-existing or gestational, as the strongest predictor of obesity at age 4–6 years. Having diabetes was independent and additive to that risk, and breastfeeding was protective. All this is useful information, but it doesn't tell us how to prevent LGA babies – particularly in women who do not have diabetes.

Reference: Diabetologia 2019;62:249–58
Abstract

Associated auto-immune disease in type 1 diabetes patients

Authors: Nederstigt C et al.

Summary: This systematic review and meta-analysis included 180 papers reporting prevalences of autoimmune diseases in cohorts of patients with type 1 diabetes (n=293,889). Autoimmune disease prevalences included 9.8% for hypothyroidism (data from 65 studies), with each 10-year increase in age associated with a 4.6% increased prevalence (54 studies), 4.5% for coeliac disease (87 studies), 4.3% for gastric autoimmunity (eight studies), 2.4% for vitiligo (14 studies), 1.3% for hyperthyroidism (45 studies) and 0.2% for adrenal insufficiency (14 studies). Statistical heterogeneity among studies was high for all analyses.

Comment: The genetic predisposition to autoimmune diseases means that some individuals may develop more than one condition during their life. Patients, parents and families of those with type 1 diabetes are often interested to know what their risk is, and as their healthcare team we want to also know whether it is appropriate to screen individuals for these conditions. This very useful systematic review provides very helpful data to inform that discussion. As we would predict, hypothyroidism is the most common associated autoimmune disease at almost 10%. Both coeliac disease and pernicious anaemia were also relatively common at 5%, but adrenal insufficiency was rare at only 0.2%. This would support the common practice of screening for thyroid dysfunction and low threshold for coeliac disease, but not for screening for Addison's disease – even when people helpfully tell us they have adrenal fatigue! These data are very helpful to carry around in our head to inform our patients.

Reference: Eur J Endocrinol 2019;180:135–44
Abstract