

Diabetes & Obesity Research Review™

Making Education Easy

Issue 19 – 2008

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Welcome to the the latest edition of Diabetes and Obesity Research Review.

This month we are pleased to announce some exciting changes to the Review. First we are delighted to welcome our new sponsor, the Ministry of Health, and thank them for their support of the initiative.

Second, we have tried to make it more interactive; we will now include discussion papers which we encourage you to respond to. The answers will come in the next edition. Go on, test yourself!

Lastly, we would like to offer you the opportunity to find some like minded people around the country. If you have a diabetes/obesity study you'd like to carry out or are currently doing and trying to recruit for, let us know. We will let the other members know (2060) and we may be able to help some collaboration on local research.

Please let us know what you think of the fresh approach and contact me directly with answers, questions or details of any exciting projects.

Kind regards,

Dr Jeremy Krebs

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Meta-Analysis of cholesterol-lowering therapy in diabetes

Authors: Cholesterol Treatment Trialists' (CTT) Collaborators

Summary: Data from 14 randomised trials of 18,686 patients with diabetes (and 71,370 without diabetes) was collated to consider the effect of statin therapy on occlusive vascular events and whether such effects depended on the type of diabetes, lipid profile, or other factors. There was a similar reduction in all-cause mortality per mmol/L reduction in LDL cholesterol for diabetics and non-diabetics, 9% vs 13% (rate ratio 0.91, $p = 0.02$ and rate ratio 0.87, $p < 0.0001$ respectively). This reduced mortality reflected a significant improvement in vascular mortality (0.87, 0.76 to 1.00; $p = 0.008$). There was also a similar and significant proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol for those with and without diabetes (0.79, $p < 0.0001$). Reductions in myocardial infarction or coronary death (0.78, $p < 0.0001$), coronary revascularisation (0.75, $p < 0.0001$), and stroke (0.79, $p = 0.0002$) were also observed in diabetic patients. The effects of statin therapy were similar irrespective of baseline history including vascular disease.

Comment: This meta-analysis is included simply to reinforce the knowledge we already have regarding the important place of statin therapy in patients with diabetes. The number needed to treat to prevent vascular events over 5 years is compelling. This study reinforces that patients with diabetes have equivalent benefit to those without diabetes. What needs to be remembered is that those with diabetes have a greater risk to start with.

[http://dx.doi.org/10.1016/S0140-6736\(08\)60104-X](http://dx.doi.org/10.1016/S0140-6736(08)60104-X)

Reference: *The Lancet* 2008; 371:117-125

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Email: jeremykrebs@researchreview.co.nz

Discussion Papers

This is the first in our new series of discussion papers. This month we focus on the issues which arise in the management of type II diabetes when glycolated haemoglobin levels remain elevated despite optimally dosed, dual oral antihyperglycemic therapy: highlighted by the case vignette below. Please do click through using the link beneath to read the discussion of treatment options and then feedback your responses to us. Also below is a second study on self-management in primary care. I would like to hear from you on what you think is most important and maybe some other factors you have identified.

Case Vignette: Management of Type 2 Diabetes

Authors: Goldberg RB

Summary: A 55-year-old woman with type 2 diabetes, obesity, and hypertension has been under your care for 2 years. She has no history of microalbuminuria, retinopathy, or neuropathy, has never had a cardiovascular event and reports no cardiac symptoms. In the past, she has successfully lost weight (from 5 to 12 kg) but has always regained it. She tries to walk 30 minutes each day. She monitors her fasting glucose levels three times weekly using a personal glucometer, and her morning fasting glucose levels have ranged between 6.1 and 7.8 mmol/L. She has been receiving metformin (1000 mg twice a day) and glipizide (10 mg twice daily). The patient has hypertension that is treated with hydrochlorothiazide (25 mg daily) and lisinopril (20 mg daily). She takes aspirin (81 mg daily) and simvastatin (20 mg daily). She notes that she consistently takes her medications. She has a family history of cardiovascular disease with early stroke. On physical examination, her body-mass index is 31. Her blood pressure is 128/78 mm Hg. Her general assessment, including cardiorespiratory, abdominal, and neurologic examinations, is normal. Her glycolated hemoglobin level is 8.1%, and her creatinine 80 mmol/L. She has no microalbuminuria, and liver-function studies are normal. She seeks advice about the management of her diabetes.

What kind of treatment would you find most appropriate for this patient? Three options are outlined in short essays written by experts in the management of type 2 diabetes. They include the addition of pioglitazone, neutral protamine hagedorn (NPH) insulin or exenatide.

Comment: Lets get this research review a bit interactive. This case discussion published in January calls for you to decide on the next step in therapy. The results of the NEJM poll were published this month, but lets see what the opinion is locally. I challenge you to read the case and reply to research reviews with you choice of therapy and I will let you know the result in the next review. Please choose between the options outlined in the article, but in addition add the 4th option of Sitagliptin 100mg daily as it is likely that this will be available in New Zealand this year. For the purposes of this exercise, lets assume that all options are fully funded, and the choice is based on best medicine rather than Pharmac medicine! Did I say that? Wash my mouth out.

<http://content.nejm.org/cgi/content/full/358/3/293>

Reference: *NEJM* 2008; 358:(3)293

What option did you pick?

Pioglitazone, neutral protamine hagedorn (NPH) insulin, exenatide or sitagliptin?

Send me your choices and comments and we'll publish the collective result next issue jeremykrebs@researchreview.co.nz

Organisational resources and supports for self management in primary care

Authors: Shetty G and Brownson CA

Summary: The authors utilised experience gained from the Diabetes Initiative's 'Advancing Diabetes Self Management' projects and collaborated with the experts and staff from this group to describe the elements of organisational resources and supports for diabetes self-management in primary care. The eight components identified were (1) the establishment of patient care teams; (2) continuity of care; (3) coordination of referrals; (4) documentation of self-management support; (5) ongoing quality improvement; (6) patient input; (7) staff training and education; and (8) integration of self-management into primary care. These elements provide direction for developing an infrastructure of organisational resources and supports for self-management in primary care settings.

Comment: The majority of patients with diabetes are managed in primary care. There is a drive to enhance self management skills. This paper describes some of the elements of systems to enhance self management. Keeping this interactive, I would be interested in hearing from you what features you feel are important in self management. These could be from the eight elements in this paper or other factors which you identify. I will report back on these again next time.

<http://dx.doi.org/10.1177/0145721707304171>

Reference: *Diabetes Educator* 2007; 33:Suppl 6:185S-192S

Effect of multifactorial intervention on mortality in type 2 diabetes

Authors: Gaede P et al

Summary: Patients with type 2 diabetes and persistent microalbuminuria (n = 160), were randomly assigned to either conventional therapy or intensified multifactorial intervention (renin-angiotensin system blockers, aspirin, lipid-lowering agents and behavioural modification). The mean treatment period was 7.8 years, following which patients were observed for a mean of 5.5 years. Only 24 patients in the intensive therapy group had died by the primary end point of 13.3 years, compared to 40 taking conventional therapy (hazard ratio 0.54; 95% CI 0.32 to 0.89; p = 0.02). Cardiovascular events and cardiovascular related deaths were less likely in the intensive therapy group (HR 0.41; 95% CI 0.25 to 0.67; p < 0.001 and HR 0.43; 95% CI 0.19 to 0.94; p = 0.04 respectively). Fewer patients receiving intensive intervention compared to those receiving conventional therapy, progressed to end-stage renal disease (1 vs 6; p < 0.04) or required retinal photocoagulation (relative risk 0.45; 95% CI 0.23 to 0.86; p = 0.02).

Comment: Cardiovascular disease is the major cause of death in patients with type 2 diabetes. Microalbuminuria is an important independent risk factor for cardiovascular events and identifies a group in whom aggressive risk factor management is targeted. The Steno 2 study reported reduced rates of non-fatal events with intensive multifactorial intervention. This report describes the extension of this study out to 13 years with demonstration that the intensive treatment resulted in an impressive reduction in cardiovascular mortality. The magnitude of this is probably underestimated as those in the original conventional arm received intensified treatment in the follow up period.

<http://content.nejm.org/cgi/content/short/358/6/580>

Reference: *NEJM* 2008; 358:6:580-91



**Independent commentary
by Dr Jeremy Krebs**

**Research Review publications
are intended for New Zealand
health professionals**

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy

Authors: Keech AC et al

Summary: The FIELD study randomised 9,795 patients (aged 50–75 years) with type 2 diabetes mellitus to either fenofibrate 200 mg/day or placebo. Patients were assessed for laser treatment for macular oedema, proliferative retinopathy and other eye conditions by ophthalmologists blind to the treatment allocation. In a further substudy (n = 1,012), retinal photographs were graded with the Treatment Diabetic Retinopathy Study (ETDRS) criteria to determine the cumulative incidence of diabetic retinopathy and its component lesions. Significantly fewer patients in the fenofibrate group required laser treatment than controls, 3.4% vs 4.9% (HR 0.69, 95% CI 0.56 to 0.84; p = 0.0002; absolute risk reduction 1.5%, CI 0.7–2.3). In the substudy no significant difference was observed between treatment groups for the primary endpoint of a 2-step progression of retinopathy grade. However for patients with pre-existing retinopathy, fewer of those in the fenofibrate group experienced a 2-step progression compared to those in the control group (3.1% vs 14.6%; p = 0.004).

Comment: The importance of glycaemic control in preventing and reducing the progression of diabetic retinopathy is well established. However, unfortunately not all patients with diabetes are able to achieve tight glucose control. Therefore any alternative strategies are welcome. The FIELD study was primarily designed to answer the question whether lipid lowering using fibrates reduces cardiovascular events. Unfortunately as we know the study became confounded by the introduction of statin therapy in many of the placebo group, and the interpretation of the data became difficult. This report from the FIELD study of the impact of fenofibrate on retinopathy raises again the potential value of fibrates in diabetes, as it would appear that they may have an effect on retinopathy independent of any lipid lowering. This may provide evidence for a subgroup of patients with diabetes where the addition of a fibrate could be considered.

[http://dx.doi.org/10.1016/S0140-6736\(07\)61607-9](http://dx.doi.org/10.1016/S0140-6736(07)61607-9)

Reference: *The Lancet* 2007; 370:1687-1697

Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials

Authors: Christensen R et al

Summary: The authors collated data from four double-blind randomised controlled trials (n = 4,105), which compared rimonabant (20 mg/day) to placebo. A significant difference in weight loss was observed at 1 year, with rimonabant patients losing 4.7 kg more than those on placebo (95% CI, 4.1 to 5.3 kg; p < 0.0001). However rimonabant was associated with significantly more adverse events (NNH 25, 95% CI 17 to 58; p = 0.0007), and serious adverse events than placebo (NNH 59, 95% CI 27 to 830; p = 0.03). Furthermore rimonabant patients were significantly more likely to discontinue treatment due to depressive mood disorders (OR 2.5, NNH 49, 95% CI 19 to 316; p = 0.01) or anxiety (OR 3.0, NNH 166, 95% CI 47 to 3,716; p = 0.03). The authors conclude that rimonabant increased the risk of psychiatric adverse events (despite depressed mood being an exclusion criteria) and recommend increased vigilance by physicians considering the FDA finding of increased risk of suicide during rimonabant treatment.

Comment: With the obesity epidemic the need to find effective pharmacological treatments to support the efforts of individuals in their quest for sustained diet and lifestyle change is urgent. To date no effective drug to enhance metabolic rate without limiting side effects has been found. Much focus has been on appetite regulation in order to reduce intake. Rimonabant, a cannabinoid receptor antagonist, has not yet reached New Zealand, other than in clinical trials. This meta-analysis crystallises the concerns that have emerged from individual trials and post marketing surveillance. An impact on mood may be expected through its mechanism of action, but the numbers needed to harm described may mean that Rimonabant heads down the path of many obesity drugs before it. I suspect we still await the magic pill!

[http://dx.doi.org/10.1016/S0140-6736\(07\)61721-8](http://dx.doi.org/10.1016/S0140-6736(07)61721-8)

Reference: *The Lancet* 2007; 370:1706-1713

Theory-based behavioural intervention to increase physical activity in an at-risk group

Authors: Kinmonth A et al

Summary: This trial of 365 sedentary adults with a parental history of type 2 diabetes, randomised patients to one of two intervention groups or a comparison group. The interventions were a one year behaviour change programme delivered by either a trained facilitator or by telephone whilst the comparison group received a brief advice leaflet. The physical-activity ratio, which compared objectively measured daytime physical activity to resting energy expenditure, had decreased by -0.04 at one year (95% CI -0.16 to 0.08). There were no significant differences in the physical activity ratios of patients receiving the intervention compared to those in the comparison group. Nor was there a difference in the ratios of patients who received the intervention by different delivery methods. The authors conclude that health care providers should be cautious in commissioning behavioural programmes since theory-based behavioural intervention was no more effective than an advice leaflet for promotion of physical activity.

Comment: Well aren't we a sad pathetic bunch of couch potatoes! This study is SAD! I'm sure it reflects the frustration that we all experience in day to day practice. Achieving realistic, meaningful and sustainable degrees of increase in physical activity in sedentary individuals is very hard. We all know that so-called "educational leaflets" have very little impact, hence the quest to find a more effective strategy. One might expect that a personal contact in the ease of ones own home would be convenient and motivating. Apparently not. This is a very useful negative study, as it should prevent the wasteful use of resource on such programmes. Maybe we need to legislate for increased physical activity – it is election year after all!

[http://dx.doi.org/10.1016/S0140-6736\(08\)60070-7](http://dx.doi.org/10.1016/S0140-6736(08)60070-7)

Reference: *The Lancet* 2008; 371:41-48

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Early life determinants of physical activity in 11 to 12 year olds

Authors: Mattocks C et al

Summary: This prospective cohort study considered physical activity levels (in counts per minute and minutes of moderate to vigorous physical activity for seven days measured by uniaxial actigraph accelerometer), in 5,451 11 to 12 year old children. Few factors in early life were found to predict later physical activity, with parent's physical activity during pregnancy and early in the child's life showing a modest association; maternal brisk walking during pregnancy (regression coefficient 5.0, 95% CI -8.5 to 18.5; cpm for < 1 h/wk and \geq 2 h/wk of physical activity 17.7, 5.3 to 30.1), maternal swimming during pregnancy (21.5, 10.9 to 32.1 and cpm for < 1 h/wk and \geq 2 h/wk of physical activity 24.2, 7.8 to 40.7), parents' physical activity when the child was aged 21 months (28.5, 15.2 to 41.8 and cpm 33.5, 17.8 to 49.3), and parity assessed during pregnancy (2.9, -7.6 to 13.4 and cpm of physical activity for 1 and \geq 2 parity 21.2, 7.1 to 35.3). The authors suggest that helping parents to increase their physical activity therefore may promote children's activity.

Comment: We have seen the ineffective nature of personal home-based educational strategies in increasing physical activity in the previous paper. However, finding an effective strategy becomes more important when we see the results of this study. Increasing the activity of parents may help to prevent obesity and diabetes in subsequent generations, though this is not specifically tested in this study. I guess it is intuitive but good to have a study to back it up. This is becoming my catch cry, "on yer bike" parents.

<http://dx.doi.org/10.1136/bmj.39385.443565.BE>

Reference: *BMJ* 2008; 336:26-2



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Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain

Authors: Ren-Rong Wu et al

Summary: This 12-week randomised controlled trial of patients with schizophrenia (n = 128), who had gained more than 10% of their body weight following initiation of an antipsychotic, assigned patients to either placebo, metformin (750 mg/d) alone, metformin (750 mg/d) and lifestyle intervention, or lifestyle intervention alone. The metformin plus lifestyle group had the greatest reductions in BMI, insulin resistance and waist circumference: 1.8 (95% CI 1.3 to 2.3), 3.6 (95% CI 2.7 to 4.5) and 2.0 cm (95% CI, 1.5 to 2.4) respectively. The metformin group had mean decreases in BMI of 1.2 (0.9 to 1.5), insulin resistance 3.5 (2.7 to 4.4) and waist circumference of 1.3 cm (1.1 to 1.5 cm). The lifestyle group had mean decreases of 0.5 (0.3 to 0.8) and 1.0 (0.5 to 1.5) for BMI and insulin resistance respectively whilst the placebo group had increased BMI, insulin resistance index and waist circumference of 1.2 (0.9 to 1.5), 0.4 (0.1 to 0.7) and 2.2cm (1.7 to 2.8 cm). Improvements in weight, BMI, and waist circumference were significantly greater for lifestyle plus metformin treatment compared to metformin or lifestyle alone.

Comment: The atypical antipsychotics have become a very important part of the management of those with psychiatric disorders. However the majority of patients gain weight and many develop metabolic side effects with glucose and lipid metabolism. Weight management is very difficult for this group of patients and any strategies that can prevent or manage weight gain associated with these drugs is welcome. This study shows that a combination of metformin and lifestyle intervention can facilitate modest weight loss and improved metabolic parameters. Although the study was only over 12 weeks, it would suggest that metformin could be started with atypical antipsychotics. A longer term study of this strategy would be worthwhile.

<http://jama.ama-assn.org/cgi/content/abstract/299/2/185>

Reference: *JAMA* 2008; 299(2):185-193

Adjustable gastric banding versus conventional therapy for type 2 diabetes

Authors: Dixon JB et al

Summary: This randomised controlled trial assigned 60 obese patients (BMI > 30 and < 40) with recently diagnosed type 2 diabetes to either conventional diabetes therapy with a focus on weight loss by lifestyle change or laparoscopic adjustable gastric banding with conventional diabetes care. Significantly more patients in the surgical group achieved remission of diabetes compared to those in the conventional therapy group, 73% versus 13% with a relative risk of remission for the surgical group of 5.5 (95% CI 2.2 to 14.0). The surgical group also lost significantly more weight than the conventional therapy group; 20.7% (SD 8.6%) and 1.7% (SD 5.2%) respectively at 2 years (p < 0.001). There was a correlation between remission and weight loss (R2 = 0.46, p < 0.001) and lower baseline HbA1c levels (combined R2 = 0.52, p < 0.001). The authors concluded that patients receiving surgical therapy were more likely to achieve remission of type 2 diabetes through greater weight loss.

Comment: Bariatric surgery for obesity management is gaining acceptance as an appropriate treatment for morbid obesity. Observational case series for both laproscopic banding and the main alternative operation, gastric bypass, have shown impressive weight losses, and perhaps more importantly improvements in glucose metabolism, lipids and blood pressure. Randomised trials in obesity surgery are rare. This study highlights the potential weight loss that can be achieved with surgery, and the extent of metabolic improvement that goes with it. Whether laproscopic banding or gastric bypass is more effective is unknown and a randomised trial to test that would be very interesting. For patients with type 2 diabetes and morbid obesity surgical treatment is an effective option that should be considered for those who are willing. All we need now is the funding for this in the public system.

<http://jama.ama-assn.org/cgi/content/abstract/299/3/316>

Reference: *JAMA* 2008; 299(3):316-323

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