

# Diabetes & Obesity Research Review™

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Issue 35 - 2011

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## Welcome to issue 35 of Diabetes and Obesity Research Review.

This month we have included two papers on the association between vitamin D and diabetes, one added two further genes involved in vitamin D metabolism to the list of those contributing to the aetiology of type 1 diabetes, and the other showed that vitamin D deficiency was a predictor of mortality, but not microvascular complications of diabetes. One of the other studies selected for this issue shows a relationship between diabetes and Parkinson's disease (PD), while another reports an association between pioglitazone use for >2 years and bladder cancer.

We hope you find the papers selected for this issue interesting and informative, and we look forward to your comments and feedback.

Kind Regards

**Dr Neale Cohen**

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## The effects of LY2189265, a long-acting glucagon-like peptide-1 analogue, in a randomized, placebo-controlled, double-blind study of overweight/obese patients with type 2 diabetes: the EGO study

**Authors:** Umpierrez GE et al, for the EGO Study Group

**Summary:** The EGO study randomised patients with type 2 diabetes mellitus (n=262) to receive weekly SC injections of: i) LY2189265 0.5mg for 4 weeks then 1.0mg for 12 weeks (LY0.5/1.0 arm); ii) LY2189265 1.0mg for 16 weeks (LY1.0 arm); iii) LY2189265 1.0mg for 4 weeks then 2.0mg for 12 weeks (LY1.0/2.0 arm); or iv) placebo. Compared with placebo, all doses of LY2189265 were associated with: i) greater changes in baseline Hb<sub>A1c</sub> at week 16 (-1.38, -1.32 and -1.59 in the LY0.5/1.0, LY1.0 and LY1.0/2.0 arms, respectively, vs. -0.24; p<0.001); ii) significantly greater decreases in fasting and postprandial blood glucose levels (p<0.05); and iii) significant dose-dependent bodyweight losses of -1.34 to -2.55kg (p<0.05). The most common adverse events in the LY1.0/2.0 arm were nausea, diarrhoea and abdominal distension (each 13.8%). While hypoglycaemia episodes only occurred at a rate of ≤0.8 per patient per 30 days, they were more common in the LY2189265 arms than the placebo arm during the first 4 weeks (p<0.05).

**Comment (PL):** The test molecule is an incretin mimetic, which as a class improve β-cell function. Incretins such as glucagon-like peptide (GLP)-1 require daily injection. The index molecule is biochemically two GLP-1 analogues modified to be resistant to the degradative action of dipeptidyl peptidase-4 (DPP-4) and combined with an immunoglobulin molecule – this structure demonstrates the sophistication of the techniques and approaches to the development of modern medicines. The half-life is 4 days, and it is being developed for the possibility of once weekly administration. The study added LY2189265 in several doses on top of two oral hypoglycaemic agents. The maximum effect was a fall in Hb<sub>A1c</sub> of 1.60%, which means that it has broken through the 1% maximum effect barrier that applies to almost all other interventions in this area. There was a fall in bodyweight as occurs for incretins. Major adverse events were gastrointestinal as for other incretins, but the levels were possibly lower. Long-term trials of cardiovascular protection of products in this category are underway.

**Reference:** *Diabetes Obes Metab* 2011;13(5):418–25

<http://onlinelibrary.wiley.com/doi/10.1111/j.1463-1326.2011.01366.x/abstract>

## RESEARCH REVIEW

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## Inherited variation in vitamin D genes is associated with predisposition to autoimmune disease type 1 diabetes

Authors: Cooper JD et al

**Summary:** This case-control study found overall lower 25-hydroxyvitamin D (25(OH)D) levels in plasma samples from patients with type 1 diabetes mellitus (n=720) compared with control samples (n=2610). Optimum 25(OH)D levels for bone health ( $\geq 75$  nmol/L) were present during the winter and summer in only 4.3% and 18.6% of samples, respectively, from patients with type 1 diabetes. The associations of four genes involved in vitamin D metabolism (*GC*, *DHCR7*, *CYP2R1* and *CYP24A1*) with 25(OH)D levels were replicated in control subjects. As well as the previously reported significant association between type 1 diabetes and *CYP27B1*, significant associations with *DHCR7* and *CYP2R1* were seen.

**Comment (PL):** Vitamin D deficiency is involved in musculoskeletal disorders, notably bone softening. It is emerging that low levels are related to a plethora of other conditions and high levels may be protective in type 1 diabetes. The main source of vitamin D arises from ultraviolet light exposure of the skin followed by several metabolic steps to produce physiologically active 1,25-dihydroxy vitamin D [1,25(OH)2D], also known as calcitriol. Foods contain very low levels of vitamin D, hence the wide use of product supplementation, and straight supplements can be taken. Up to 50% of the vitamin D level in an individual can be genetically determined. This study links the genetic determinates with the risk of acquiring type 1 diabetes. The evidence goes as far as to suggest that vitamin D may play a causative role in type 1 diabetes, and underpins the need for large studies on the potentially protective role of vitamin D in type 1 diabetes based on mechanistic evidence for the role of vitamin D levels in immune cells.

Reference: *Diabetes* 2011;60(5):1624-31  
<http://diabetes.diabetesjournals.org/content/60/5/1624.abstract>

## Vitamin D levels, microvascular complications, and mortality in type 1 diabetes

Authors: Joergensen C et al

**Summary:** This prospective observational study explored vitamin D as a predictor of all-cause mortality, micro- or macroalbuminuria and retinopathy in a cohort of 220 patients with type 1 diabetes mellitus diagnosed between 1979 and 1984. Cox proportional hazards modelling showed that severe vitamin D deficiency increased the risk of mortality (adjusted hazard ratio 2.7 [95% CI 1.1-6.7; p=0.03]). No relationship was seen between severe baseline vitamin D deficiency and the development of microvascular complications.

**Comment (PL):** This study looked at vitamin D levels at diagnosis of type 1 diabetes and the occurrence of microalbuminuria or death. The premise is that vitamin D is protective of deleterious effects and hence low levels are permissive. Note elsewhere in this issue of comments on the association of vitamin D levels and the risk of type 1 diabetes. Severe deficiency was associated with higher rates of death, but surprisingly not with microalbuminuria. The association of low vitamin D levels and higher rates of death in the absence of diabetes has been demonstrated. Trials are required to determine the effect of vitamin D on both the onset and consequences of type 1 diabetes, and most likely for other chronic conditions.

Reference: *Diabetes Care* 2011;34(5):1081-5  
<http://care.diabetesjournals.org/content/34/5/1081.full>

## Diabetes & Obesity Research Review

Independent commentary by Professor Peter Little and Dr Neale Cohen.

**Peter Little** is Professor and Head of Pharmacy and Leader, Diabetes Complications Group, Health Innovations Research Institute at RMIT University, Bundoora, Victoria. Peter is a past national President of Diabetes Australia.

**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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## Physical activity advice only or structured exercise training and association with Hb<sub>A1c</sub> levels in type 2 diabetes

**Authors:** Umpierre D et al

**Summary:** This was a systematic review and meta-analysis of 47 RCTs (n=8638) investigating changes in Hb<sub>A1c</sub> after ≥12 weeks of structured exercise training or physical activity advice, with or without dietary cointervention, in patients with type 2 diabetes mellitus. Compared with controls, a significant decrease in Hb<sub>A1c</sub> of -0.67% was seen with structured exercise programmes (I<sup>2</sup>=91.3%), including structured aerobic exercise programmes (-0.73%; I<sup>2</sup>=92.8%), structured resistance training programmes (-0.57%; I<sup>2</sup>=92.5%) and both combined (-0.51%; I<sup>2</sup>=67.5%). Furthermore, Hb<sub>A1c</sub> decreased by -0.89% with structured exercise programmes of >150 min/week, compared with -0.36% for ≤150 min/week. Overall, Hb<sub>A1c</sub> decreased by -0.43% with physical activity advice versus controls (I<sup>2</sup>=62.9%), but the reduction was greater (-0.58%) when such advice was combined with dietary advice (I<sup>2</sup>=57.5%), and there was no reduction in Hb<sub>A1c</sub> with physical activity advice on its own.

**Comment (PL):** Exercise, or even just physical activity, is universally accepted as beneficial for health and especially metabolic improvement in obese and those susceptible to diabetes; the major limiting factor can be restrictions due to physical ailments associated with ageing and obesity. Research questions have moved on to identify and define the most efficient and efficacious exercise regimens to improve insulin resistance and prevent diabetes and cardiovascular disease. This meta-analysis, ironically a desk-research study of exercise, found that structured exercise training of multiple types led to improved Hb<sub>A1c</sub> levels in patients with diabetes, and more exercise gave a greater response. Physical activity advice was ineffective, and only became effective when combined with dietary advice. Structured exercise training was defined as "intervention in which patients were engaged in planned, individualised and supervised exercise programs". So as a minimum for 'lifestyle modification therapy', both dietary and physical activity advice is required, and for more certain outcomes, actual structured interventions are required.

**Reference:** *JAMA* 2011;305(17):1790–9  
<http://jama.ama-assn.org/content/305/17/1790.abstract>

## Are the 2005 dietary guidelines for Americans associated with reduced risk of type 2 diabetes and cardiometabolic risk factors? Twenty-year findings from the CARDIA study

**Authors:** Zamora D et al

**Summary:** This analysis of data from 4381 Americans who underwent repeated examinations over a 20-year period found no relationship between Diet Quality Index scores (based on compliance with recommendations conveyed in the 2005 Dietary Guidelines for Americans) and diabetes risk after adjustment for confounding factors. Higher Diet Quality Index scores were found to be associated with improvements in HDL cholesterol level and blood pressure (p<0.05 for trend), but also with increased insulin resistance among black participants (p<0.01 for trend).

**Comment (PL):** The CARDIA study was of coronary artery disease in the young, and amongst its findings has been that early cholesterol is associated with later coronary artery calcium. Here the impact of recommending the Dietary Guidelines for Americans was investigated—the guidelines are a diet that is low in fat and high in fruits, vegetables and grains—essentially high carbohydrate. The finding was no impact on the incidence of diabetes. Taken with other evidence of the lack of efficacy of physical activity advice (alone), it appears that a minimum of both diet and physical activity advice and preferably stronger interventions, meaning more interventional and structured, are required to make a real difference.

**Reference:** *Diabetes Care* 2011;34(5):1183–5  
<http://care.diabetesjournals.org/content/34/5/1183.abstract>

## Effects of rosiglitazone, glyburide, and metformin on β-cell function and insulin sensitivity in ADOPT

**Authors:** Kahn SE et al, and the ADOPT Study Group

**Summary:** Patients with newly diagnosed, treatment-naïve type 2 diabetes mellitus (n=4630) received rosiglitazone, metformin or glibenclamide (glyburide) monotherapy for a median of 4 years in the ADOPT trial. This analysis of oral glucose tolerance test data from these study participants showed that rosiglitazone was associated with more favourable measures of β-cell function and insulin sensitivity than either metformin or glibenclamide. Participants who completed 4 years of treatment had persistent improvements, while those in who adequate glucose control was not achieved with initial monotherapy experienced marked deterioration in β-cell function.

**Comment (NC):** In the ADOPT study, the long-term durability of hypoglycaemic therapy with rosiglitazone was compared with metformin or a sulphonylurea (glibenclamide) monotherapy in type 2 diabetes. Previously published results showed better long-term glycaemic control in the rosiglitazone arm. This analysis demonstrated that β-cell function was the most favourable in the rosiglitazone group, particularly in those who completed the 4 years of the study. This is an important finding as β-cell function is known to deteriorate with time in type 2 diabetes and is a key factor in achieving good glycaemic control. Unfortunately, the glitazones are becoming increasingly difficult to use clinically because of concerns over a growing number of adverse effects.

**Reference:** *Diabetes* 2011;60(5):1552–60  
<http://diabetes.diabetesjournals.org/content/60/5/1552.abstract>

## Diabetes and the risk of developing Parkinson's disease in Denmark

**Authors:** Schernhammer E et al

**Summary:** This analysis of Danish hospital registry data found 36% and 35% increased risks of developing Parkinson's disease (PD) among patients who had ≥1 diabetes-related admission and/or outpatient visit and any antidiabetes medication use, respectively. This risk was greatest in: i) women when diabetes was defined as oral antidiabetes medication use; and ii) patients with early-onset PD when diabetes was defined as any antidiabetes drug prescription.

**Comment (NC):** This study demonstrated an association between diabetes and PD, but does not establish a causal link. This is a large study based on Danish registry data, including hospital records and a prescription database. Although the numbers were small, there was a consistently high odds ratio for early-onset PD in people with diabetes. Further studies are needed to establish the cause of this association. As discussed, it seems unlikely that glucose is directly responsible, but there may be plausible links with mitochondrial dysfunction and the two conditions.

**Reference:** *Diabetes Care* 2011;34(5):1102–8  
<http://care.diabetesjournals.org/content/34/5/1102.abstract>

## Persistence of individual variations in glycated hemoglobin

**Authors:** Wilson DM et al, for the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial

**Summary:** The persistence of the relationship between mean sensor glucose levels and Hb<sub>A1c</sub> was investigated in participants from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomised trial. Mean glucose levels were calculated using data from continuous glucose monitors 3 months prior to Hb<sub>A1c</sub> measurements at 3, 6, 9 and 12 months among participants assigned to continuous glucose monitoring, and at 9 and 12 months among control group participants. The analysis included a mean glucose to Hb<sub>A1c</sub> ratio for participants with average continuous glucose monitoring of >4 days per week. The Spearman coefficients for the ratio of mean glucose level to Hb<sub>A1c</sub> between consecutive 3-month periods were 0.70–0.79, with slightly smaller correlations seen among paediatric participants. There were no meaningful differences seen by type of device or change in Hb<sub>A1c</sub>. The investigators concluded that individual variations in haemoglobin glycation rates contribute to inaccuracies when mean glucose levels are calculated using Hb<sub>A1c</sub> measurements.

**Comment (NC):** Hb<sub>A1c</sub> is the gold standard measure of long-term glycaemic control. However, it is well known that haemoglobin variants and various causes of anaemia or altered RBC turnover will affect Hb<sub>A1c</sub> results. There is some evidence that glycation rates may vary between different patient groups, and this may be reflected in Hb<sub>A1c</sub> values. This study from the JDRF continuous glucose monitoring trial does confirm differences between subgroups and, in particular, apparently higher glycation rates in younger age groups. The clinical implications of this are not clear and need to be explored further. It is possible that those with higher glycation rates may be at higher risk of complications, or alternatively that those with higher glycation rates are at risk of overtreatment.

**Reference:** *Diabetes Care* 2011;34(6):1315–7  
<http://care.diabetesjournals.org/content/34/6/1315.abstract>

## Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes

**Authors:** Hermida RC et al

**Summary:** Patients with hypertension and type 2 diabetes mellitus were randomised to take all their antihypertensive medications upon awakening in the morning or to take at least one of them in the evening prior to bedtime. The risk of cardiovascular (CV) events over a median follow-up of 5.4 years was significantly lower among participants who took  $\geq 1$  of their medications at bedtime compared with those who took all their antihypertensives in the morning (hazard ratio 0.33 [95% CI 0.21–0.54;  $p < 0.001$ ], and the risk remained reduced when only major CV events were considered (0.25 [0.10–0.61;  $p = 0.003$ ]). Participants who took  $\geq 1$  antihypertensive medication at bedtime also had a significantly lower mean blood pressure (BP) and a greater prevalence of controlled ambulatory BP (62.5% vs. 50.9%;  $p = 0.013$ ). The CV risk was reduced by 12% for every 5mm Hg decrease in sleep-time systolic BP ( $p < 0.001$ ).

**Comment (NC):** This is a fascinating study that concluded that taking evening antihypertensive agents compared with morning agents markedly reduced CV events over a period of 5 years. The results are remarkable and exceed expectations with reductions of the order of 60–70% in event rates with one or more evening antihypertensive doses. If this is true, it would have a major impact on prescribing habits in hypertensive diabetic patients. Not many therapeutic interventions have had an impact of this size on CV events, and for this reason further studies are required to confirm these findings.

**Reference:** *Diabetes Care* 2011;34(6):1270–6  
<http://care.diabetesjournals.org/content/34/6/1270.full>

## Risk of bladder cancer among diabetic patients treated with pioglitazone

**Authors:** Lewis JD et al

**Summary:** This analysis of data from 193,099 patients aged  $\geq 40$  years from the Kaiser Permanente Northern California diabetes registry identified 90 cases of bladder cancer among pioglitazone recipients ( $n = 30,173$ ) and 791 among non-pioglitazone recipients. While the risk of bladder cancer associated with pioglitazone use overall was not significant (hazard ratio 1.2 [0.9–1.5]), use for  $> 2$  years was (1.4 [1.03–2.0]). The majority (95%) of pioglitazone users who developed bladder cancer were diagnosed during the early stage of the disease.

**Comment (NC):** Previous signals from animal and clinical studies have prompted a request from the US FDA to conduct a safety study into pioglitazone and its possible relationship with bladder cancer. This is the midpoint analysis of the 10-year Kaiser Permanente study, in which so far 90 cases of bladder cancer in pioglitazone users have been identified. Although there was no increase in bladder cancer rates overall between pioglitazone and non-pioglitazone users, there was a 50% increase in risk in patients exposed for  $> 24$  months to pioglitazone. No doubt as this study continues we will learn more, but it is a signal of concern. This puts regulatory agencies in a difficult position, and has already resulted in the withdrawal of pioglitazone in France and Germany.

**Reference:** *Diabetes Care* 2011; 34(4):916–22  
<http://care.diabetesjournals.org/content/34/4/916.full>

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