Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 135 – 2020

In this issue:

Abbreviations used in this issue
ACE = angiotensin converting enzyme
ARB = angiotensin-2 receptor blocker
BMI = body mass index
BP = blood pressure
COVID = coronavirus disease
CV = cardiovascular
HbA_{1c} = glycosylated haemoglobin
HDL/LDL = high/low-density lipoprotein
SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

Welcome to issue 135 of Diabetes and Obesity Research Review.

With the need to minimise physical contact with our patients during the COVID-19 pandemic, the role of telehealth has come to the fore. The first paper in this issue provides valuable information to help successfully implement such a service for diabetes care. There are also three recent papers from the N Engl J Med reporting on associations between the use of ACE inhibitors or ARBs and risks in patients with COVID-19. Sugar-sweetened beverages take focus for two papers: one compared reported all-cause mortality associated with consumption of sugar-sweetened, artificially sweetened and naturally sweet beverages, while the other investigated the impact of a UK levy for soft drinks on the sugar content of beverages.

We hope you enjoy the papers selected for this issue. Your feedback and suggestions are always welcome.

Best regards,

Professor Jeremy Krebs
jeremykrebs@researchreview.co.nz

Top 10 tips for successfully implementing a diabetes telehealth program

Authors: Crossen S et al.

Summary: This article reviewed background information, recommendations for effective implementation and a future vision pertinent to the use of telehealth within diabetes care. Ten recommendations for integrating telehealth into diabetes practice were presented, which covered technological requirements (hardware and software for both videoconferencing and diabetes care), clinical operations (scheduling, standardising processes and health record integration) and maximising the benefits in terms of patient expectations, patient-centred care and culture changes for providers and institutions. The authors note that while some barriers remain, they are encouraged by recent advances that have facilitated the implementation and use of telehealth services for diabetes management.

Comment: COVID-19 has forced changes on us all, and over the last few months we have moved rapidly down a path of remote, virtual healthcare that many would not have dreamed of. For many, myself included, this has been at times very challenging. Adapting to the differences in interactions, arranging appointments, technology glitches, accessing information, etc were all issues when our service radically changed overnight. As we are coming out of COVID, many are calling for the ongoing use of telehealth. This paper therefore caught my eye as it discusses many of these issues and provides some insights to consider if you are also considering adopting greater telehealth interactions in your service.

Reference: Diabetes Technol Ther; Published online April 21, 2020
Abstract

Identification of ALK in thinness

Authors: Orthofer M et al.

Summary: These researchers undertook a genome-wide association study on metabolically healthy individuals from the lowest sixth BMI percentile of a population-wide uniquely phenotyped Estonian cohort, and identified the gene for Alk (anaplastic lymphoma kinase) as a candidate gene for thinness. RNAi-mediated knockdown of Alk in drosophila resulted in decreased triglyceride levels, and genetic deletion of Alk in mice resulted in thin animals that were markedly resistant to diet- and leptin-mutation-induced obesity. They found that *ALK* expression in hypothalamic neurons was associated with control of energy expenditure via sympathetic control of adipose tissue lipolysis.

Comment: Is this the secret to why that annoying friend of yours can seemingly eat anything and not get fat? We know that genetics play a major role in obesity, but most studies to date looking at the whole genome have only found a handful of genes that individually contribute a small percentage to the observed weight differences between carriers of an allele and those with the wild type gene. This paper reports on the opposite approach, of looking for the thinness gene, with very exciting results. By using genome-wide association, they identified a gene associated with thinness. They then used a knockout approach in drosophila and mice to study its effect. Most compelling was that in mice they demonstrated resistance to weight gain in models traditional of obesity. Furthermore, they have identified a potential mechanism in the hypothalamus for the neural control of adipose tissue lipolysis. This is very exciting, because if these observations are replicated, there is potential to target this mechanism with drugs. That is all a long way off and I hasten caution, as no obesity drug targeting energy expenditure has yet been successful.

Reference: Cell; Published online May 21, 2020
Abstract

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Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Cardiovascular disease, drug therapy, and mortality in Covid-19

Authors: Mehra MR et al.

Summary: Relationships of CV disease and drug therapy with in-hospital mortality were explored for 8910 patients admitted for COVID-19 to 169 hospitals across Asia, Europe and North America in this observational research. Mortality for this cohort was 5.8%. Factors independently associated with an increased risk of in-hospital death were age >65 vs. ≤65 years (10.0% vs. 4.9%; odds ratio 1.93 [95% CI 1.60, 2.41]), coronary artery disease (10.2% vs. 5.2%; 2.70 [2.08, 3.51]), heart failure (15.3% vs. 5.6%; 2.48 [1.62, 3.79]), cardiac arrhythmia (11.5% vs. 5.6%; 1.95 [1.33, 2.86]), chronic obstructive pulmonary disease (14.2% vs. 5.6%; 2.96 [2.00, 4.40]) and current versus former/nonsmoking (9.4% vs. 5.6%; 1.79 [1.29, 2.47]), but not ACE inhibitor or ARB use (2.1% vs. 6.1%; 0.33 [0.20, 0.54] and 6.8% vs. 5.7%; 1.23 [0.87, 1.74], respectively).

Reference: N Engl J Med; Published online May 1, 2020
Abstract

Renin-angiotensin-aldosterone system blockers and the risk of Covid-19

Authors: Mancia G et al.

Summary: This population-based study among 6272 case patients with SARS-CoV-2 infection from the Lombardy region of Italy and 30,759 matched controls explored the relationship between ACE inhibitor or ARB use and COVID-19 risk. The use of ACE inhibitors, ARBs and other drugs (including other antihypertensives) was more common among the patients with SARS-CoV-2 infection than it was among controls. The patients with SARS-CoV-2 infection also had worse clinical profiles. There was no association evident between ACE inhibitor or ARB use and COVID-19 (respective adjusted odds ratios 0.96 [95% CI 0.87, 1.07] and 0.95 [0.86, 1.05]), including among patients with a severe or fatal disease course (0.91 [0.69, 1.21] and 0.83 [0.63, 1.10]); no associations were seen between these variables according to sex.

Reference: N Engl J Med; Published online May 1, 2020
Abstract

Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19

Authors: Reynolds HR et al.

Summary: Associations between prior ACE inhibitor, ARB, β-blocker, calcium-channel antagonist and thiazide diuretic treatments and COVID-19 test results and severe COVID-19 illness (intensive care, mechanical ventilation or death) were explored in a cohort of 12,594 individuals who had undergone COVID-19 testing. Overall, 46.8% of the participants returned a positive COVID-19 test and 17.0% developed severe COVID-19 illness; among those with a history of hypertension (n=4357), these proportions were 59.1% (positive test) and 24.6% (severe illness). The likelihood of a positive test was not significantly increased by use of any of the medication classes evaluated, and among participants who tested positive, none of the medication classes predicted a substantial increase in the risk of severe illness.

Reference: N Engl J Med; Published online May 1, 2020
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.

Comment: In our special issue of Diabetes and Obesity Research Review on COVID in April, I highlighted the potential issues of ACE inhibitor and ARB use and risks of infection or adverse outcomes with COVID-19. Because this is such an important issue and very relevant to people with diabetes, I have included three additional papers with a related editorial from the N Engl J Med in this month's issue, which add further to our understanding. All are observational studies that carry risks of confounding, but the conclusions are concordant. The first study, by Mancia *et al.*, was a case-control study in Italy comparing 6272 people who contracted COVID-19 with 30,759 controls. In this analysis, ACE inhibitors or ARBs were not associated with an increased likelihood of catching COVID or with more severe disease. The second by Mehra *et al.*, reports on 8910 patients admitted to hospitals across Asia, Europe and North America. Increased risk of in-hospital death was associated with age >65 years, coronary artery disease and heart failure, amongst others, but not with ACE inhibitor use or with diabetes as reported elsewhere. In fact, ACE inhibitor and statin use was associated with reduced risk of mortality. The third study, by Reynolds *et al.*, reports on 12,954 patients screened for COVID-19 in New York. Of the 5894 positive cases, 1002 had severe disease requiring admission to ICU or mechanical ventilation, or resulting in death. An analysis using propensity matching to assess whether the likelihood of infection, or severity of infection, was related to any particular class of antihypertensive did not show any such relationship with any class of antihypertensive. These three additional studies add further support to the previous summaries that despite a theoretical risk of ACE inhibitors or ARBs increasing the risk of infection with COVID, this is not the case in clinical practice. This further strengthens the recommendation to continue to use and prescribe these agents as clinically indicated. The study by Mehra *et al.* does raise the possibility that rather than being harmful, these agents may in fact be protective. A causal association cannot be drawn from that study, and the benefit may well be related to better management of the underlying hypertension or heart failure. Equally important, we mustn't conclude from this study that prescription of these agents to someone who has COVID-19 will improve their outcome; however, we wait with interest any publications of randomised trials in that setting. Hopefully we won't have the opportunity to participate in such trials in NZ!

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Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults

Authors: Ge L et al.

Summary: This meta-analysis of 121 trials (n=21,942) examined the relative effectiveness of 14 popular diet programmes for weight loss and CV risk factor improvement in overweight or obese adults. Low-carbohydrate and low-fat diets had similar mean results at 6 months on weight loss (4.63 and 4.37kg, respectively) and reductions in systolic (5.14 and 5.05mm Hg) and diastolic (3.21 and 2.85mm Hg) BP. Slightly lower weight loss and BP reductions were observed with moderate macronutrient diets, while low-carbohydrate diets had less effect than low-fat diets and moderate macronutrient diets on LDL cholesterol level reduction (1.01 vs. 7.08 and 5.22 mg/dL, respectively), while low-carbohydrate but not low-fat and moderate macronutrient diets increased HDL cholesterol levels (2.31 vs. –1.88 and –0.89 mg/dL). Among named diets, the largest effects on weight reduction and BP at 6 months were achieved with the Atkins, DASH and Zone diets. No diets improved HDL cholesterol or C-reactive protein levels. Weight loss diminished at 12 months among all diets, and CV risk factor benefits of all interventions disappeared except with the Mediterranean diet.

Comment: There may have been more written about weight loss in books, lay press and scientific literature than any other health/behavioural change/cosmetic topic. That would suggest that there is no single approach that is most effective and durable. With such an abundance of contradictory 'evidence', it is therefore no wonder that the average person wanting to lose weight is confused and doesn't know how best to go about it. The world of dietary intervention studies is complex, with confounding issues in study design of comparator diets, degree of energy restriction, macronutrient composition and even methods of measuring dietary intake. This systematic review and network meta-analysis includes 121 studies, with a variety of dietary prescriptions. There are two key messages from this study. The first is that multiple dietary strategies achieve similar beneficial weight loss over 6 months, but that the effect is attenuated by 12 months with whichever strategy is adopted. The second is that the associated benefits in CV risk factors parallel the changes in weight across that time. So in the debate over which diet we should advise, the diet zealots are all right but all wrong at the same time! We need to find the tool that enables people to maintain their motivation and adherence to whichever dietary pattern they choose. That's the million dollar book.

Reference: BMJ 2020;369:m696
Abstract

Heterogeneity in the uptake, attendance, and outcomes in a clinical trial of a total diet replacement weight loss programme

Authors: Astbury NM et al.

Summary: This analysis of data from a trial of total diet replacement for clinical weight loss investigated differences among the invitees (n=272) who agreed to participate. Acceptance of the trial invitations was less likely by males than females (RR 0.59 [95% CI 0.47, 0.74]), and acceptance was greater among individuals from the middle and highest versus lowest BMI tertile (2.88 [1.97, 4.22] and 4.38 [3.05, 6.07], respectively) and those from practices in the most and intermediate versus least deprived tertile (1.84 [1.81, 2.59] and 1.68 [1.18, 2.85], respectively); age, pre-existing type 2 diabetes (1.10 [0.81, 1.50]) and hypertension (0.81 [0.62, 1.04]) did not significantly impact on enrolment. In the total diet replacement arm, 13% of participants were low engagers, 8% engaged in the weight loss phase only and 79% engaged in both the weight loss and maintenance phases, with those engaging in the entire programme achieving the greatest weight loss. Older participants and those with higher baseline BMIs appeared to have greater weight loss at 1 year compared with their comparators.

Comment: In NZ where there are very clear differences in rates of obesity and diabetes between ethnicities and by levels of deprivation, it is vitally important that any interventions we promote at a population level do not increase disparities. This study is therefore informative, analysing outcome data from a meal replacement very-low calorie diet intervention to explore who was most likely to benefit. Women and those who were most overweight were more likely to take part, which is almost universal in weight loss studies. However, people from more deprived areas were more likely to participate. Furthermore, the more engaged with the programme a person is, the more weight they lost. Whether these observations translate to clinical practice outside of the research setting needs reporting, but the signs are positive that promoting meal replacement very-low calorie diets will not increase inequity.

Reference: BMC Med 2020;18:86
Abstract

The associations of sugar-sweetened, artificially sweetened and naturally sweet juices with all-cause mortality in 198,285 UK Biobank participants

Authors: Anderson JJ et al.

Summary: Associations of consumption of sugar-sweetened or artificially sweetened drinks or 100% fruit/vegetable juice with all-cause mortality were explored for a prospective population-based cohort of 198,285 individuals from the UK Biobank study. Over mean follow-up of 7 years, 1.6% of the cohort died. There were no significant differences for total energy intake, total sugar intake or percentage of energy derived from sugar among participants who consumed >2 sugar-sweetened beverages per day and those who consumed >2 fruit/vegetable juice drinks per day. Individuals with the highest quintile of total sugar intake had increased all-cause mortality risk (adjusted hazard ratio 1.28 [95% CI 1.06, 1.55]) as did those who consumed >2 sugar-sweetened beverages per day (1.84 [1.42, 2.37]); these associations persisted in sensitivity analyses. An association between consumption of artificially sweetened beverages and mortality did not persist after deaths during the first 2 years of follow-up were excluded or when participants with recent weight loss were excluded. An inverse association between fruit/vegetable juice intake and mortality did not persist after adjustment for diet quality.

Comment: The battle of sugar and its contribution to ill health continues. Recent years have seen multiple reports of adverse health outcomes, including dental disease, obesity and diabetes, CV disease and cancers, corelated to sugar intake. Some of the strongest associations are with sugar-sweetened beverages, which has driven calls to either add a tax or ban them completely. This paper puts a nuance on this, which I'm not sure is really helpful from a public health perspective. It finds the same association between sugar-sweetened beverages and mortality, but not for fruit/vegetable juices. Whilst there may be plausible reasons for this, including micronutrient content, the contribution of any juice to calorie intake cannot be ignored. The distinction between types of juices and beverages can be manipulated by the food industry and becomes very difficult for the public to differentiate – tricky stuff.

Reference: BMC Med 2020;18:97
Abstract

Optimization of metformin in the GRADE cohort: effect on glycemia and body weight

Authors: Sivitz WI et al., and the GRADE Research Group

Summary: This prespecified analysis of GRADE study participants receiving metformin monotherapy for type 2 diabetes investigated the impact of metformin dosage optimisation on glycaemia and bodyweight; metformin ≥500 mg/day had been adjusted to 2000 mg/day or a maximally tolerated lower dosage during a 4- to 14-week run-in. After adjustment for run-in duration, the respective mean changes in HbA_{1c} levels associated with a metformin dosage increase by 1000 mg/day (n=2169), no dosage change (n=3548) and a dosage decrease (n=192) were –7.1, –5.2 and –2.5 mmol/mol (–0.65%, –0.48% and –0.23%). A higher HbA_{1c} level at study entry significantly predicted a greater reduction in HbA_{1c} level (p<0.001). There was an average weight loss of 0.91kg associated with an increase in metformin dosage by ≥1000 mg/day (n=1894) after adjustment for run-in duration.

Comment: This study is music to my ears. Metformin is a great drug and remains the first-line therapy in type 2 diabetes. Whilst the maximum dosage is 3g daily, side effects often increase when pushed above 2g and the incremental benefit in glucose lowering is often minimal. Furthermore, if prescribed as a three times daily regimen, the lunchtime dose is often missed anyway. These are all messages that I push to medical students. It is therefore pleasing to see this study supporting the notion that optimising the dosage to 2g daily, with an emphasis on adherence, provides the most effective glycaemic effects.

Reference: Diabetes Care 2020;43:940–7
Abstract

The sugar content of children's and lunchbox beverages sold in the UK before and after the soft drink industry levy

Authors: Chu BTY et al.

Summary: These researchers reported sugar and energy content for 131 fruit juices, juice drinks or smoothies specifically targeted at UK children. They also identified beverages for which the UK SDIL (soft drinks industry levy) would apply and compared the sugar content of these beverages before and after application of the SDIL. The overall mean sugar content of all 131 beverages was 6.3g per 100mL, with wide variation from 0.1 to 15.2g per 100 mL. The highest sugar content was seen in smoothies (11.55 g/mL). Only seven juice drinks were found to be eligible for the SDIL, four of which had reformulated their ingredients since prior analyses to lower the sugar content to <5g per 100mL.

Comment: …and here is why the debate about sugar-sweetened beverages is so tricky and not over. In the UK, the strategy to reduce sugar intake at a population level has been to add a levy to sugar-sweetened beverages related to the sugar content, with an intention for this to drive reformulation by the food industry to lower the sugar content. This study reviewed beverages targeted to children, and found that only seven of 131 products were eligible for the levy, making it an ineffective tool in promoting reformulation. Sugar content of the majority of beverages was still well above guidelines. We still have no regulation in NZ. If we can move on from COVID, this is one issue that needs to be back on the agenda.

Reference: Eur J Clin Nutr 2020;74:598–603
Abstract