

Diabetes & Obesity Research Review™

Making Education Easy

Issue 30 - 2011

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Welcome to the 30th issue of Diabetes and Obesity Research Review.

In our first edition for 2011, sodium and potassium dietary intakes of patients with type 2 diabetes are put under the spotlight, and the results are not encouraging. There is also some discouraging news for the ongoing role of inhaled insulin, with evidence that resultant amyloid deposits could be the cause of reported declines in lung function. We start this issue with an observational study supporting the use of metformin in patients with known cardiovascular (CV) disease, and finish up with an Australian study demonstrating high CV risks among individuals working in sedentary environments.

We look forward to another year of Diabetes and Obesity Research Reviews, and as always we welcome your comments and feedback.

Kind Regards

Prof. Peter Little

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Metformin use and mortality among patients with diabetes and atherothrombosis

Authors: Roussel R et al, for the Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators

Summary: This study reported mortality rates among 19,691 patients with diabetes and established atherothrombosis from the Reduction of Atherothrombosis for Continued Health (REACH) registry. A multivariate analysis revealed that participants who had received metformin had a significantly lower 2-year mortality rate than those who had not received the agent (6.3% vs. 9.8%; adjusted hazard ratio 0.76 [95% CI 0.65–0.89; $p < 0.001$]). Subgroup analyses revealed consistently lower 2-year mortality rates among metformin users for: i) participants with a history of congestive heart failure (hazard ratio 0.69 [95% CI 0.54–0.90; $p = 0.006$]); ii) those aged >65 years (0.77 [0.62–0.95; $p = 0.02$]); and iii) those with an estimated creatinine clearance 30–60 mL/min/1.73m² (0.64 [0.48–0.86; $p = 0.003$]).

Comment (NC): This is a large observational study that supports the use of metformin in patients with known CV disease. The reduction in mortality was seen overall and in subgroups including cardiac failure, elderly patients and renal impairment. This was not a randomised trial and clearly there are many potential confounders; however, the findings are consistent with other studies including the UKPDS. Although the mechanism of this benefit is not clear, there is accumulating evidence for the use of metformin as a cardioprotective agent.

Reference: *Arch Intern Med* 2010;170(21):1892–9

<http://archinte.ama-assn.org/cgi/content/abstract/170/21/1892>

RESEARCH REVIEW

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Patient-reported outcomes from a 16-week open-label, multicenter study of insulin pump therapy in patients with type 2 diabetes mellitus

Authors: Rubin RR et al

Summary: This study investigated patient-reported outcomes associated with insulin pump therapy over 16 weeks in patients with type 2 diabetes treated with oral antidiabetic agents only at baseline (n=17), basal insulin with or without oral antidiabetic agents (n=17) or multiple daily insulin injections with or without oral antidiabetic agents (n=20); all baseline medications except metformin were discontinued when insulin pump therapy was started. Overall, there were significant reductions in Diabetes Symptom Checklist-Revised and EuroQol-5 Dimensions visual analogue scale scores. Health-related quality of life scores were not significantly altered among the subgroup of participants receiving oral antidiabetic agents alone at baseline, but did improve in the baseline insulin subgroups. There were improvements in the overall group for all measures of treatment satisfaction, as assessed by the Insulin Delivery System Rating Questionnaire, with the exception of treatment interference. In subgroups, the participants who had received oral antidiabetic agents alone at baseline experienced significant improvements in perceived clinical efficacy and overall treatment preference, while the baseline insulin subgroups experienced improvements in five of the seven treatment satisfaction measures.

Comment (NC): The use of insulin pump therapy in type 2 diabetes is not established. This is a short-term study looking at patient-reported outcomes that mostly improved with pump therapy, except in the group initially on oral agents only. It is interesting, but not surprising in a short-term trial, to see patient-reported benefits with a new treatment. Given the high cost of pump therapy, it is unlikely that it will have a large role in the treatment of type 2 diabetes unless there is a significant clinical benefit.

Reference: *Diabetes Technol Ther* 2010;12(11):901-6
<http://www.liebertonline.com/doi/abs/10.1089/dia.2010.0075>

Metformin and cancer occurrence in insulin-treated type 2 diabetic patients

Authors: Monami M et al

Summary: The effect of metformin treatment on cancer incidence was investigated in 112 patients who developed incident cancer during a median follow-up period of 75.9 months and 370 matched controls from a cohort of 1340 patients. Metformin use was associated with a significantly reduced cancer incidence (adjusted odds ratio 0.46 [95% CI 0.25–0.85; p=0.014]); while the proportion of participants exposed to sulfonylureas was lower among cases than it was among controls, the adjusted odds ratio for reduced cancer risk was not statistically significant.

Comment (NC): The issue of cancer and type 2 diabetes treatments continues to be a hot topic. This brief report in insulin-treated patients shows similar results to other studies, but is not conclusive. It is a fairly small retrospective analysis, with only 112 cases of cancer. The reduction in cancer incidence is impressive and not related to insulin dose. The mechanism of a potential effect on cancer is therefore not obvious from this trial, and further studies are needed in this space. Nevertheless, there is often good reason to prescribe metformin and very little downside. It therefore continues to be first-line therapy, and important long-term maintenance therapy, for type 2 diabetes.

Reference: *Diabetes Care* 2011;34(1):129-31
<http://care.diabetesjournals.org/content/34/1/129.abstract>

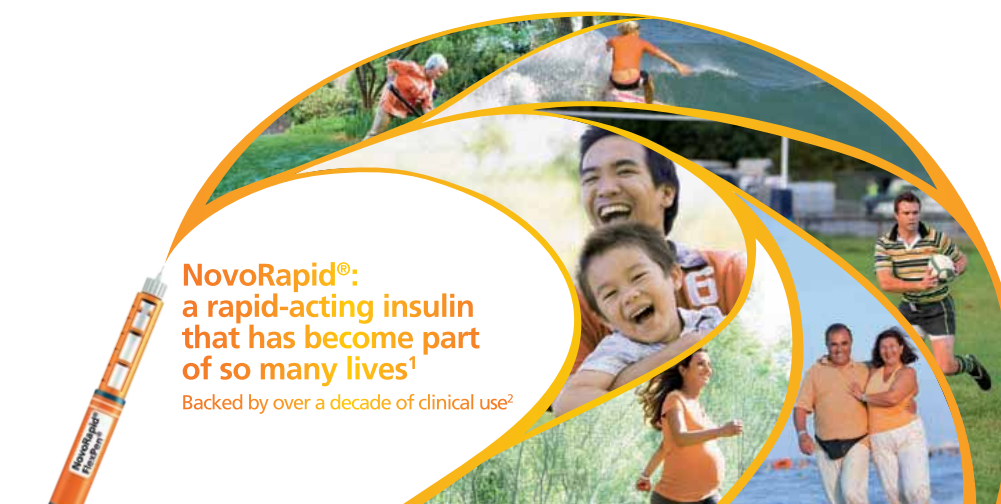
Diabetes & Obesity Research Review

Independent commentary by **Professor Peter Little and Dr Neale Cohen.**

Peter Little has taken up a new position as Professor of Pharmacy and Foundation Head, Discipline of Pharmacy and Group Leader, Diabetes Complications Group, Health Innovations Research Institute, RMIT University Bundoora, Victoria. Peter will continue to provide comments for Diabetes and Obesity Research Reviews.

Dr Cohen is a physician specialising in Diabetes and Endocrinology, and is currently the General Manager of Diabetes Services at the Baker IDI Heart and Diabetes Institute.

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References: 1. IMS Health Inc. IMS MIDAS (MATQ209). 2. NovoRapid® Approved Product information. 3. Home P et al. *Diabet Res Clin Prac* 2006; 71:131-139. 4. Home P et al. *Diabet Med* 2000;17:762-770. 5. Raskin P et al. *Diabetes Care* 2000;23:583-588. 6. Bretzel R et al. *Diabetes Care* 2004;27:1023-1027. 7. Pala A et al. *Diab Res Clin Pract* 2007;78:132-135. 8. Chlup R et al. *Diabet Technol & Ther* 2007;9:223-231. PBS dispensed price for maximum quantity (5x5x3mL): \$264.22; vial price (2x5x10mL): \$159.27.

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A1C and cardiovascular outcomes in type 2 diabetes

Authors: Colayco DC et al

Summary: The relationship between average glycosylated haemoglobin (Hb_{A1c}) and CV outcomes was investigated in this case-control analysis of adults with type 2 diabetes from Kaiser Permanente Southern California health data. Cases ($n=11,157$) were patients who had experienced nonfatal myocardial infarction, nonfatal stroke or CV-related death over a 3-year period. CV events were 20% more likely in participants with an $Hb_{A1c} \leq 6\%$, compared with those with an $Hb_{A1c} > 6-8\%$ ($p < 0.0001$). Furthermore, the risk of CV events was 16% greater among participants with an $Hb_{A1c} > 8\%$ ($p < 0.0001$). Evidence of significant statistical interactions was found between Hb_{A1c} category and: i) LDL-cholesterol levels; ii) use of CV medications; and iii) use of antipsychotics.

Comment (NC): This study increases the concern regarding intensive Hb_{A1c} lowering in type 2 diabetes. Increased risk of CV outcomes was seen in patients with high and low Hb_{A1c} levels. This echoes a recent publication showing a 'U'-shaped curve for mortality in type 2 diabetes and Hb_{A1c} . Increased events with insulin, sulfonylureas and antipsychotic drugs were also highlighted. Importantly, there were missing data, including BMI, smoking status and duration of diabetes that may confound these results. There may also be considerable selection bias here, so one must interpret these results with caution.

Reference: *Diabetes Care* 2011;34(1):77-83

<http://care.diabetesjournals.org/content/34/1/77.abstract>

Improving epinephrine responses in hypoglycemia unawareness with real-time continuous glucose monitoring in adolescents with type 1 diabetes

Authors: Ly TT et al

Summary: This study investigated the use of real-time continuous glucose monitoring (CGM) with preset alarms at specific glucose levels for the avoidance of hypoglycaemia and the improvement of counter-regulatory response to hypoglycaemia in adolescents with type 1 diabetes with hypoglycaemia unawareness. Following baseline hyperinsulinaemic hypoglycaemic clamp studies, the participants were randomised to real-time CGM or standard therapy for 4 weeks, after which the clamp studies were repeated. Compared with the standard therapy group, the CGM group had greater adrenaline (epinephrine) responses during hypoglycaemia following the intervention.

Comment (NC): Managing adolescents with type 1 diabetes and hypoglycaemia unawareness is an extremely challenging problem (it is indeed impressive that someone was brave enough to tackle this with an RCT). Previous studies with real-time CGM have shown variable results in terms of hypoglycaemia and glycosylated haemoglobin (Hb_{A1c}) changes; however, the participants in this study were mostly excluded from these trials. It concluded that 4 weeks of real-time CGM improved hypoglycaemia awareness in this brittle patient group. Whether this translates into fewer episodes of severe hypoglycaemia remains to be seen, but it may prove to be an important intervention for some of the most difficult patients.

Reference: *Diabetes Care* 2011;34(1):50-2

<http://care.diabetesjournals.org/content/34/1/50.abstract>

Cardiovascular risk prediction in adults with type 1 diabetes: the Fremantle Diabetes Study

Authors: Davis WA & Davis TME

Summary: This study evaluated the performance of the Fremantle Diabetes Study (FDS) CV risk equation, which was derived from 1240 patients with type 2 diabetes, in a parallel cohort of 117 adult patients with type 1 diabetes. The equation was successful at identifying patients with type 1 diabetes who were at increased CV risk in this cohort, despite their significantly different phenotypic characteristics.

Comment (PL): This is ongoing work by the highly-regarded and productive Davis group from Perth based on the 20-year FDS and providing Australian population-specific data and risk analyses. It is widely accepted that general and international data should be confirmed for individual populations to obtain the most rigorous risk assessment. Risk equations have common parameters, but vary in parameters such as lipids and renal function. The actual equation is available at <http://fds.meddent.uwa.edu.au/go/fds/cvd-risk-calculator>, and the authors indicate that those with a 5-year and 5% risk of an event should be identified for more intensive medical therapy.

Reference: *Diabetes Res Clin Pract* 2010;90(3):e75-8

<http://tinyurl.com/DRCP-90-e75>

Assessing treatment barriers in young adults with type 1 diabetes

Authors: Lancaster BM et al

Summary: Barriers to achieving glycaemic control were explored in 83 young adults (mean age 22.2 years) with type 1 diabetes in this study. A multiple regression analysis of questionnaire results, correlated with glycosylated haemoglobin (Hb_{A1c}) measurements, identified family conflict, psychological issues and carbohydrate counting as the most prominent barriers.

Comment (PL): Young adults with type 1 diabetes typically have poor glycaemic control for a plethora of mostly apparent reasons, some of which are cultural and relatively intransigent. This study shows that standard educational approaches are not all that successful in this group, due to entrenched cultural issues in this age group that apply inside and outside the diabetes setting, and the technical issue of carbohydrate counting is a problem. Educational institutions are belatedly in a very active mode of improving teaching modalities, including the use of technologies such as iPods etc. A quantum shift up in the use of such technologies, with which this group is very familiar, may be needed to improve glycaemic control, and thus long term, a reduction in complications in this very important group of people with type 1 diabetes.

Reference: *Diabetes Res Clin Pract* 2010;90(3):243-9

<http://tinyurl.com/DRCP-90-243>

High sodium and low potassium intake in patients with type 2 diabetes

Authors: Ekinçi EI et al

Summary: Dietary sodium and potassium intake and adherence according to the Australian National Heart Foundation guidelines were investigated over 8 years in 122 and 782 Australian patients with type 2 diabetes in these longitudinal and cross-sectional analyses, respectively. In the longitudinal analysis, the recommended dietary sodium intakes were achieved in only 3% and 14% of males and females, respectively, and the respective values for the recommended dietary potassium intakes were 14% and 3%. Independent predictors of urinary sodium levels were BMI, urea, urine volume and urinary glucose (adjusted $r^2 = 0.57$; $p < 0.0001$), and the mean intra-individual coefficient of variation for corrected urinary sodium was 21%. These findings were confirmed in the cross-sectional analysis, where no temporal trends were observed and no correlation with glycosylated haemoglobin (Hb_{A1c}) was evident to suggest natriuresis with hyperglycaemia.

Comment (PL): The area of metal ion intake and vascular responsiveness leading to hypertension is one of the older areas of research, but remains important due to the high sodium nature of modern diets and the persistence of hypertension as a leading CV risk factor. Traditionally, it was considered that people varied in their responsiveness or otherwise to the deleterious vascular effects of sodium, such that there was a sodium-sensitive subset of patients, but defining this group in a clinically applicable manner has proven elusive. This study from the highly respected Jerums' group in Melbourne shows that most patients with type 2 diabetes do not meet recognised standards for sodium and potassium intake. Males had higher levels of urinary sodium. Intriguingly some data suggest that longer diabetes leads to desensitisation to the taste of salt, and hence rising consumption. Almost all (80%) of dietary salt is derived from processing and addition, not the actual basic foodstuff itself, which we notice especially when TV chefs shovel on what they call 'just a pinch of salt' or 'seasoning to taste'. Long-term interventional studies are lacking in this area, and perhaps if conducted may provide the evidence base for an even stronger public health campaign in this area.

Reference: *Diabetic Med* 2010;27(12):1401-8

<http://tinyurl.com/DiabetMed-27-1401>

Inhaled insulin forms toxic pulmonary amyloid aggregates

Authors: Lasagna-Reeves CA et al

Summary: This *in vivo* study demonstrated that although insulin inhalers are effective, reported decreases in pulmonary capacity are due to an air-tissue interface in the lungs that predisposes to the formation of insulin aggregates. The insulin deposits that formed in mice when inhaled insulin was administered resembled amyloid structures that have been implicated in protein misfolding disorders (e.g. Alzheimer's and Parkinson's diseases), and the authors warned of their potential deleterious nature.

Comment (PL): On the basis that the pain and inconvenience of using insulin by SC injection is a barrier to its use when indicated in patients with type 2 diabetes, various other approaches to the administration of insulin are being investigated, including administration by inhalation. This modality recently reached the clinic through a specific product from a major pharmaceutical company. The product only lasted a very short time before being withdrawn, mostly due, to this commentator's knowledge, to a commercially unsustainable take up of the product (rather than any toxicity). As a biological issue, the introduction of proteins to mucous surfaces invokes potentially toxic outcomes well worth close investigation. The current study used the human clinical product to administer insulin, and studied the effect in the lungs of mice. The investigators found amyloid deposits after only brief administration of the product. Such amyloid deposits are otherwise associated with neurological and degenerative diseases, and reflect the improper processing of proteins. The study raises concerns as to the potential toxicity associated with long-term inhalation of insulin (or any protein for that matter), so it is comforting that other pathways of administration, such as patches as well as the discovery of orally active insulin mimetics, is progressing in parallel.

Reference: *Endocrinology* 2010;151(10):4717-24
<http://endo.endojournals.org/cgi/content/abstract/151/10/4717>

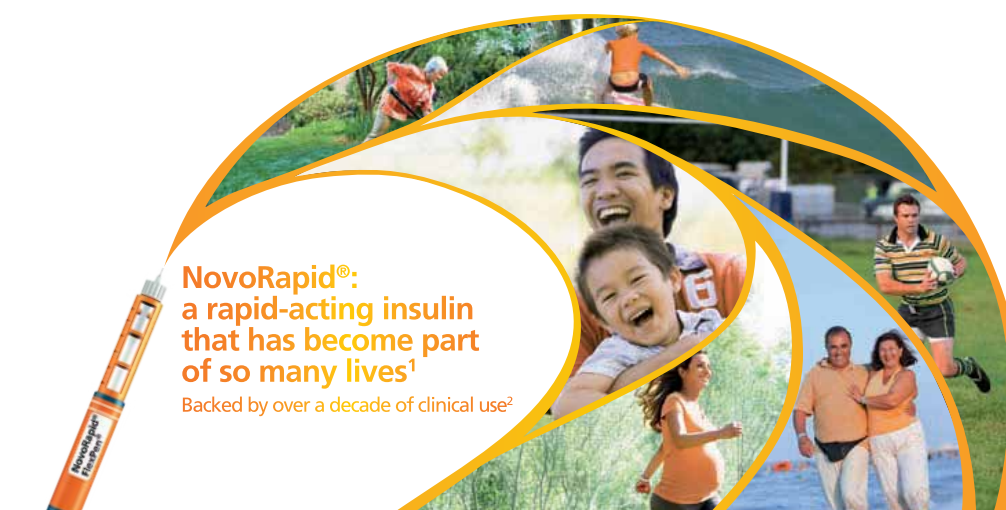
Risk of cardiovascular disease and diabetes in a working population with sedentary occupations

Authors: Freak-Poli R et al

Summary: CV disease and type 2 diabetes risks were explored in 762 employees from ten Melbourne workplaces with physical activity programmes. Guideline recommended levels were not being achieved for: i) physical activity in 62% of the employees; ii) fruit intake in 70%; iii) vegetable intake in 86%; iv) BMI in 58%; and iv) waist circumference in 53%. Seven percent and 53% were judged to be at high and intermediate risk, respectively, for developing type 2 diabetes.

Comment (PL): This commentator has always felt uncomfortable and somewhat concerned for those career taxi drivers who seem to have the worst possible situation of an obesogenic diet and highly sedentary lifestyle. Dunstan at BakerIDI in Melbourne has published several papers demonstrating clearly that the outcomes in terms of diabetes and CV diseases associated with a sedentary existence are worse than simply extrapolating down from a low activity state. Most of the people recruited to the current study had jobs that rendered them highly deskbound. Most of the group did not meet a wide range of activity and dietary targets, and were assessed as being at intermediate or high risk of acquiring diabetes. The study is the baseline data for a lifestyle intervention study, and we will await the outcomes with interest for the providing of evidence to strengthen the already compelling public health need to improve diet and increase activity in the community.

Reference: *J Occup Environ Med* 2010;52(11):1132-7
<http://tinyurl.com/JOEM-52-1132>



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