Welcome to issue 54 of Diabetes and Obesity Research Review.

The first issue for 2012 kicks off with confirmation that our current practice of second-line therapy with sulphonylureas for patients with type 2 diabetes inadequately controlled with metformin is cost effective. Two papers report positive effects of breastfeeding for women, namely lower visceral adiposity and reduced abnormal glucose tolerance postpartum. We conclude with an intriguing paper describing glucose level measurements in teardrops.

I hope you find the selection for this issue interesting, and as always your feedback and comments are welcome.

Best regards,

Dr Jeremy Krebs
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Cost-effectiveness of second-line antihyperglycemic therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin

Authors: Klarenbach S et al

Summary: These researchers estimated diabetes-related complications, quality-adjusted life-years (QALYs) and costs associated with second-line therapies following inadequate control with metformin in Canadian patients with type 2 diabetes. Using the UK Prospective Diabetes Study Outcomes Model and clinical data from a systematic review and mixed treatment comparison meta-analysis, a sulphonylurea added to metformin versus metformin monotherapy was most cost-effective (incremental cost $12,757 per QALY), while cost effectiveness was unfavourable for thiazolidinediones and dipeptidyl peptidase-4 inhibitors.

Comment: As the number of people with type 2 diabetes increases and as people are being diagnosed at younger ages, the cost burden to the health sector to minimise complications explodes. As indicated in this paper, metformin has an undisputed place as first-line therapy, but with newer agents being developed, there is increased uncertainty on what is optimal second-line therapy. Much of this debate is centred around the potential for agents to preserve or even improve β-cell function and to minimise side effects such as weight gain and hypoglycaemia, which are the negative aspects of sulphonylureas or insulin. The jury remains out on the issue of β-cell function, but as this paper points out, on current pricing the cost-benefit analysis still supports sulphonylureas as second-line agents of choice. This is in line with current practice in NZ. However, individualisation of therapy is very important, and there are many patients where an alternative agent may be a better choice – it’s just who pays?

http://www.cmaj.ca/content/183/16/E1213.full

Independent commentary by Dr Jeremy Krebs, Endocrinologist & Clinical Leader at Wellington Hospital. For full bio CLICK HERE.
Research Review publications are intended for New Zealand health professionals.
Associations between the use of metformin, sulphonylureas, or diet alone and cardiovascular outcomes in 6005 people with type 2 diabetes in the FIELD study

Authors: Sullivan D et al, for the FIELD Study Investigators

Summary: This analysis of FIELD study data found that metformin therapy was: i) more common among younger, female or obese participants; and ii) associated with higher lipid (other than LDL cholesterol) and homocysteine levels. Sulphonylurea therapy was: i) more common in participants with a longer history of diabetes and more cardiovascular (CV) or microvascular disease; and ii) associated with higher plasma creatinine levels and lower plasma HDL cholesterol levels. Compared with diet alone, sulfonylurea use was associated with an increased risk of diabetes and more cardiovascular (CV) or microvascular disease. Compared with female users, males had higher BMI and greater prevalences of diabetes and heart disease. Duration of treatment for 12 months was completed by <2%, and of those who purchased ≥4 months of treatment (25%), BMI decreased slightly, but significantly, from 33.02 to 32.04 kg/m² (p<0.001). A multivariate analysis showed that adherence for ≥4 months was significantly associated with use of sibutramine (versus orlistat; odds ratio 2.08 [95% CI 1.76, 2.45]) and diabetes prevalence (1.20 [1.01–1.25]).

Comment: Sulphonylureas have been in use for many years, but some of the earlier agents were tainted by a question over CV risk—an issue that continues to be raised, and has been explored in analyses of the UKPDS data also. This paper looked at the FIELD study, which was primarily an RCT of fibrate therapy on CV outcomes. This paper specifically examines the outcomes relative to the use of metformin versus sulphonylurea therapy at baseline. The two key findings are that after adjustment for diabetes duration and other CV disease risk factors, there was no adverse effect of sulphonylureas. The second is that there was no interaction with fibrate.


Adherence to weight loss medications; post-marketing study from HMO pharmacy data of one million individuals

Authors: Hemo B et al

Summary: This population-based analysis of patients treated for the first time with bodyweight loss drugs in the US revealed doubling of the use of orlistat and sibutramine over 5 years and greatest usage rates around summer months (May–August). Users of bodyweight loss drugs (n=7175; versus 1038,828 nonusers) were more likely to be female, have a higher BMI, have a history of bariatric surgery or be receiving pharmacotherapy for diabetes, depression or cardiovascular disease. Compared with female users, males had higher BMI and greater prevalences of diabetes and heart disease. Duration of treatment for 12 months was completed by <2%, and of those who purchased ≥4 months of treatment (25%), BMI decreased slightly, but significantly, from 33.02 to 32.04 kg/m² (p<0.001). A multivariate analysis showed that adherence for ≥4 months was significantly associated with use of sibutramine (versus orlistat; odds ratio 2.08 [95% CI 1.76, 2.45]) and diabetes prevalence (1.20 [1.01–1.25]).

Comment: There is no quick fix! The last few decades have seen the coming and going of multiple bodyweight loss agents. Many come with fanfare, and virtually all go with failure, some with significant adverse effects that only become apparent well after the agents are approved and widely used. Of the agents to reach and remain in the market for any length of time in the last few years, both orlistat and sibutramine had good RCT evidence to support clinically meaningful weight loss—at least over 2 years. However, as this analysis of postmarketing data shows, weight loss trials, perhaps more than most other clinical trials, do not reflect the real world when it comes to adherence and results. The very poor long-term adherence reflects not only the ineffective agents, but probably more so the patients’ expectations that pills with a relatively weak action on appetite control substitute for the need for substantive dietary and lifestyle change! No magic pill.


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Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study

Authors: Sjöström CD et al

Summary: This analysis of participants from the Swedish Obese Subjects (SOS) intervention study 10 years on included 959 and 842 surgically and conventionally treated obese individuals, respectively, stratified by amount of bodyweight loss. The results showed that 10–44kg of bodyweight loss was necessary for significant improvements in cardiovascular risk factors. Significant increases in systolic blood pressure, pulse pressure and HDL cholesterol and glucose levels, and significant decreases in diastolic blood pressure and levels of total cholesterol, triglycerides and insulin, occurred over 10 years in participants with no weight change.

Comment: Well this is all a bit depressing! For many years we have been advising patients that 5–10% of bodyweight loss is associated with health improvements, even if it doesn’t achieve the cosmetic dreams that they might have. This paper from the largest and longest bariatric surgery study suggests that this may not be correct, and that greater weight loss may be required for long-term benefits. For a 100kg person, this equates to 10–40% reduction in bodyweight. Most people are able to achieve a 5% reduction if they really try, but few can achieve more than 10% and sustain this with diet and lifestyle changes alone. The mixed nature of the weight loss methods and the variety of surgical procedures in the SOS study confound this analysis. It would be preferable to see the same study conducted in a group who had achieved their weight loss purely with diet and lifestyle changes, but sadly few ever get close to a 40% reduction this way. It is vital that we do not start promoting unachievable goals, but perhaps preferable to see the same study conducted in a group who had achieved their weight loss purely with diet and lifestyle changes alone. The mixed nature of the weight loss methods and the variety of surgical procedures in the SOS study confound this analysis. It would be preferable to see the same study conducted in a group who had achieved their weight loss purely with diet and lifestyle changes, but sadly few ever get close to a 40% reduction this way. It is vital that we do not start promoting unachievable goals, but perhaps we should be setting the bar at 10%, not 5%.

http://www.nature.com/jo/journal/v35/n11/full/jo2010282a.html

Relative muscle mass is inversely associated with insulin resistance and prediabetes: findings from the third National Health and Nutrition Examination Survey

Authors: Srikanthan P & Karlamangla AS

Summary: This cross-sectional analysis of NHANES III data from 13,644 individuals found that homeostasis model assessment of insulin resistance (HOMA-IR), blood Hb A1c level, prevalence of transitional/pre- or overt diabetes (PDM) and prevalence of overt diabetes all decreased from the lowest to highest quartiles of skeletal muscle index (total skeletal muscle mass/total bodyweight). Each 10% skeletal muscle index increase was associated with adjusted relative reductions in HOMA-IR and PDM prevalence by 11% and 12%, respectively. The associations between skeletal muscle index and both HOMA-IR and PDM were stronger in those without diabetes.

Comment: Reduced relative lean mass is associated with obesity and with a more sedentary lifestyle; both are key risk factors for type 2 diabetes. A cross-sectional study of this nature cannot differentiate whether lower levels of lean muscle mass per se are the causative factor. There is evidence from other studies that interventions such as resistance training designed to specifically increase lean mass improve insulin sensitivity. This study is therefore of more interest for the prospect of informing the design of a longitudinal RCT to test the potential of an intervention to specifically improve lean body mass and the incidence of diabetes.

Reference: J Clin Endocrinol Metab 2011;96(9):2898–903
http://jcem.endojournals.org/content/96/9/2898

Metabolic sequelae of β-blocker therapy: weighing in on the obesity epidemic?

Authors: Lee P et al

Summary: These authors found 50%, 32% and 30% reductions in diet-induced thermogenesis, fat oxidation rate and weekly habitual activity, respectively, in 11 volunteers with uncomplicated hypertension treated with β-blockers compared with 19 untreated matched controls. In separate cross-sectional analyses, β-blocker recipients who attended diabetes and hypertension clinics were a mean 9.2kg and 17.2kg heavier, respectively, than nonrecipients, while β-blocker recipients from the ADVANCE trial were a mean 5.2kg heavier at baseline (p=0.0003); similar differences were seen for BMI.

Comment: Nice hypothesis, but these studies do not prove it. Cross-sectional studies of this nature can only ever be hypothesis generating. There is certainly biological plausibility that β-blockade will result in reduced energy expenditure, but it is equally plausible that patients requiring β-blockers have underlying conditions that make it more likely that they will have reduced energy expenditure irrespective of medication. As always, a prospective RCT is the only way to sort this out, but the issue is certainly relevant. However, for many patients the indication for a β-blocker will outweigh any potential adverse weight gain in terms of clinical decision making.

http://www.nature.com/ijo/journal/v35/n11/full/ijo2010284a.html
Breastfeeding and subsequent maternal visceral adiposity

Authors: McClure CK et al

Summary: The effect of (self-reported) breastfeeding on visceral adiposity was explored in 351 women by these researchers. Compared with mothers who had breastfed all their children for ≥3 months, premenopausal/early-perimenopausal mothers who had never breastfed had: i) 28% greater visceral adiposity (p<0.001); ii) 4.7% greater waist-hip ratio (p<0.001); and iii) 6.49cm greater waist circumference (p<0.001). Visceral adiposity was comparable between nulliparous women and mothers who breastfed all their children for ≥3 months, while compared with nulliparous women, premenopausal/early-perimenopausal mothers who had never breastfed had: i) 42% greater visceral adiposity (p<0.001); ii) 6.15cm greater waist circumference (p<0.001); and iii) 3.7% greater waist-hip ratio (p=0.02). There were no significant associations seen for late perimenopausal/postmenopausal women.

Comment: Breast is best. Although there are many reasons why women choose to breastfeed or not, and many women who wish to breastfeed find that they are unable to, here is another study that supports the push to encourage women to breastfeed if they are able. Once again it is a cross-sectional study, so there may be confounding factors that explain this observation and are unrelated to breastfeeding. Sadly, the apparent protective effect is not preserved after the menopause, which can often be a very challenging time for women!

http://www.nature.com/oby/journal/v19/n11/full/oby2011185a.html

Atlantic DIP: high prevalence of abnormal glucose tolerance post partum is reduced by breast-feeding in women with prior gestational diabetes mellitus

Authors: O'Reilly MW et al

Summary: Postpartum oral glucose tolerance test (OGTT) results from 300 women with gestational diabetes were compared with results from 220 controls in this study. The postpartum dysglycaemia rate was significantly greater among women with gestational diabetes than those with normal gestational glucose tolerance (19% vs. 2.7%; p<0.001). Persistent dysglycaemia was significantly more likely in women of non-European ethnicity (odds ratio 3.40 [95% CI 1.45, 8.02; p=0.005]), those with a family history of type 2 diabetes (2.14 [1.06, 4.32; p=0.034]) and those who had received insulin during gestation (2.62 [1.17–5.87; p=0.019]). Women who had breastfed postpartum were significantly less likely to experience persistent hyperglycaemia than those who bottlefed (8.2% vs. 18.4%; p<0.001).

Comment: Continuing the theme of ‘breast is best’, this study looked at factors predicting persistent dysglycaemia after pregnancy in those with gestational diabetes. Compared with women who did not have gestational diabetes, the expected variables were more common in those who had persistent dysglycaemia and reflect the well-documented population risk factors. Of note though is that women who breastfed had lower rates of dysglycaemia than women who bottlefed. Whether this is a specific metabolic effect of breastfeeding or related to the increased energy requirements of breastfeeding, or some other associated factor of those who do breastfeed, is unclear from this study. Nevertheless, the findings do support the promotion of breastfeeding where possible.

http://www.eje-online.org/content/165/6/953.abstract

Relationship between interstitial and blood glucose during hypoglycaemia in subjects with type 2 diabetes

Authors: Choudhary P et al

Summary: These researchers explored the relationship between blood and interstitial glucose levels during experimental hypoglycaemia in 20 patients with type 2 diabetes, including 10 treated with sulphonylureas and 10 with insulin, and 10 control participants. Interstitial glucose levels were significantly greater than blood levels for all levels of hypoglycaemia, and the difference increased significantly by 0.32 mmol/L for every 1 mmol/L blood glucose level decrease (p<0.001). Neither the presence of type 2 diabetes nor treatment modality affected this difference.

Comment: The use of subcutaneous continuous glucose monitoring has become increasingly useful for managing patients with type 1 diabetes. This is both for diagnosing unrecognised hypoglycaemia, but also increasingly for daily management, particularly for those with insulin pumps. The disparity between blood and interstitial glucose levels has been one of the potentially limiting factors of this technology. This study adds to the understanding of this, extending to those with type 2 diabetes. It is of note that the relationship between interstitial and blood glucose levels during hypoglycaemia seen in this group is opposite to that seen in patients with type 1 diabetes, and not what one would intuitively expect. The clinical importance being that it may underestimate the frequency of hypoglycaemia, where detecting this is the purpose of its use.


Measurement of tear glucose levels with amperometric glucose biosensor/capillary tube configuration

Authors: Yan Q et al

Summary: This paper described and explored the use of an amperometric needle-type electrochemical sensor intended to measure glucose levels in tears collected via a capillary tube. The sensor is designed to have enhanced selectivity for glucose over potential interferences in tear fluid, such as ascorbic acid and uric acid, and is optimised to detect glucose levels with a sensitivity of 0.032 (±0.02) nA/μM in 4–5 μL of tear fluid. A strong correlation was seen between tear and blood glucose levels over an 8-hour period in anaesthetised rabbits. The researchers concluded that “measurement of tear glucose is a potential noninvasive substitute for blood glucose measurements, and the new sensor configuration could aid in conducting further research in this direction”.

Comment: Obtaining accurate and precise estimates of blood glucose levels to inform day-to-day management of diabetes is a fundamental necessity of modern diabetes care. This is particularly important for those with type 1 diabetes and type 2 diabetes on insulin. One of the barriers to patient adherence with this is the invasiveness of finger pricking. This report of a new technology to estimate glucose levels in tears is therefore of great interest. It certainly has the potential to overcome the ‘finger prick’ barrier, but only time will tell if it becomes a useable clinical tool. The time and inconvenience factors will still be relevant, and undoubtedly the cost will have funding bodies quivering!

http://pubs.acs.org/doi/full/10.1021/ac107000c

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