Diabetes & Obesity RESEARCH REVIEW™

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Issue 153 – 2022

In this issue:

Abbreviations used in this issue

BMI = body mass index
CV = cardiovascular
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
HOMA-IR = homeostatic model assessment of insulin resistance
HR = hazard ratio
LDL = low-density lipoprotein
OR = odds ratio
RCT = randomised controlled trial

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Welcome to issue 153 of Diabetes and Obesity Research Review.

The first issue for 2022 begins with research investigating diabetes progression in patients with the condition after starting statin therapy. The next paper reports on the effects of a range of intermittent fasting diets on bodyweight in an umbrella review of meta-analyses of RCTs, after which we have a systematic review with network meta-analysis of pharmacological therapies for weight loss. Often overlooked among our patients with diabetes is sexual dysfunction, and there is a paper in this issue reporting the results of a survey of patients suggesting it is a common problem in men and women. Another interesting paper asks how ageing is accelerated among diabetics.

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

Best regards,

Professor Jeremy Krebs
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Association of statin therapy initiation with diabetes progression

Authors: Mansi IA et al.

Summary: The impact initiation of statin therapy has on diabetes progression was assessed in this retrospective matched-cohort study. The study population consisted of 83,022 matched pairs of statin versus active control (histamine-2 receptor antagonist or proton pump inhibitor) initiators aged ≥30 years with diabetes entered in the US Veterans Affairs health system. Compared with active controls, a greater proportion of statin initiators experienced diabetes progression (new insulin initiation, increase in the number of glucose-lowering medication classes, ≥5 measurements of blood glucose level ≥200 mg/dL or a new diagnosis of ketoacidosis or uncontrolled diabetes; 55.9% vs. 48.0%; OR 1.37 [95% CI 1.35, 1.40]), with each individual component of the composite outcome significantly greater among statin users. A greater LDL cholesterol level lowering intensity was found to be associated with increased diabetes progression.

Comment: Statins have been reported to increase the risk of developing diabetes in other cohort studies. The absolute increase in risk has been small and generally agreed to be outweighed by benefits in CV disease risk reduction. This present paper is a retrospective case-control study in the US that again reports an increased risk of not only diabetes, but progression or poor glycaemic outcomes of diabetes with statin use. I think that this paper must be interpreted with great caution. There are many reasons why a person who is prescribed a statin may also have increased risk for diabetes and/or poor control and progression of diabetes; e.g. obesity, poor diet, physical inactivity, family history, etc. In a retrospective study of this nature, it is simply not possible to control for these. Therefore whilst it raises the issue again of the effect of statins on glucose metabolism, I don't think we should be changing practice based on this paper.

Reference: JAMA Intern Med 2021;181:1562–74
Abstract

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Educational Series on Countering Vaccine Misinformation: A Practical Guide for Healthcare Providers

This article discusses vaccine misinformation and how it can undermine vaccine confidence and lead to vaccine hesitancy. Evidence-based strategies for countering vaccine hesitancy and misinformation are summarised. Techniques to support healthcare providers when engaging with individuals whose vaccine hesitancy has resulted from exposure to vaccine misinformation are provided.

Intermittent fasting and obesity-related health outcomes

Authors: Patikorn C et al.

Summary: This was an umbrella review with 11 meta-analyses of 130 RCTs investigating the effects of intermittent fasting on obesity-related health outcomes among adults. Among 104 unique associations described across these RCTs for different types of intermittent fasting with obesity-related health outcomes, 28 statistically significant associations were identified for benefits in terms of BMI, bodyweight, fat mass, HOMA-IR, blood pressure, and LDL cholesterol, total cholesterol, triglyceride, fasting plasma glucose and fasting insulin levels. Intermittent fasting was also found to be associated with reduced fat-free mass. The evidence for a 1- to 2-month modified alternate-day fasting diet being associated with a moderate reduction in BMI in adults (healthy weight, overweight, obesity or with nonalcoholic fatty liver disease) was deemed to be of high quality, while six associations were supported by moderate quality evidence and the rest by very low quality evidence.

Comment: Intermittent fasting has become a popular approach for weight loss. The term covers a range of regimens that all have periods of no or very low calorie intake at their core. These may be by days of the week such as the 5:2 diet or alternate-day fasting, or by extended periods of fasting during the day. This paper reported an umbrella review of 11 meta-analyses of studies of the effect of intermittent fasting on obesity-related health outcomes. The results show a broad range of benefits on weight, glucose metabolism and lipids, which is encouraging. However, as is too often the case in nutrition research, the vast majority of studies were small and of short duration. Any approach to energy restriction is usually effective in motivated people over 3 months, but sustained behaviour change over the long-term is required for meaningful clinical benefit. So yes, it is a good tool in the weight loss toolbox that might suit some people well, but as the authors state, we need a well-conducted, large, long-term RCT to really test the efficacy of intermittent fasting.

Reference: JAMA Netw Open 2021;4:e2139558
Abstract

Pharmacotherapy for adults with overweight and obesity

Authors: Shi Q et al.

Summary: This systematic review with network meta-analysis included 143 RCTs (n=49,810) investigating pharmacotherapies for weight loss in overweight or obese adults. Compared with lifestyle modification alone, all agents investigated, except for levocarnitine, were associated with greater reductions in bodyweight, with the most effective (moderate-to-high certainty) being phentermine-topiramate (OR for a ≥5% reduction in bodyweight, 8.02 [95% CI 5.24, 12.27]), followed by GLP-1 receptor agonists (6.33 [5.00, 8.00]). With respect to adverse events leading to discontinuation, naltrexone-bupropion and phentermine-topiramate posed the greatest risk, followed by GLP-1 receptor agonists and then orlistat (respective ORs 2.69 [95% CI 2.11, 3.43], 2.40 [1.69, 3.42], 2.17 [1.71, 2.77] and 1.72 [1.44, 2.05]). A *post hoc* analysis revealed that the GLP-1 receptor agonist semaglutide was considerably more likely than the other drugs to induce bodyweight loss of >5% with a similar risk of adverse events (OR 9.82 [95% CI 7.09, 13.61]).

Comment: Drugs for weight loss have a long and chequered past. There have been many agents which have shown promise and good results in clinical trials, which have subsequently been taken off the market after widespread real-world use because of side effects. We all know how hard it is to achieve weight loss, particularly of more than 5–10% bodyweight, which is required for most health benefits. An effective, safe and cheap drug could make a big difference for the worlds growing obese population. This meta-analysis reviewed the RCTs of weight loss drugs compared with lifestyle modification. The best agent was the GLP-1 agonist semaglutide, which I reviewed the clinical trial of last year. It stands out from the pack for weight loss, but is incredibly expensive and would never stack up in terms of cost economics.

Reference: Lancet 2022;399:259–69
Abstract

Associations of quantity and quality of carbohydrate sources with subjective appetite sensations during 3-year weight-loss maintenance

Authors: Zhu R et al.

Summary: Maintenance phase data from the PREVIEW interventional study were used to explore longitudinal associations of carbohydrate source quantity and quality with changes in subjective appetite sensations during weight-loss maintenance; PREVIEW was a randomised trial of diet and physical activity investigated in a 2×2 factorial design in 1279 individuals with prediabetes and a BMI ≥25 kg/m². During weight-loss maintenance, the participants' average total carbohydrate consumption was 160.6 g/day, with a glycaemic index and load of 53.8 and 85.3 g/day, respectively, and their average dietary fibre consumption was 22.3 g/day. Each 30g incremental increase in total carbohydrate consumption and each 20-unit incremental increase in glycaemic load were significantly associated with increased hunger, desire to eat, including specifically sweet foods, and weight regain. Increasing glycaemic index was associated with weight regain but not appetite sensations. After adjustment for carbohydrate or glycaemic load, there were also significant associations between dietary fibre intake and increased desire to eat.

Comment: The great macronutrient debate continues. One of the purported benefits of low carbohydrate diets for weight loss hinges on satiety and the relative effects of the different macronutrients. Protein and fat have been shown in some studies to have greater satiating effects than carbohydrate. However, the quality/type of carbohydrate has also been shown to have differing effects. This question is examined again here in a secondary analysis of the PREVIEW study, using pooled data from all the participants as a longitudinal cohort. The authors have specifically looked at the effects of quantity and type of carbohydrate on satiety and weight regain during the weight loss maintenance phase of that trial after a period of initial intensive weight loss. Greater total carbohydrate intake was associated with greater hunger and weight regain. Counter to expectations, so was greater fibre intake, which is a great surprise, as fibre has been shown in numerous studies to be associated with metabolic and CV health benefits. More work is needed to tease out these observations, but don't discount fibre yet!

Reference: Clin Nutr 2022;41:219–30
Abstract

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Meta-analysis of randomized controlled trials of the effects of probiotics on type 2 diabetes in adults

Authors: Zhang C et al.

Summary: This was a meta-analysis of 33 comparisons (n=1927) from RCTs investigating the effects of probiotics on markers of glycaemic homeostasis in patients with type 2 diabetes. Compared with placebo, probiotic ingestion at ~109 cfu/day was significantly associated with reductions in HbA_{1c} level (mean difference, –0.19 percentage points [p=0.003]; low certainty evidence), fasting blood glucose level (–1.00 mmol/L [p<0.0001]; low certainty), fasting insulin level (–5.73 pmol/L [p=0.08]; moderate certainty) and HOMA-IR (–1.00 [p<0.00001]; high certainty). The authors noted that the reduction in HbA_{1c} level with probiotic supplementation was not clinically significant, while the reductions in fasting glucose and insulin levels were deemed to be marginally clinically significant. The benefits of probiotics on glycaemic homeostasis were found to be greater for multi-strain and high-dose probiotics than with single-strain and low-dose probiotics, and it was also noted that older patients and those with a high baseline BMI may derive the greatest benefit.

Comment: The role of the gut microbiome in health generally, and in obesity and diabetes particularly, has become a hot topic of research over the last few years. There are many observational studies linking microbiome patterns with obesity and with impaired glucose metabolism. There have been some interesting rodent studies showing improvements in both weight and glucose with faecal transplants. Therefore, there is considerable interest in whether modification of the microbiome using probiotics may be an effective strategy for weight and metabolic health. The use of probiotics is complex, because of both dose and strain effects and whether single strain or combinations are used. This meta-analysis of probiotics in people with type 2 diabetes shows that there may be some improvement in glucose metabolism, but the effect size is small. Whether this can be enhanced by better strain selection or combination with prebiotics remains to be seen.

Reference: Clin Nutr 2022;41:365–73
Abstract

Independent commentary by Professor Jeremy Krebs MBChB, FRACP, MD

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. As well as clinical and teaching activities, Professor Krebs maintains active research interests in the area of obesity and diabetes, with a particular focus on the association between obesity and type 2 diabetes, both from an aetiology and management perspective, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery.

Prevalence of and risk factors for sexual dysfunctions in adults with type 1 or type 2 diabetes

Authors: Van Cauwenberghe J et al.

Summary: These researchers surveyed 756 adults with diabetes on sexual function, general emotional well-being, anxiety and diabetes distress. Sexual dysfunction was reported by around a third of respondents, with 20% and 33% of men with type 1 and type 2 diabetes, respectively, reporting erectile dysfunction, and 22% and 27% reporting orgasmic dysfunction. Among men, independent associations were detected between sexual dysfunction and older age (OR 1.05 [p=0.022]), larger waist circumference (1.04 [p<0.001]) and longer duration of diabetes (1.04 [p=0.007]). Furthermore, men with sexual dysfunction were more likely to report diabetes distress (20% vs. 12% [p=0.026]). Among women, 22% and 15% of those with type 1 and type 2 diabetes, respectively, reported decreased sexual desire and 9% and 11% reported decreased arousal, and those who reported sexual dysfunction were more likely to report diabetes distress (36% vs. 21% [p=0.003]), impaired emotional well-being (36% vs. 25% [p=0.036]) and symptoms of anxiety (20% vs. 11% [p=0.026]).

Comment: Sexual dysfunction is one of the morbidities of diabetes and its management that is often forgotten and not as well monitored or addressed as retinal screening, foot care or renal review. This may be because patients are less likely to report their problems and clinical teams don't ask. This paper reminds us that sexual dysfunction is common and affects both men and women with diabetes. It would be interesting to know what the rates of sexual dysfunction are in the general population matched for age. It is also noted from this research that sexual dysfunction is associated with diabetes distress and impaired emotional well-being, which may well be causally bidirectional. This paper is a reminder to us to ask the question.

Reference: Diabet Med 2022;39:e14676
Abstract

Mediterranean diet and diabetes risk in a cohort study of individuals with prediabetes

Authors: Cea-Soriano L et al., the PREDAPS Study Group

Summary: These researchers reported the development of diabetes for a prospective cohort of 1184 individuals with prediabetes according to adherence to a Mediterranean diet. Over a mean 4.2 years of follow-up, 210 of the individuals progressed to type 2 diabetes. Compared with individuals with low or medium adherence to a Mediterranean diet, those with high adherence had a lower incidence rate of developing diabetes (2.9 vs. 4.8 per 100 person-years), with the risk significantly decreased in propensity score analyses by inverse probability weighting and 1:2 matching (respective HRs 0.63 [95% CI 0.43, 0.93] and 0.56 [0.37, 0.84]).

Comment: The Mediterranean dietary pattern has been shown to be associated with lower risks of diabetes and CV disease in population cohort studies, and is therefore promoted as a good option for people to follow. This paper reports specifically on the rate of progression to type 2 diabetes in people who have prediabetes according to their adherence to a Mediterranean dietary pattern. It shows an almost 50% reduction in the rate of progression confirming the benefit of following this approach. So how do we encourage people to follow this pattern? The small amounts of red wine are easy, but the reduction in red meat and increase in legumes and pulses are more challenging. What is needed is a way to help people to try new foods and ways of preparing these. NZ has a wealth of foods that fit into a Mediterranean dietary pattern, and so we are well placed to move down that pathway.

Reference: Diabet Med; Published online Dec 11, 2021
Abstract

How does diabetes accelerate normal aging? An examination of ADL, IADL, and mobility disability in middle-aged and older adults with and without diabetes

Authors: Tsai Y-H et al.

Summary: These researchers extracted data from 5131 individuals aged ≥50 years from the 1996 Taiwan Longitudinal Study in Aging to derive an age norm for quantifying and comparing different progression rates of disability in individuals with and without diabetes. It was found that the occurrence and progression of disabilities were accelerated during ageing by diabetes. The ages at which patients with diabetes typically developed problems with mobility, instrumental activities of daily living, and activities of daily living were 55, ~60 and ~70 years, respectively, and diabetes accelerated the onset of these by 3, 7 and 11 years, respectively. Diabetes persisted as a robust predictor for levels of disability and the rate of change for developing mobility disability in a fully adjusted model.

Comment: Unfortunately we know that having diabetes reduces life expectancy compared with those who don't have diabetes, and this gap has not reduced despite decades of research, new treatments and understanding of pathogenic mechanisms. This study caught my eye because it looks at morbidity rather than mortality, and therefore speaks to quality of life. In this Taiwanese study, diabetes was associated with earlier development of poor mobility and other aspects of ageing than those without diabetes. This raises the question of what diabetes specific process is responsible, and therefore what approaches might be taken to reduce the impact. It may be the result of glycation of various proteins and therefore amenable to tight glycaemic control. It would be interesting to know what a similar analysis of participants from the UKPDS study might show.

Reference: Diabetes Res Clin Pract 2021;182:109114
Abstract

Association between weight change and incidence of cardiovascular disease events and mortality among adults with type 2 diabetes

Authors: Strelitz J et al.

Summary: This was a systematic review of 14 observational studies of behavioural (nonsurgical and nonpharmacological) bodyweight changes and CV disease events among adults with type 2 diabetes, and three trials of behavioural interventions targeting weight loss; the risk of bias was high in three studies and moderate in most of the rest. Compared with no change in bodyweight gain, weight gain increased the likelihoods of CV disease events (HRs 1.13–1.63) and all-cause mortality (HRs 1.26–1.57). Unintentional weight loss was associated with an increased risk of all-cause mortality, whereas associations with intentional weight loss were not clear. Moreover, behavioural interventions targeting weight loss had no significant impact on the risk of CV disease events (pooled HR 0.95 [95% CI 0.71, 1.27]).

Comment: This is an important study. Obesity increases the risk of diabetes and CV disease. There are numerous weight loss trials with many different dietary and behavioural approaches to achieving weight loss. Many have shown improvements in glucose metabolism and CV disease risk factors such as blood pressure and lipids. However, we know that weight regain is common and what we are trying to prevent is long-term adverse CV events, not simply short-term risk factor improvement. The bariatric surgery literature has shown long-term reduction in CV disease events and mortality. However, the long-term literature on behavioural/lifestyle weight loss is sparce as shown here, by only 17 out of 13,227 studies meeting the inclusion criteria for this meta-analysis. The outcome is not promising. As we might expect weight gain is bad, but despite short-term benefits, there is no clear reduction in CV disease and mortality with weight loss. I agree with the authors, we desperately need more long-term data, but who is going to pay for such studies to be done?

Reference: Diabetologia; Published online Dec 2, 2021
Abstract

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Diets for weight management in adults with type 2 diabetes

Authors: Churuangsuk C et al.

Summary: Nineteen meta-analyses of weight-loss diets, involving 2–23 primary trials (n=100–1587), were included in this umbrella review of diets for diabetes remission; seven were high-quality studies, and 12 were critically low or low quality. Very low energy diets for 8–12 weeks resulted in the greatest weight loss, at 6.6kg greater than for low-energy diets. Weight loss was 2.4kg greater with formula meal replacements over 12–52 weeks. There was no significant difference for weight loss between low-carbohydrate diets and higher-carbohydrate/low-fat diets, and minimal or nil weight loss for high-protein, Mediterranean, high-monounsaturated-fatty-acid, vegetarian and low-glycaemic-index diets compared with control diets. Sixteen sources were identified for type 2 diabetes remission, and these showed that 1-year remission was seen in a median 54% of participants in RCTs of initial low-energy total diet replacement, and 11% and 15% for meal replacements and Mediterranean diets, respectively; the quality of evidence for remission on ketogenic/very low-carbohydrate and very low-energy food-based diets (20% and 22%, respectively) was very low.

Comment: To continue on a similar theme, this umbrella meta-analysis reviewed the question of remission of type 2 diabetes through weight loss and the relative benefits of different dietary approaches. The result supports what has been incorporated into many diabetes guidelines, in that there is not one specific dietary approach or macronutrient profile that is optimal. There are a range of approaches that can be used, and as we see in clinical practice, individual choice is important in the likelihood of success. Notably, very low energy diets are the most effective for diabetes remission, which is not surprising as they induce greater weight loss in the short-term. However, to sound like a broken record, we still need long-term outcome studies. These need to be more than 2 years. We need 5- and 10-year studies to really guide practice.

Reference: Diabetologia 2022;65:14–36
Abstract

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