Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 140 – 2020

In this issue:

Abbreviations used in this issue
AUC = area under the curve
BMI = body mass index
CV = cardiovascular
DPP = dipeptidyl peptidase
GFR = glomerular filtration rate
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
HDL = high-density lipoprotein
HR = hazard ratio
RCT = randomised controlled trial
SGLT = sodium glucose cotransporter

Welcome to issue 140 of Diabetes and Obesity Research Review.

This issue begins with research reporting that bariatric surgery prolongs life expectancy when compared with usual obesity care, but still falls short when compared with the general population. More benefits associated with metformin use have been reported in the form of reduced cognitive decline and dementia among ageing individuals receiving the agent for type 2 diabetes. Other included research found that compared with DPP-4 inhibitors or sulfonylureas, SGLT-2 inhibitors and GLP-1 receptor agonists for type 2 diabetes were associated with better renal outcomes. There is also research linking loneliness with an increased incidence of type 2 diabetes, independently of other factors including depressive symptoms, living alone and social isolation.

We hope you enjoy this update in diabetes and obesity research. We look forward to your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Life expectancy after bariatric surgery in the Swedish Obese Subjects study

Authors: Carlsson LMS et al.

Summary: Mortality and life expectancy were compared between obese patients who had undergone bariatric surgery (n=2007) versus those who had received usual care (n=2040) and a reference cohort from the general population of Sweden (n=1135); the median follow-up periods of the three groups were 20–24 years. Compared with the usual care cohort, the surgery cohort had a lower mortality rate (22.8% vs. 26.4%; HR 0.77 [95% CI 0.68, 0.87]), including death from CV disease and cancer (respective HRs 0.70 [0.57, 0.85] and 0.77 [0.61, 0.96]). Adjusted mean life expectancy was 3.3 years longer in the surgery group when compared with the usual care group, but 5.5 years shorter when compared with the general population. In the surgery group, the 90-day postoperative mortality rate was 0.2%, and 2.9% required repeat surgery.

Comment: The SOS (Swedish Obesity Study) has given us rich data on the effects of bariatric surgery in obesity. Although not an RCT, which is very important to remember, the strength of the study is the long-term follow-up and a comparator group of individuals with obesity who did not undergo surgery. In this very long-term report on mortality, the researchers have also used a comparator group from the general population. Bariatric surgery in obese individuals reduced premature mortality by 23%, which translates to approximately 3 more years of life. This is not only from CV disease, but also from cancers. However, obese individuals who have undergone bariatric surgery still have shorter life expectancy than the general population. It is also important to remember that the range of bariatric procedures utilised in the SOS differs to those most commonly used now. Therefore it can't be assumed or directly translated to our advice to patients that the current most common procedure, the gastric sleeve, will have the same benefits.

Reference: N Engl J Med 2020;383:1535–43
Abstract

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Dapagliflozin in patients with chronic kidney disease

Authors: Heerspink HJL et al., for the DAPA-CKD Trial Committees and Investigators

Summary: The DAPA-CKD trial randomised 4304 patients with an estimated GFR of 25–75 mL/min/1.73m^2 and a urinary albumin-to-creatinine ratio of 200–5000 to receive dapagliflozin or placebo. Compared with placebo, a significantly smaller proportion of dapagliflozin recipients experienced a primary endpoint event (≥50% decline in estimated GFR, end-stage kidney disease or CV-related death (9.2% vs. 14.5%; HR 0.61 [95% CI 0.51, 0.72]; NNT to prevent one primary endpoint event, 19). Dapagliflozin recipients also had lower likelihoods than placebo recipients of: i) a composite of sustained decline in estimated GFR of ≥50%, end-stage kidney disease and death from renal causes (HR 0.56 [0.45, 0.68]); ii) a composite of death from CV causes and hospitalisation for heart failure (0.71 [0.55, 0.92]); and iii) death from any cause (0.69 [0.53, 0.88]). Dapagliflozin had similar effects in participants with and without type 2 diabetes, and its safety profile was consistent with known data.

Comment: The evidence for the renal protective effects of the SGLT-2 inhibitors continues to grow. This trial of dapagliflozin in people with renal impairment showed major benefits in reducing decline of renal function, but also CV events, hospitalisation for heart failure and death. Two important features of this trial are that the benefits were seen in those with and without diabetes, again showing that the effects are independent of the glucose-lowering effects of the class. Furthermore, the trial included people with an estimated GFR down as low as 25 mL/min/1.73m^2. It is increasingly clear that these renoprotective and cardioprotective effects of the SGLT-2 inhibitor agents are a class effect, and that they are probably the more important effects over and above the glucose-lowering actions. I can only beg that the ongoing deliberations over special authority criteria do not further delay the access to these agents for those who can easily be identified as likely to benefit the most.

Reference: N Engl J Med 2020;383:1436–46
Abstract

Metformin use is associated with slowed cognitive decline and reduced incident dementia in older adults with type 2 diabetes

Authors: Samaras K et al.

Summary: Relationships between metformin use and incident dementia and cognitive decline were explored in 1037 participants from the Sydney Memory and Ageing study, 123 of whom had diabetes and 67 of whom were metformin recipients. Compared with metformin nonrecipients with diabetes, metformin recipients with diabetes exhibited significantly slower global cognition and executive function decline, with the metformin nonrecipients having a significantly greater likelihood of incident dementia (odds ratio 5.29 [95% CI 1.17, 23.88]).

Comment: There have been mixed reports on the effects of metformin on risk for dementia. This well-conducted large observational study of factors associated with the risk of developing dementia sheds some light on this. Those older adults with diabetes who were receiving metformin were 5-fold less likely to develop dementia over a 6-year period than those not on metformin. Of course, this result could be confounded by many other factors that influence metformin prescribing, but it is a very strong observation. An RCT is now required before metformin is put in the drinking water!

Reference: Diabetes Care 2020;43:2691–701
Abstract

For more information, please go to www.medsafe.govt.nz

A shift toward a plant-centered diet from young to middle adulthood and subsequent risk of type 2 diabetes and weight gain

Authors: Choi Y et al.

Summary: Associations between change in plant-centred diet quality and type 2 diabetes risk and change in body size were explored in this analysis of data from the prospective CARDIA study of US adults followed over a 30-year period. Over mean follow-up of 9.3 years, 206 individuals with incident diabetes were recorded. The risk of incident diabetes over 10 years was reduced by 48% for individuals with the greatest increases in APDQS (*A Priori* Diet Quality Score; higher scores favour nutritionally rich plant foods) over 20 years ($p<0.001$ for trend) compared with individuals whose scores remained stable. Each standard deviation incremental increase in APDQS over 20 years was significantly associated with lower increases in BMI (–0.39 kg/m^2 [$p=0.004$]), waist circumference (–0.90cm [$p<0.001$]) and bodyweight (–1.14kg [$p<0.001$]) during the same period, but not with subsequent changes.

Comment: There is increasing interest in reducing animal-based protein consumption, partly driven by climate change observations and partly by health. This paper reports an analysis of the CARDIA study, which is a long-term prospective observational study of the risk of developing CV disease in young adults, which started in 1985. Here the authors report data on dietary pattern over the first 20 years and the subsequent risk of developing diabetes in the following 10 years. Dietary data were recorded in a manner to enable a classification of plant-based foods. Those who increased their plant-based food consumption over the first 20 years were less likely to gain weight and less likely to develop diabetes compared with those who stayed the same or reduced intake. These data support the need to specifically test this idea in an RCT.

Reference: Diabetes Care 2020;43:2796–803
Abstract

Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of kidney outcomes

Authors: Xie Y et al.

Summary: Renal outcomes over 3 years were compared for US veterans starting SGLT-2 inhibitor (n=18,544), GLP-1 receptor agonist (n=23,711), DPP-4 inhibitor (n=39,399) or sulfonylurea (n=134,904) therapy. Compared with sulfonylureas, SGLT-2 inhibitors, GLP-1 agonists and DPP-4 inhibitors were associated with lower risks for a composite outcome of estimated GFR decline >50%, end-stage kidney disease or all-cause mortality (respective HRs 0.68 [95% CI 0.63, 0.74], 0.72 [0.67, 0.77] and 0.90 [0.86, 0.95]), with no significant difference between SGLT-2 inhibitors and GLP-1 agonists, but lower risks with SGLT-2 inhibitors and GLP-1 agonists compared with DPP-4 inhibitors (0.76 [0.70, 0.82] and 0.79 [0.74, 0.85], respectively). SGLT-2 inhibitors and GLP-1 agonists appeared to be associated with lower risks of the composite outcome than sulfonylureas across estimated GFR categories, including <45 mL/min/1.73m^2. Compared with DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists were associated with a reduced risk of the composite outcome for the estimated GFR categories of <45, 45–<60 and 60–<90 mL/min/1.73m^2.

Comment: It must seem that it's all I can talk about at the moment, but here is another study providing support for the use of SGLT-2 inhibitors and GLP-1 agonists. I have previously included several recent large RCTs of these agents in people with diabetic nephropathy showing reduced risk of progression to end-stage renal failure and dialysis. This study is a nonrandomised real-world report of the comparison between common diabetes drugs in a very large population sample. It has all the inherent possible biases of such a study, but shows similar magnitude of benefits for SGLT-2 inhibitors and GLP-1 agonists to the RCTs, which is important in the translation of the tightly controlled clinical trial environment into clinical practice. More evidence to underpin the importance of funded access for these drugs in NZ.

Reference: Diabetes Care 2020;43:2859–69
Abstract

Effects of low-fat, Mediterranean, or low-carbohydrate weight loss diets on serum urate and cardiometabolic risk factors

Authors: Yokose C et al.

Summary: This secondary analysis of the DIRECT trial explored the effects of weight loss diets on serum urate levels and cardiometabolic risk factors. The trial had randomly assigned moderately obese individuals to a low-fat, restricted-calorie diet (n=85), a Mediterranean, restricted-calorie diet (n=76) or a low-carbohydrate, nonrestricted-calorie diet (n=74). Average serum urate level decreases of 48 and 18 µmol/L were recorded at 6 months and 24 months, respectively, with no between-group differences. All three groups also experienced significant improvements in bodyweight, HDL cholesterol level, total cholesterol-HDL cholesterol ratio, triglyceride level and insulin level at 6 months. Changes in bodyweight and fasting plasma insulin level remained significantly associated with serum urate level changes after adjusting for covariates. Significant serum urate level reductions were seen in participants with hyperuricaemia from the respective low-fat, Mediterranean and low-carbohydrate diets (113, 119 and 143 µmol/L at 6 months and 65, 77 and 83 µmol/L at 24 months), with no significant between-group differences.

Comment: Gout is a common condition in NZ, particularly for Māori. It is linked with type 2 diabetes and shares the risk factors of obesity and insulin resistance. Therefore it is important to know what effect dietary recommendations designed to reduce weight and/or prevent and manage type 2 diabetes have on serum urate levels and risk for gout. One such dietary pattern is a low-carbohydrate diet, which often results in increased protein and fat consumption, which theoretically could worsen urate level. This secondary analysis of the DIRECT study (not the one from Roy Taylor's group in the UK) compared three diets that could all increase urate level depending on the actual consumed protein content. Importantly, when the diet facilitated weight loss and improved insulin resistance, there was actually a lowering of urate level and therefore a reduced risk for gout.

Reference: Diabetes Care 2020;43:2812–20
Abstract

Impact of daily physical activity as measured by commonly available wearables on mealtime glucose control in type 1 diabetes

Authors: Ozaslan B et al.

Summary: The relationship between physical activity measured by an off-the-shelf activity tracker and postprandial blood glucose control was explored in this retrospective analysis of data from 37 participants with type 1 diabetes and 845 days of data from two clinical studies. Significant negative relationships were seen between postmeal glucose level AUC and both total daily step count and total time spent performing higher than light-intensity physical activity. Individuals with higher median total daily physical activity had significantly lower average postprandial glucose level AUCs. Additional analyses revealed that daily physical activity is likely to have both immediate and delayed effects on glucose level control.

Comment: This is something we and our patients all observe commonly. The impact of being physically active, as opposed to structured physical exercise, on blood glucose control can be a difficult factor to manage. This is particularly true if it varies considerably day-to-day. This is a nice little study to demonstrate this and quantify the effect, using a wearable device to measure activity. These are increasingly common and can be very helpful for people to monitor their activity levels, but the standard ones do have significant limitations in accuracy. Nonetheless, the study showed that greater activity was associated with lower postprandial glucose excursion after the evening meal. Therefore, this should be taken into account when individuals with type 1 diabetes make decisions about their bolus insulin to avoid hypoglycaemia. It is likely that the same, if not a greater effect, would be true in those with type 2 diabetes.

Reference: Diabetes Technol Ther 2020;22:742–8
Abstract

Association of early-onset diabetes, prediabetes and early glycaemic recovery with the risk of all-cause and cardiovascular mortality

Authors: Kim SM et al.

Summary: The impact of early-onset diabetes, prediabetes and glycaemic recovery on CV disease and mortality was explored in a longitudinal cohort of 2,502,375 Koreans aged 20–39 years without diabetes mellitus or CV disease at baseline. Individuals with normal baseline fasting glucose levels who subsequently developed diabetes or prediabetes were at increased risk of death from any cause (respective HRs 1.60 [95% CI 1.44, 1.78] and 1.13 [1.09, 1.18]) and CV disease (1.13 [1.05, 1.23] and 1.04 [1.01, 1.07]). In individuals with diabetic fasting glucose levels at baseline, early recovery to normal and impaired fasting glucose levels decreased their risks of death from any cause (respective HRs 0.57 [95% CI 0.46, 0.70] and 0.65 [0.53, 0.81]) and CV disease (0.70 [0.60, 0.81] and 0.78 [0.66, 0.91]). Among individuals with impaired fasting glucose levels at baseline, early recovery to normal fasting glucose levels decreased their risk of CV disease-related mortality (HR 0.74 [95% CI 0.59, 0.93]).

Comment: We are becoming increasingly aware of the relevance and risk of developing prediabetes and type 2 diabetes at an early age. This is especially important in NZ as we see the greatest increase in prevalence in Pacific, Indian and Māori populations. This very large prospective cohort study from Korea enables a look at the effects of increasing or decreasing fasting glucose levels over time in a cohort of young adults aged 20–39 years at baseline. Importantly, those who were normal at baseline but developed prediabetes or type 2 diabetes had a 40% increase in mortality over the 10-year follow-up. Conversely, those who were abnormal at baseline but reverted to normal had a 43% lower risk. This suggests that intervening to prevent prediabetes and/or resolve existing prediabetes could have very major benefits in a young population.

Reference: Diabetologia 2020;63:2305–14
Abstract

Loneliness and type 2 diabetes incidence

Authors: Hackett RA et al.

Summary: These researchers explored the relationship between loneliness and onset of type 2 diabetes in 4112 participants from the English Longitudinal Study of Ageing with a mean age of 65 years and without diabetes at baseline, of whom 264 developed diabetes during the follow-up period (2006–2017). Loneliness was identified to be a significant predictor of incident type 2 diabetes independent of age, sex, ethnicity, wealth, smoking status, physical activity, alcohol consumption, BMI, HbA_{1c} level, hypertension and CV disease (HR 1.46 [95% CI 1.15, 1.84]), and was found to be significantly associated with type 2 diabetes onset independently of depressive symptoms, living alone and social isolation in additional analyses (1.41 [1.04, 1.90]); no significant association of living alone or social isolation with type 2 diabetes onset was detected.

Comment: I don't know what to make of this one, but I thought it was interesting and worth including to promote thought and discussion. We know many of the risk factors for type 2 diabetes, with family history and obesity being the strongest. However, this observational study of ageing in the UK has shown that loneliness is a new risk factor. It is important to be specific that this is not the same as living alone or being depressed. It is also independent of other factors that you might think it could be a proxy for, such as alcohol intake, BMI or age. This is a very intriguing observation that could imply some effect on central regulation of glucose metabolism. We all need mates!

Reference: Diabetologia 2020;63:2329–38
Abstract

Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes

Authors: Wagner R et al.

Summary: These researchers identified six distinct subphenotype clusters using partitioning on variables derived from oral glucose tolerance tests, bodyfat distribution on MRI, liver fat content and genetic risk in a cohort of extensively phenotyped individuals at increased type 2 diabetes risk. Increased glycaemia was present in three of the subphenotypes (clusters 3, 5 and 6), but intrinsic diabetes risk was only seen in individuals from clusters 3 and 5, while those from cluster 6 had moderate type 2 diabetes risk but increased risks of kidney disease and all-cause mortality. The researchers replicated their findings in an independent cohort using simple anthropomorphic and glycaemic constructs.

Comment: There has been a lot of discussion about the relevance of prediabetes, especially as defined by HbA_{1c} level. Some previous data from glucose-based definitions suggesting high rates of progression to type 2 diabetes have been questioned, and there is a lot of uncertainty about whether to target interventions individually or at a public health level. This paper therefore caught my eye as it attempts to form subgroups of people with prediabetes and relate their characteristics to risk of progression to type 2 diabetes and complications. The obvious objective being the ability to target individuals most likely to benefit from an intervention. What is interesting, and probably intuitive, is that the cluster at most risk have high visceral fat and impaired insulin secretory capacity. The authors point out that this isn't yet at a level to be used clinically, but watch this space. I think we will see more of this type of work to try to personalise prevention and treatment.

Reference: medRxiv 2020.10.12.20210062
Abstract

Independent commentary by Professor Jeremy Krebs
MBChB, FRACP, MD

Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He is a Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established. **FOR FULL BIO CLICK HERE.**

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