Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 149 – 2021

In this issue:

Welcome to issue 149 of Diabetes and Obesity Research Review.

This issue is packed full of diabetes research that we hope you will find helpful. We begin with a systematic review with meta-analysis that is perhaps a little unexpected – the effect of melatonin supplementation on diabetes outcomes! Another systematic review and meta-analysis of RCTs included in this issue has reported on the impact that low glycaemic index and glycaemic load diets have in diabetes. Norwegian GPs are put in the spotlight in another included paper, which surveyed how well they are doing with respect to recommended diabetes processes of care, and the effect this has on CV risk and glycaemic control. Our Australian neighbours have been crunching the numbers to project the diabetes-related ESKD incidence for type 2 diabetes out to 2040 according to different scenarios of diabetes prevention and SGLT-2 inhibitor use. We conclude with another meta-analysis, this one reporting reduced risks of several important outcomes with GLP-1 receptor agonists, regardless of structural homology, for treating patients with type 2 diabetes.

Please keep sending those comments and suggestions.

Best regards,

Professor Jeremy Krebs
jeremykrebs@researchreview.co.nz

Effects of melatonin supplementation on diabetes

Authors: Delpino FM et al.

Summary: Pooled data in this systematic review and meta-analysis of 16 RCTs revealed that 56% reported benefits in diabetes parameters with melatonin supplementation versus placebo, with differences reported for fasting blood glucose level (mean difference –4.65 [p≤0.01]; I^2=58%), HbA_{1c} level (–0.38 [p=0.30]; I^2=18%) and insulin resistance (–0.58 [p=0.17]; I^2=35%).

Comment: Well, I have to confess that the effect of melatonin on glucose metabolism was not on my radar. The role of melatonin in sleep is well known, but here is a meta-analysis of studies that have examined the effect of melatonin on fasting glucose level, HbA_{1c} level and insulin resistance. It is notable that almost all of the studies come from Iran, where there is clearly an interest in this area. The doses used ranged from 3mg to 10mg, and overall there were benefits seen in all three parameters, which were not only statistically significant, but clinically relevant. For example, the effect size for HbA_{1c} level was –0.38%; and to think you can buy it over the counter in Walmart!

Reference: Clin Nutr 2021;40:4595–605

Abstract

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Abbreviations used in this issue

BMI = body mass index
BP = blood pressure
CSII = continuous subcutaneous insulin infusion
CV = cardiovascular
ESKD = end-stage kidney disease
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
HDL/LDL = high/low-density lipoprotein
HR/OR = hazard/odds ratio
MDI = multiple daily injections
RCT = randomised controlled trial
SGLT = sodium glucose cotransporter
SNP = single-nucleotide polymorphism

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Effect of low glycaemic index or load dietary patterns on glycaemic control and cardiometabolic risk factors in diabetes

Authors: Chiavaroli L et al.

Summary: This was a systematic review with meta-analysis of 29 RCT comparisons of low glycaemic index/glycaemic load diets in 1617 patients with type 1 or 2 diabetes; the participants were predominantly middle-aged, overweight or obese with moderately controlled type 2 diabetes on antihyperglycaemia drugs or insulin. Compared with higher glycaemic index/load diets, there was high certainty evidence supporting a significant reduction in HbA_{1c} level with low glycaemic index/load diets (mean difference −0.31% [p<0.001]; I^2=75%), and there was also mostly moderate certainty evidence that the low glycaemic index/load diets reduced fasting glucose level, LDL and non-HDL cholesterol levels, apolipoprotein B level, triglyceride levels, bodyweight, BMI, systolic BP and C-reactive protein level, but not blood insulin level, HDL cholesterol level, waist circumference or diastolic BP. Significant positive dose-response gradients were seen for differences in glycaemic load and HbA_{1c} level, and for absolute dietary glycaemic index and systolic BP.

Comment: Dietary composition is such a critical component of the management of both type 1 and type 2 diabetes. Yet there remains so much controversy over the most appropriate dietary advice. Often central to that debate is the role of carbohydrate, both qualitatively and quantitatively. One of the conceptual tools to measure the effect of carbohydrate has been the glycaemic index and load, the hypothesis being that certain foods promote less excursion in postprandial glucose through less demand on insulin release. Whilst promising and useful conceptually, the evidence has not always been consistent that we should promote a low glycaemic index diet, particularly when foods are consumed as mixed meals and the effect of protein or fat modifies the glycaemic index of the carbohydrate food. Therefore, this meta-analysis is very useful, and it is more compelling that a low glycaemic index dietary pattern is beneficial in people with diabetes.

Reference: BMJ 2021;374:n1651
Abstract

Body-mass index and diabetes risk in 57 low-income and middle-income countries

Authors: Teufel F et al.

Summary: Associations between BMI and diabetes in low- and middle-income countries were explored in this cross-sectional study of 685,616 nationally representative adults aged ≥25 years from 57 such countries. The respective overall prevalences of overweight, obesity and diabetes were 27.2%, 21.0% and 9.3%. Compared with BMIs of 18.5–22.9 kg/m² ('normal'), men and women with BMIs of ≥23 kg/m² ('upper normal') had 43% and 41% greater risks of diabetes, respectively. The risk of diabetes also increased steeply in individuals aged 35–44 years and in men aged 25–34 years from sub-Saharan African regions. Stratified analyses revealed considerable regional variability in the association. The optimal BMI thresholds for diabetes screening ranged from 23.8 kg/m² for men from east, south and southeast Asia to 28.3 kg/m² for women from the Middle East and north Africa and from Latin America and the Caribbean.

Comment: This is an important, if not directly relevant to NZ, study examining the association between BMI and risk of diabetes. As we know, obesity is the main modifiable risk factor for type 2 diabetes, and has been increasing globally for the last 50 years. In parallel with that there has been an explosion of diabetes in low- and middle-income countries. There are many factors to consider in that observation, including changes in dietary patterns and exercise, independent of the increase in obesity itself. There are also genetic and ethnicity factors, such as those we observe in NZ. What is important about this current analysis is the reminder about what BMI is telling us. BMI is a crude estimate of body fatness, which was derived in a Caucasian population, and principally associated with CV risk. It has been well linked to risk of diabetes too. However, the thresholds to define overweight and obesity are specific to Caucasian populations. Other populations have very different body compositions and lean-to-fat mass ratios, meaning that the estimate of body fatness from BMI is different. This is highlighted by the variation across the global regions in this paper.

Reference: Lancet 2021;398:238–48
Abstract

Effects of probiotics on body adiposity and cardiovascular risk markers in individuals with overweight and obesity

Authors: da Silva Pontes KS et al.

Summary: This was a systematic review and meta-analysis of 26 RCTs (n=1720) investigating probiotic supplementation in overweight and obese individuals. Pooled data revealed that compared with control groups, probiotic supplementation groups had significant reductions in bodyweight (mean difference –0.70kg [p<0.0001]), BMI (–0.24 kg/m² [p=0.0001]), waist circumference (–1.13cm [p<0.0001]), fat mass (–0.71kg [p=0.0004]), tumour necrosis factor-α level (–0.16 pg/mL [p=0.0001]), insulin level (–0.85 μU/mL [p=0.010]), total cholesterol level (–0.16 mmol/L [p=0.003]) and LDL cholesterol level (–0.09 mmol/L [p=0.006]). Studies that investigated probiotic supplementation with both single and multibacterial species also reported significant reductions in bodyweight, BMI and waist circumference. Only studies investigating probiotic doses of ≥10^{10} colony-forming units and for ≥8 weeks duration reported decreases in body adiposity parameters.

Comment: The field of probiotics and potential health benefits related to the microbiome is controversial. There are many studies showing associations between characteristics of the gut microbiome and many diseases, including obesity, diabetes and CV disease. It is therefore not surprising that there is interest in whether probiotics can not only modify the microbiome, but also improve these health outcomes. However, it is messy! Many factors come in to play, including whether single or multiple bacterial probiotics are used, differences among strains and doses. This makes interpretation of the literature difficult, and indeed the ability to derive meaningful conclusions from meta-analyses more so. With all of that uncertainty, I include this meta-analysis of RCTs of probiotics on weight and CV risk outcomes, which suggests a potential benefit. Buyer beware.

Reference: Clin Nutr 2021;40:4915–31
Abstract

Diabetes distress and glycaemic control in young adults with type 1 diabetes: associations by use of insulin pumps and continuous glucose monitors

Authors: Nagel KE et al.

Summary: Patients aged 19–31 years with type 1 diabetes receiving care at a US specialty clinic (evaluable n=419) completed an online survey to explore if high levels of diabetes distress were associated with higher HbA_{1c} levels, along with the impact of insulin pumps and/or continuous glucose monitors on this association; 35%, 42% and 24% of the respondents used both, either and neither device, respectively. The respondents' mean HbA_{1c} level was 64 mmol/mol (or 8.0%), and 24% had high levels of diabetes distress. Respondents with high diabetes distress had an HbA_{1c} level that was on average 10 mmol/mol (or 0.9 percentage points) higher than those without such distress, with the differences similar regardless of device use (9 mmol/mol [or 0.8 percentage points] both for users of both devices and device nonusers).

Comment: Living with type 1 diabetes is not easy. It is relentless and adds a layer of additional complexity to everything that the person must deal with in everyday life. It is not surprising that rates of distress associated with type 1 diabetes are high, and I think we all see that most of our patients go through periods where diabetes distress becomes a major factor. This paper reminds us that diabetes distress is associated with higher HbA_{1c} levels, which is not surprising. The additional new finding is that there is no difference in this association depending on whether people are using insulin pumps and/or continuous glucose monitors. Once again, this highlights that technology is only one helpful tool in managing type 1 diabetes, but not a panacea for good outcomes. Indeed, for some the burden of extra data or enforced interaction with a device can in itself cause distress.

Reference: Diabet Med; Published online July 26, 2021
Abstract

Projecting the incidence of type 2 diabetes-related end-stage kidney disease until 2040

Authors: Morton JI et al.

Summary: The effects of two diabetes prevention approaches and of widespread SGLT-2 inhibitor use in patients with diabetes on diabetes-related ESKD were examined using a life table model to project the incidence of type 2 diabetes-related ESKD in Australia out to 2040. Based on current trends, it was estimated that the annual diabetes-related ESKD incidence will increase from 3.7 to 5.7 per 100,000 between 2014 and 2040; however, with diabetes prevention approaches incorporated, the annual incidence is projected to be 5.2–5.5 per 100,000 by 2040. In scenarios where 50% and 70% of eligible patients with diabetes are prescribed SGLT-2 inhibitors, it was projected that the respective annual diabetes-related ESKD incidences would be 4.7 and 4.3 per 100,000 by 2040, with a reduction in cases of 12–21% compared with current trends, whereas ESKD cases would be expected to be reduced by 1–3% by diabetes prevention.

Comment: This study presents an interesting, if not slightly depressing, concept. ESKD is one of the major complications of diabetes that we strive to prevent. Until recently, the main way to do so was through tight glycaemic and BP control and the use of ACE (angiotensin-converting enzyme) inhibitors. The development of SGLT-2 inhibitors has now added an extra level of drug treatment that is effective in reducing the progression to ESKD. At a population level, preventing people developing diabetes in the first place and early resolution of diabetes would also be effective strategies in reducing the burden of ESKD. This study has modelled the effect of current diabetes prevention interventions and of use of SGLT-2 inhibitors in those with established diabetes, and reports that SGLT-2 inhibitors would be more effective in reducing ESKD. This is of course only one component of the morbidity and premature mortality of diabetes, so does not mean we should give up on prevention!

Reference: Diabetes Care 2021;44:1515–23
Abstract

Endocrinologist Dr Ole Schmiedel reviews Contrave®(Naltrexone/Bupropion)

This review discusses the use of naltrexone/bupropion, a new treatment for weight management in patients with obesity or who are overweight with at least one weight-related comorbidity.

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The impact of hypoglycaemia on the quality of life of family members of adults with type 1 or type 2 diabetes

Authors: Jensen MV et al., the Hypo-RESOLVE Consortium

Summary: These authors undertook a systematic review of eight studies reporting qualitative evidence regarding the impact that hypoglycaemia has on the quality of life of family members of adults mostly with type 1 but also type 2 diabetes. Six analytical themes associated with hypoglycaemia were identified: i) alterations to everyday life, reduced freedoms and increased disruptions; ii) adverse impact on sleep; iii) negative impact on the relationship with the person with diabetes; iv) negative impact on emotional well-being; v) time and energy involved in its detection, prevention and treatment; and vi) unmet informational and emotional needs for family members.

Comment: The impact of living with a chronic disease extends beyond the person with the disease and touches on the lives of family and whānau. As health professionals, it is often easy to forget this broader impact. This systematic review of qualitative studies focuses on the effect of hypoglycaemia on family members. It highlights several themes which serve to remind us just how pervasive diabetes can be. The effects range from simply consuming time and energy, through to disrupted sleep to more significant emotional and relationship stresses. The paper points out how these are largely unmet needs that merit consideration in how we deliver services and how we support families.

Reference: Diabet Med 2021;38:e14666
Abstract

High adherence to recommended diabetes follow-up procedures by general practitioners is associated with lower estimated cardiovascular risk

Authors: Nøkleby K et al.

Summary: Associations of 275 GPs performances of recommended processes of care with estimated CV risk and poor glycaemic control were explored in this Norwegian cross-sectional study of 6015 patients aged <75 years with type 2 diabetes and without CV disease. The respective mean total and modifiable 10-year CV disease risk estimates were 12.3% and 3.3%. Patients of GPs in the lowest versus highest performance quintile had adjusted total and modifiable CV disease risks that were 1.88 and 1.78 percentage points greater (relative mean increases, 16.6% and 74.8%, respectively) and a greater likelihood of having poor glycaemic control (OR 1.77 [95% CI 1.27, 2.46]).

Comment: The management of type 2 diabetes sits largely in primary care in NZ. As a long-term condition, there are certain regular or planned activities that are recommended for patients, and importantly assessment and management of CV risk is equally important to glycaemic control. The success of this is always a combination of both patient factors and system/practitioner factors. This paper examined the impact of primary care process factors in Norway. It identified important variation between the best and worst performing general practitioners. Some of this will be confounded by practice demographics and other determinant of health in the enrolled populations, but it does point out the importance of having systems that enable quality planned care.

Reference: Diabet Med 2021;38:e14586
Abstract

Profiles of glucose metabolism in different prediabetes phenotypes, classified by fasting glycemia, 2-hour OGTT, glycated hemoglobin, and 1-hour OGTT

Authors: Tura A et al., for the IMI DIRECT Consortium

Summary: The longitudinal IMI DIRECT study explored differences in glucose metabolism in 2111 participants according to prediabetes classification (impaired fasting glucose, impaired glucose tolerance and HbA_{1c} level-based). Compared with healthy controls, participants with isolated defects had impaired β-cell function and insulin sensitivity at baseline, with further deterioration evident in pooled groups with 2–3 defects. Among groups with isolated defects, individuals with impaired glucose tolerance had significant reductions in insulin sensitivity, insulin secretion at reference glucose and insulin secretion potentiation, whereas in those with HbA_{1c}-based prediabetes, insulin sensitivity and insulin secretion at reference glucose were significantly greater. For individuals with two glucose metabolism defects, similar differences were seen for both β-cell function and insulin sensitivity. The incidence of type 2 diabetes after 48 months increased progressively as the number of prediabetes defects increased (OR >2 [p<0.008]).

Comment: I found this paper absolutely fascinating. We find ourselves in a confused position with regard to prediabetes. We now have three separate diagnostic criteria for prediabetes, including impaired fasting glucose, impaired glucose tolerance and impaired overall glycaemia based on HbA_{1c} level. It cannot be assumed that these groups identify the same people, represent the same dysregulated physiology or confer the same risks for progression to diabetes or indeed CV disease. This paper takes a fresh look at these concepts, and for anyone with an interest in the debate, it is highly worth a read. The take-home messages are that of the three, impaired glucose tolerance is the worst phenotype, but despite that, over 4 years the rates of progression to diabetes are similar. Furthermore, as you might predict, if you meet the criteria for two of the three, your risk of progression is greater than if you only meet one, and that if you meet all three, then your risk is exponentially higher. This paper raises two interesting debates. The first is whether we should complete screens of all three in everyone who is picked up with one, and the second whether we can use the underlying differences in physiology to guide interventions to reverse or prevent diabetes.

Reference: Diabetes 2021;70:2092–106
Abstract

Stratification of type 2 diabetes by age of diagnosis in the UK Biobank reveals subgroup-specific genetic associations and causal risk profiles

Authors: Noordam R et al.

Summary: These researchers sought to gain insight into the genetics and causal risk factors of type 2 diabetes across different age groups. Genome-wide association studies were undertaken on a total of 24,986 cases of type 2 diabetes and subgroups according to age of diagnosis (<50, 50–60, 60–70 and >70 years), with 187,130 nondiabetic individuals aged ≥70 years used as controls. There were 208 independent lead SNPs identified, mapped to 69 loci, that were significantly associated with type 2 diabetes. Among others, stronger associations were seen for SNPs mapped to *CDKN2B-AS1* and multiple independent SNPs mapped to *TCF7L2* with diabetes diagnosed after age 70 years versus prior to age 50 years. Two-sample Mendelian randomisation performed according to the different case groups revealed that of investigated risk factors, the association between BMI and type 2 diabetes attenuated as age of diagnosis increased.

Comment: This is another paper that looked at the differences in pathogenesis between people with type 2 diabetes. Here the focus is identifying genetic factors that might explain differences in presentation by age. One of the most notable epidemiological shifts in diabetes incidence over the last 30–40 years has been presentation at younger ages. This has paralleled the rise in obesity, and would logically suggest that the effect is driven by an increase in the effect of insulin resistance induced by obesity. That concept is supported by this paper, which also identified different genetic polymorphisms that track with age of presentation. It is likely that these will specifically relate to the physiology associated with the more obvious (at least to me) phenotypic characteristics; i.e. more β-cell dysfunction in skinny older people versus more insulin resistance in overweight younger people.

Reference: Diabetes 2021;70:1816–25
Abstract

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Sodium-glucose cotransporter-2 inhibitors for type 2 diabetes mellitus in adults

Authors: Augusto GA et al.

Summary: This was an overview of 46 systematic reviews (covering 175 RCTs and 136,096 participants) comparing SGLT-2 inhibitors with placebo or active comparators for type 2 diabetes. Their was clear evidence of benefit with respect to myocardial infarction (ORs/HRs 0.85–0.91), CV-related mortality (0.67–0.86); heart failure (0.64–0.69), albuminuria progression and a composite renal outcome (0.55–0.63) and HbA_{1c} level and bodyweight (respective mean differences versus placebo, 5.4–8.4 mmol/mol [or 0.49–0.77 percentage points] and –1.09 to –2.99kg). A possible benefit of SGLT-2 inhibitors also emerged for major adverse CV events (ORs/HRs 0.80–0.89), all-cause mortality and nonalcoholic fatty liver disease, but there was equivalence or no clear evidence of effect for stroke or for fractures, and there was evidence of harm for genital infections (2.06–5.25) and ketoacidosis (1.36–2.20). No conclusion could be drawn regarding the effect of SGLT-2 inhibitors on amputation risk or on urinary tract infections.

Comment: There have been many studies published on SGLT-2 inhibitors, including RCTs, systematic reviews and now this review of reviews! The evidence for the benefits and risks of this class have become more apparent and nicely summarised in this paper. What was developed as a glucose-lowering drug class has become much more than that, and in fact you could argue that the glucose-lowering effect is relatively modest and perhaps the least of its benefits. The meta-analysis reports an effect size compared with placebo of 5.4–8.4 mmol/mol for HbA_{1c} level. This is not insignificant, but less than that of the now much maligned sulfonylureas. Aside from the reduced risk of hypoglycaemia and weight benefits, however, the main reason this class is now so important is the improved CV and renal outcomes. However, compared with the GLP-1 analogues it is clear that there is not a stroke benefit, and it remains to be fully seen how significant the issue of euglycaemic ketoacidosis will become. Both will influence the relative place of these two important classes of drugs.

Reference: Diabetes Obes Metab 2021;23:2289–302
Abstract

Effect of diet quality and genetic predisposition on hemoglobin A1c and type 2 diabetes risk

Authors: Zhuang P et al.

Summary: Interactions between diet quality and genetic predisposition to incident type 2 diabetes were evaluated in this analysis of 357,419 individuals from the UK Biobank. Over an average 8.1-year follow-up period, 5663 incident cases of type 2 diabetes were recorded. A significant negative interaction was observed between a genetic risk score (based on 424 variants associated with type 2 diabetes risk) and a diet quality score (based on ten important dietary components). After major risk factor adjustments, each standard deviation incremental increase in the genetic risk score was associated with a 54% increase in the risk of type 2 diabetes, whereas each standard deviation increase in the diet quality score was associated with a 9% decrease in risk; the antagonistic interaction meant that a simultaneous incremental increase of one standard deviation in both scores decreased the risk by 3%. When the genetic risk score was >95%, the type 2 diabetes risk decreased by 23% with each standard deviation incremental increase in the diet quality score. There was a strong, significant negative interaction between the genetic risk score and the diet quality score on baseline HbA_{1c} level.

Comment: It is well accepted that two of the most important risk factors for type 2 diabetes are family history and adverse lifestyle patterns. Family history is essentially genetic factors, and lifestyle is a combination of diet and activity. What this study does is examine the interaction of these factors in a large group of people with data stored in the UK biobank. It uses a genetic risk score derived from a composite of multiple genetic polymorphisms associated with diabetes, and diet quality score derived from ten components of diet. As expected, a worse diet and greater genetic risk were both associated with increased risk of diabetes. What is interesting is the interaction. Those with greater genetic risk had a more significant reduction in risk by adhering to a more healthy diet than those with lower genetic risk. This begins to show that targeted dietary interventions may be the way of the future for population health approaches to reduce rates of diabetes.

Reference: Diabetes Care 2021; Published online Aug 25, 2021
Abstract

Continuous subcutaneous insulin infusion therapy is associated with reduced retinopathy progression compared with multiple daily injections of insulin

Authors: Reid LJ et al.

Summary: This Scottish study compared diabetic retinopathy outcomes for patients with type 1 diabetes between 204 who started using CSII therapy after its introduction and 211 who elected to continue MDIs; the CSII recipients were significantly younger and were from less socially deprived areas, and had lower HbA_{1c} levels and higher diastolic BPs at baseline. Compared with the MDI group, the CSII group had a greater reduction in HbA_{1c} level at 1 year (–6 vs. –2 mmol/mol, or –0.6 vs. –0.2 percentage points [p<0.01]), and a smaller proportion experienced diabetic retinopathy progression over a mean 2.3-year follow-up period (26.5% vs. 18.6% [p=0.0097]). A significant association was detected between high baseline HbA_{1c} level and diabetic retinopathy progression among MDI recipients (p=0.0049) but not among CSII recipients (p=0.93). Diabetic retinopathy progression was not significantly impacted by change in HbA_{1c} level at follow-up, irrespective of baseline glycaemic status, in either group.

Comment: There already exists a large body of literature to support the use of insulin pump therapy for people with type 1 diabetes. This study adds to that evidence. It is a retrospective, nonrandomised cohort study, so is susceptible to bias and confounding by factors external to those measured and reported. Furthermore, the group who were on pump therapy had a number of factors at baseline that were identified as potentially important, including age, deprivation and baseline HbA_{1c} level. These were adjusted for in the analysis, but that is never as compelling as a randomisation and even distribution between groups. Nevertheless, pump therapy was associated with a greater reduction in HbA_{1c} level and with less progression of retinopathy. That might seem intuitive, but the authors report that the change in HbA_{1c} level did not significantly affect the retinopathy outcome, suggesting that there is some other factor associated with pump use that is protective, such as glycaemic variability perhaps. This needs to be interpreted with great caution given the study design.

Reference: Diabetologia 2021;64:1725–36
Abstract

Erectile function in men with type 2 diabetes treated with dulaglutide

Authors: Bajaj HS et al.

Summary: This exploratory analysis of REWIND trial data sought to assess the effects of treatment with dulaglutide on erectile dysfunction in 3725 men with type 2 diabetes; the trial had randomised patients (both sexes; aged >50 years) to receive dulaglutide or placebo. A history of CV disease was recorded for 39.9% of the men, and 56.5% had reported moderate or severe erectile dysfunction at baseline. Following randomisation, the erectile dysfunction incidences among men assigned to the dulaglutide and placebo arms were 21.3 and 22.0 per 100 person-years (HR 0.92 [95% CI 0.85, 0.99]). Men assigned to dulaglutide also had a lesser decline in erectile function subscore compared with those assigned to placebo (least squares mean difference, 0.61 [p=0.006]).

Comment: Is this the new Viagra? Perhaps not. This paper reports a secondary analysis of the REWIND study data, comparing dulaglutide with placebo on erectile function. The REWIND study was not designed to test this hypothesis, but the data were collected prospectively. It is also important to remember that the participants had previous or high risk of CV events and were on many medications that can influence erectile function in addition to the effect of diabetes itself, and more than half of the participants had some degree of erectile dysfunction at baseline. This present analysis shows that dulaglutide was associated with a statistically significant lower incidence in new dysfunction and less progression of existing dysfunction. It's hard to know how relevant this really is in clinical practice.

Reference: Lancet Diabetes Endocrinol 2021;9:484–90
Abstract

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Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes

Authors: Sattar N et al.

Summary: This was a systematic review with meta-analysis of eight randomised trials (n=60,080) reporting CV benefits and risks of GLP-1 receptor agonists for type 2 diabetes. GLP-1 receptor agonists were associated with reduced risks of major adverse CV events (HR 0.86 [95% CI 0.80, 0.93], with no significant heterogeneity across GLP-1 receptor agonist structural homology or eight other examined subgroups), all-cause mortality (0.88 [0.82, 0.94]), hospitalisation for heart failure (0.89 [0.82, 0.98]) and a composite renal outcome (0.79 [0.73, 0.87]), with no increased risk of severe hypoglycaemia, retinopathy or adverse pancreatic effects. The benefits increased slightly when the only trial restricted to patients with an acute coronary syndrome was excluded.

Comment: We now finally have access to a funded GLP-1 agonist in NZ. Together with SGLT-2 inhibitors, we now have the contemporary suite of medications to choose from to best tailor treatment for an individual patient. The evidence for CV benefits for both classes came out first, and we have subsequently seen additional renal benefits and reductions in heart failure for the SGLT-2 inhibitors. Now that we have a GLP-1 agonist, but can't coprescribe them in a funded capacity, the obvious question is how do you choose between them. This meta-analysis of RCTs of GLP-1 agonists adds useful data on this question. It shows that these drugs also have a clear renal benefit and reduce heart failure. Therefore, important factors such as side effects and patient preference for tablet versus injectable agent come into play and may be the most relevant.

Reference: Lancet Diabetes Endocrinol; Published online Aug 20, 2021
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. **FOR FULL BIO CLICK HERE.**