

# Diabetes2007

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## Hypoglycemia: The Dark Side of Insulin



Important data on diabetes presented at the 67th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2007**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc., Merck & Co., Inc., Novo Nordisk Inc., and Amylin Pharmaceuticals, Inc./Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2007** will be followed by a **Diabetes 2007** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

**Diabetes 2007** is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the important association between insulin resistance/metabolic syndrome and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination antihyperglycemic therapy, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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Hypoglycemia is recognized as a major obstacle to achieving glucose control in Type 1 diabetes. Patients' fear of hypoglycemia is such that they are often unwilling to aggressively treat their diabetes. This results in significant hyperglycemia with its increased risk of microvascular disease. Hypoglycemia has become an area of intense research as well as an area of debate, evident in the number of sessions dedicated to this complication at the ADA Sessions. Most prominent of these was the award of this year's Banting Medal to Dr. Robert Sherwin of Yale University, New Haven, CT, who gave a lecture titled, "Bringing Light to the Dark Side of Insulin: A Journey Across the Blood-Brain-Barrier".

In his lecture, Dr. Sherwin noted that he first became aware of the problem with hypoglycemia when he, with colleagues, developed the insulin pump. Patients returned to the clinic with much improved glucose control, but often appeared to tolerate low glucose levels with no apparent symptoms, a condition we now recognize as "hypoglycemia unawareness." He showed data from diabetic patients included in the Diabetes Care and Complications Trial (DCCT), who, following intensive insulin therapy, did not start to produce significant rises in epinephrine, the main counterregulatory hormone, until they reached much lower glucose levels than the conventionally-treated control group. Dr. Sherwin then summarized studies in rodents and human subjects that his group has been conducting over the last two decades to investigate why this might occur. The first question he asked himself was, "Where does the body sense hypoglycemia?" We now recognize that there are a number of glucose-sensors in the body that play a major role in regulating glucose homeostasis. These can be found in the periphery (e.g., pancreas and portal system) and brain, with the most important sensing region probably the hypothalamus. Dr. Sherwin's group has focused on one particular region in the brain, the ventromedial hypothalamus (VMH). He then asked the question: "How does the brain sense hypoglycemia?" The answer to that appears to be via neurons that use glucose as a signaling molecule rather than just as fuel, using sensing mechanisms very

similar to the ones we recognize in the pancreas. The final question was, "Why do things go wrong over time in Type 1 diabetes?" Hypoglycemia is a complex physiological event that leads to many adaptive changes in these sensing systems. Recent work has generated the hypothesis that hypoglycemia induces a neurohormonal stress response, altering corticotropin-releasing factor (CRF) receptor function within the VMH that may in turn promote more hypoglycemia. In summarizing, Dr. Sherwin noted the results from the EDIC trial, a follow-up of the patients in the DCCT. Despite frequent and often severe hypoglycemia in the course of their disease, no evidence of cognitive decline over time was demonstrated. Perhaps, he commented, the brain was not as susceptible to hypoglycemia as we previously thought, and many of the changes we see are in the long run protective. He felt that, given the choice, physicians caring for individuals with Type 1 diabetes should still be advocating intensive insulin therapy and tight glycemetic control.

Acute hypoglycemia has obvious major effects on cognition and these are important to know when educating individuals and their families. One of the more interesting issues concerns decision making processes, for example the decision of whether or not to drive. Hypoglycemia impairs driving ability, and in an interesting study Stork *et al.*, Netherlands, examined Type 1 and Type 2 diabetic patients during a hypoglycemic test in a driving simulator (168-OR). At the end of the study, patients were asked whether they would continue to drive or not; 42.9% of the Type 1 patients with impaired awareness of hypoglycemia said they would "continue to drive in comparison with only 4.2% of Type 1 patients with normal hypoglycemia awareness. Even more concerning, 25% of patients with Type 2 diabetes and normal hypoglycemia awareness said they would continue to drive. Clearly, those higher executive functions that affect decision making processes are impaired in certain patients with hypoglycemia whether or not they are aware of it. It is important for families and relatives to know this so that they can encourage safe behaviors.



## A “Sensitive” Topic!



The thiazolidinedione (TZD) insulin sensitizers continue to raise a lot of interest and controversy relative to their use in Type 2 diabetes patients. The recent, widely publicized meta-analysis of rosiglitazone and cardiovascular (CV) events published in the *New England Journal of Medicine* has prompted considerable discussion and debate in both the lay and medical press. In a “Just Added” session on Monday, Drs. Nissen from the Cleveland Clinic, co-author of the paper, and Dr. Phillip Home of the UK presented their opposing views regarding the data to a capacity crowd at the McCormick Place Convention Center in Chicago. Dr. Nissen first reviewed the events that led to the decision to conduct the analysis. In brief, upon FDA approval in 1999, there was an early, non-significant “signal” for rosiglitazone and ischemic heart disease. He contends that the agency was primarily focused on hepatic safety (given the recent experience with troglitazone) and simply requested a 4-year study (ADOPT) to address CV concerns. That study, which was ultimately completed and published in 2006, did not properly address the safety issue from a methodological standpoint. Both ADOPT and DREAM, a diabetes prevention study, reported CV outcomes, but as secondary endpoints; neither showed statistical significance (with the exception of CHF, a well documented adverse event associated with TZD use). However, the point estimates were consistently in the wrong direction for patients assigned to rosiglitazone. To Nissen, a concerning pattern of excess events had emerged.

For this reason, he conducted the meta-analysis and included some 40 additional trials, most of which had not been published but were found on the manufacturer’s website. His paper concluded that therapy with rosiglitazone was associated with an odds ratio for myocardial infarction (MI) of 1.43 (95% confidence intervals [CI] 1.03-1.98;  $p=0.03$ ) and for CV death of 1.65 (0.98-2.74;  $p=0.06$ ), compared to placebo or active comparator drug. He also shared that two independent analyses were conducted by the manufacturer and the FDA, each identifying a similarly increased risk. Nissen reminded the audience of the PPAR agonist (dual,  $\alpha/\gamma$ ), muraglitazar, that had been withdrawn shortly before final FDA approval under similar circumstances. It was emphasized, however, that each PPAR agonist activates different genes and needs to be viewed individually. The PROActive trial, for example, involving 5000+ high-risk diabetic patients treated with the other TZD, pioglitazone, trended

favorably toward cardioprotection and demonstrated a significant 16% relative risk reduction in the secondary endpoint of MI, stroke, and mortality.

In closing, Dr. Nissen shared what he felt were missed opportunities relative to rosiglitazone and this unresolved public health issue: (1) The FDA rushed to approve an alternative to troglitazone, a regulatory mistake; (2) a strong safety signal was ignored at the time of review; (3) surrogate endpoints (i.e., blood glucose) were used for approval; this should be acceptable only in the absence of safety concerns; (4) failure to enforce the completion of post-marketing surveillance; (5) none of post-marketing data/studies were designed to assess health outcomes; (6) events identified in an internal analysis remain unpublished; and, (7) the need for review of PPAR agonists as distinct entities.

Dr. Phillip Home, Chair of the RECORD Steering Committee, was the next presenter. He criticized several aspects of the meta-analysis, including the fact that the hypothesis was not pre-stated; that in almost none of the individual studies were cardiovascular events actually adjudicated; that no patient-specific data were available for analysis; and that many of the smaller studies had but one event each. He felt strongly that such data can only be used to pose a hypothesis that would then require further testing. Dr. Home proceeded to describe the events leading to the interim analysis of the RECORD trial—the ongoing long-term European study of rosiglitazone and CV safety/efficacy. In RECORD, rosiglitazone, metformin, or a sulfonylurea is being added to patients not achieving adequate control with metformin or a sulfonylurea. Although interim analyses are generally inappropriate, because of the hyperacute reaction to the Nissen publication, leading to subject withdrawals from the trial, it appeared to be the “lesser of evils.” With the exception of heart failure, the interim analysis of 2200 patients in the rosiglitazone group of

RECORD revealed no significant difference in cardiovascular outcomes (Table 1). Home identified the strengths of RECORD as being a study (1) specifically designed to evaluate CV outcomes; (2) intended as a long-term trial in a large cohort; and (3) involving an active comparator. Weaknesses include (1) low event rates to date; (2) a 10% loss to follow up; (3) the open-label design; (4) a broad primary endpoint; and (5) the comparators, metformin and sulfonylurea, have different actions and degrees of efficacy. Home concluded with several comments. The Nissen paper was important to publish; however, meta-analyses provide poor data for making clinical decisions. Instead, large, randomized clinical trials are needed to identify varying degrees of CV risk/benefit with diabetes medications. He stated emphatically that regulators (i.e., the FDA) should be responsible for risk assessment of drug safety, not journals, newspapers, or the US Congress. Dr. Home also stressed that TZDs have an important, continuing role but that this may need to be redefined.

The session included a panel discussion with three experts, Drs. John Buse, Barry Goldstein, and David Nathan. The general consensus was that if a patient is already optimally managed on rosiglitazone (including glycemic as well as lipid parameters), therapy should be maintained. However, in newly diagnosed patients or in those not under good control with rosiglitazone, the panel was in agreement that alternatives should be sought until definitive safety data are known. Lastly, there also appeared to be consensus that publication of the meta-analysis was entirely appropriate and warranted; however, the media’s handling of the information given the public health implications was less than ideal. It was noted that the FDA will hold a hearing on the TZDs and cardiovascular safety in July where further data will be discussed, including a requested meta-analysis of the pioglitazone clinical trial experience.

**Table 1. Interim Analysis of RECORD Trial Data at 3.75 Years - Rosiglitazone Versus Comparator**

<i>Adjudicated Events</i>	<i>Hazard Ratio*</i>	<i>p-value</i>
Death	1.08	NS
Death from CV causes	0.83	NS
Acute MI	1.16	NS
CHF	2.24	0.006
Death from CV causes, MI, stroke	0.97	NS

\* Rosiglitazone vs. comparator.



## Insulin – One Size Doesn't Fit All



Last year the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) produced a consensus statement on the approach to the management of hyperglycemia in individuals with Type 2 diabetes (see [http://care.diabetesjournals.org/cgi/reprint/30/suppl\\_1/s4](http://care.diabetesjournals.org/cgi/reprint/30/suppl_1/s4); Figure 1, pg S11). Essentially, the recommendation was for early intervention with metformin combined with lifestyle changes, followed by aggressive augmentation of therapy with additional agents as a means of achieving and maintaining the glycemic target of HbA1c <7%. The early initiation of insulin therapy was also advised for those patients failing oral agents. Given the increasing numbers of individuals with diabetes in the US, and that at least 30% of them at any one time will be on or require insulin therapy, physicians need to be aware of the available options. This is clearly an area where a 'one-size fits all' approach is not ideal.

One option for basal insulin therapy in diabetes is insulin detemir. Meneghini *et al.* from Miami, Florida, presented the data from the PREDICTIVE study (n=5603) (197-OR). In this study, patients with Type 2 diabetes were divided into two groups. The first group self-adjusted their basal insulin detemir every three days based on the simple algorithm: mean FBG <80 mg/dl, reduce dose by 3U; between 80-110mg/dl, no change; >110 mg/dl, increase by 3U. Group 2 adjusted detemir on the basis of a physician's recommendations. After 26 weeks, mean HbA1c decreased similarly in both groups (8.5 to 7.9%, and 8.5 to 8.0% for groups 1 and 2, respectively). 88% of all patients remained on once daily dosing (0.68 and 0.53 units/kg, respectively.) Rates of hypoglycemia were low and body weight changes were small in both groups. These findings suggest that a simple patient-driven titration regimen can be safely applied in clinical practice.

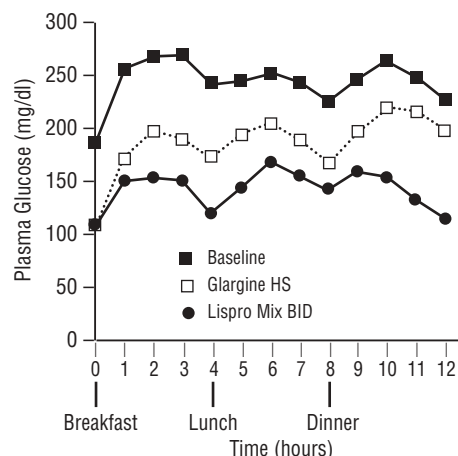
Philis-Tsimikas and international colleagues presented data from a 20-week, multicenter, open-label, randomized parallel group study of 331 obese patients with Type 2 diabetes uncontrolled on oral agents (487-P). Insulin detemir (n=168) was compared with NPH insulin (n=163) with the target of 108 mg/dl pre-breakfast and pre-dinner. Both insulins proved effective at reducing HbA1c (-1.6 vs. -1.7% for detemir vs. NPH, respectively), as well as FBG (-74 vs. -67 mg/dl). The presenters found that despite patients requiring the same dose of insulin (~0.4 units/kg), those on detemir had less weight gain over the course of the trial (0.7 vs. 1.6 kg, p=0.005). In another report of 475 patients with Type 2 diabetes on oral antihyperglycemic agents who were randomized to detemir or NPH insulin and followed for 24

weeks, targeting a HbA1c ≤7%, Hermansen *et al.* (489-P) reported that excellent glycemic control was achieved in both groups (~70% in both reaching a HbA1c ≤7%). However, the use of detemir insulin was associated with significantly less hypoglycemia (47% lower) and less weight gain (1.2 vs. 2.8 kg, p<0.001). A more interesting, and perhaps more relevant, comparison would have been between insulins detemir and glargine, the two truly basal insulins.

Despite the interest in basal insulin therapy, optimal treatment in many patients may also require targeting post-prandial glucose. In an interesting study of 369 patients with Type 2 diabetes taking part in the prospective two year South Danish Diabetes Study (SDDS), Henriksen and co-investigators reported that targeting post-prandial glucose with insulin aspart alone was more effective at lowering HbA1c than nocturnal NPH (-0.41%; p<0.001) (195-OR). The researchers also noted that the addition of metformin and/or rosiglitazone reduced HbA1c on average by an additional 0.6%, while those patients on triple therapy showed the greatest decrease in HbA1c. In another study from New Haven, CT, Sakharaova and colleagues compared twice-daily 75/25 Lispro mix (LPM) with bedtime glargine in a group of 13 patients with Type 2 diabetes inadequately controlled on at least two oral agents (mean HbA1c 9.7±2.4%) using a cross-over design (526-P). (LMP consists of 25% lispro + 75% neutral protamine lispro, the latter of which has pharmacokinetics similar to NPH.) At baseline and after three months, patients underwent a 12-hour meal tolerance test consisting of three isocaloric meals at 8AM, 12PM, and 4PM. Fasting glucose achieved in both groups was similar upon completion of the trial (108±22 vs. 110±22 mg/dl for LPM vs. glargine, respectively), but post-prandial glucose was significantly better controlled with LPM (Figure 1), as was HbA1c (7.2±0.7 vs. 8.0±1.1, p=0.009). The data seemed to suggest that by targeting both post-prandial and fasting glucose, better overall glycemic control can be achieved.

A number of studies also addressed inhaled insulins. Tu *et al.*, Paramus, NJ, compared inhaled technosphere insulin with insulin aspart in an open-label, randomized, prospective study of 110 patients with Type 1 diabetes and 309 patients with Type 2 diabetes (471-P). Glargine was the basal insulin being used in these studies. Interestingly, while both inhaled insulin and aspart produced similar improvements in HbA1c, the inhaled form was associated with more desirable changes in body weight (Type 1

**Figure 1. Glycemic Profiles of Glargine QHS vs. 75/25 Lispro Mix BID**



diabetes: -0.45 kg versus + 0.80 kg with aspart; Type 2 diabetes: -0.78 kg versus +0.23 kg with aspart). The clinical relevance of such small changes, however, is debatable. Hollander *et al.* (472-P), Dallas, TX, and Cefalu *et al.* (473-P), Baton Rouge, LA, reported on the pulmonary safety following discontinuation and re-administration of inhaled insulin (Exubera®). Exubera® has been shown to produce a small non-progressive decrease in FEV1 over time. Subjects in both these trials stopped their Exubera® therapy for a period of six months, during which time they reverted to their original insulin replacement regimen and then restarted Exubera®. In both studies, the small changes in FEV1 and diffusing capacity reverted to normal on discontinuation of inhaled insulin. When re-introduced, the lung function changes re-emerged, suggesting these changes do not reflect a pathological process in the lungs.

It is important for physicians to be aware of the various choices of insulin available for patients, as well as their differences. Basal insulin replacement may be sufficient in some patients with Type 2 diabetes, usually those earlier on in their disease course. In this case, the newer analogues, while no more efficacious in reducing HbA1c than NPH, do seem to be associated with less hypoglycemia, and detemir may result in less weight gain. For many patients, however, additional prandial therapy with rapid insulin analogues, given either alone or in a pre-mixed formulation, may be preferred to achieve HbA1c targets. These would likely be individuals who have more impaired β-cell function. In the future, inhaled insulins may prove a more attractive option for selected patients, but we await more long-term safety data.



## Pre-Diabetes Update: FPG vs. OGTT



With 50 million Americans having pre-diabetes and who require, at a minimum, periodic screening for diabetes, it remains controversial as to whether fasting plasma glucose (FPG) or the oral glucose tolerance test (OGTT) should be used for diagnostic purposes. Dr. Kokkoris and collaborators from Greece performed an OGTT in 267 individuals who were not known to be diabetic, with a FPG between 100 and 115 mg/dl (970-P). There were 134 individuals in 'group A' (2-hour post-load glucose [PG] <140 mg/dl) with a mean HbA1c  $5.4 \pm 0.7\%$ , 79 individuals in 'group B' (2-hour PG 140-199 mg/dl) with mean HbA1c  $5.6 \pm 0.6\%$ , and 54 individuals in 'group C' (2-hour PG  $\geq 200$  mg/dl) with mean HbA1c  $6.1 \pm 0.9\%$ . There was a statistically significant positive correlation between HbA1c and plasma glucose at 120 minutes ( $r=0.36$ ,  $p<0.05$ ). When each group was compared to the other two for HbA1c, a significant difference ( $p<0.05$ ) was found between groups A and C, and between groups B and C, but not between groups A and B ( $p=0.13$ ). Therefore, HbA1c could distinguish between normal and diabetics, or between those with impaired glucose tolerance (IGT) and diabetes, but not between normal individuals and those with IGT.

There is a high prevalence of glucose intolerance in patients with coronary artery disease (CAD). Delgado *et al.* from Spain presented data on the results of OGTT in a general population

**Table 2. Fasting Plasma Glucose vs. OGTT for Diagnosis of Diabetes**

	Diabetes	Unknown Diabetes		Total Diabetes (Known and unknown)	
		OGTT (WHO 1999)	FPG (ADA 2003)	OGTT (WHO 1999)	FPG (ADA 2003)
Population with Coronary Artery Disease	28.8%	16.2%	3.9%	45%	32.7%
General Population (30-75 years)	4.0%	7.5%	3.5%	11.5%	7.5%

FPG = fasting plasma glucose; OGTT = oral glucose tolerance test.

( $n=1,034$ , age of  $53 \pm 13$  years, 54% females) and in patients undergoing percutaneous coronary intervention (PCI) ( $n=338$ , age 64.9 years, males 80%) (2341-PO). In the PCI cohort, the OGTT was performed two weeks after discharge. In both groups, WHO (1999) and ADA (2003) diagnostic criteria were used. As shown in Table 2, OGTT is twice as likely as FPG to diagnose diabetes in the general population. In a CAD population, however, it is four times as likely. It is therefore tempting to conclude that this higher risk group may benefit from earlier screening, and, potentially, earlier treatment.

Patients with prediabetes (impaired fasting glucose [IFG], IGT) progress to diabetes at a predictable rate, but certain risk factors accelerate this conversion. Wilson and colleagues from

Atlanta, Georgia followed 1004 Framingham Heart Study Offsprings (45% female, 23% >65 years old) with IFG and/or IGT over seven years to determine those metabolic traits that could predict the onset of Type 2 diabetes (43-OR). With 118 incident cases of Type 2 diabetes developing during follow-up, logistic regression models revealed the following characteristics to be independently associated with the onset of diabetes: parental history of Type 2 diabetes (OR 2.28,  $p=0.004$ ), excess adiposity (BMI  $\geq 30$  kg/m<sup>2</sup> or waist circumference  $\geq 101.6$  cm) (OR 2.04,  $p=0.0005$ ), and low HDL-cholesterol (<39 mg/dl in males or <51 mg/dl in females) (OR 2.77,  $p<0.0001$ ). Understanding the key characteristics that predict greatest diabetes risk may help us identify those patients who would benefit most from preventive strategies (see Issue 2).



## Neuropathy News



A frequent complication of diabetes is neuropathy, which affects up to one half of all patients and has myriad manifestations. Colin *et al.* from Belgium conducted a cross-sectional study on a cohort of 1,194 Type 1 and Type 2 diabetic patients to estimate the prevalence of diabetic polyneuropathy (DPN) and of painful DPN (PDPN) (795-P). The overall prevalence was 43% and 14%, respectively. The prevalence rates of both DPN (51%) and PDPN (18%) were higher in the subgroup of Type 2 diabetes patients ( $n=784$ ) in comparison with Type 1 patients (25% and 6%, respectively). Patients with DPN tended to have higher prevalence of features of metabolic syndrome as shown in Table 3 and are more likely to suffer from other diabetic complications as well. There were no differences based on gender or HbA1c. Multivariate analysis showed the following variables to be independently associated with DPN: age, diabetes duration, Type 2 diabetes, nephropathy, retinopathy, foot problems, and HDL-cholesterol. The higher prevalence of DPN in Type 2 patients

could be due to the involvement of other disturbances involved in obesity and the metabolic syndrome.

Pregabalin has been in use for several years for the treatment of painful peripheral neuropathy. Freeman and collaborators from Boston pooled data from seven randomized controlled trials of 5-13 weeks duration to assess its efficacy across a wide dosing range (150-600 mg/day, BID or TID) (2275-PO). 1510 patients comprised the pooled treatment population: 557 received placebo and 953 pregabalin (176, 266, and 511 patients received 150, 300, and 600 mg/day). Reductions in mean pain score from baseline to endpoint were significantly larger in pregabalin-treated patients than in those receiving placebo: 150 mg/day, -2.05 ( $p=0.0065$ ); 300 mg/day, -2.36 ( $p<0.0001$ ); 600 mg/day, -2.75 ( $p<0.0001$ ); placebo, -1.49. Pregabalin was associated with significantly greater improvement in sleep interference and health related quality of life. On a neuropathy self-assessment survey, 65%, 74%,

and 80% of patients treated with pregabalin 150, 300, and 600 mg/day rated themselves as improved versus 54% of control patients ( $p<0.0001$  for the 300 and 600 mg doses).

Animal and *in vitro* studies suggest that both statins and fibrates may protect against nerve damage. Davis *et al.* from Australia assessed the relationship between lipid-lowering therapy and the prevalence and incidence of peripheral neuropathy in a large cohort of two groups of patients with Type 2 diabetes: a cross-sectional sample comprising all 1294 Type 2 patients recruited to the Fremantle Diabetes Study between 1993 and 1996, and a longitudinal sub-group of 531 who had attended six comprehensive annual assessments by November 2001 (4-OR). At study entry, the 1294 participants had a mean age of  $64.1 \pm 11.3$  years, 48.8% were male, and had been diagnosed a median of 4.0 (1.0-9.0) years previously; 30.9% had peripheral neuropathy. Fibrates and statins were used by only 3.5% and 6.8%, respectively. In multiple

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## Neuropathy News

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logistic regression analysis involving a range of sociodemographic, anthropometric, clinical, biochemical, and other variables, older age, longer diabetes duration, central adiposity, increasing height, higher fasting plasma glucose, systolic blood pressure, urinary albumin:creatinine, and indigenous racial background were independently associated with prevalent peripheral neuropathy at baseline ( $p < 0.03$ ); the use of fibrate therapy was negatively associated (OR 0.30; 95% CI, 0.10-0.86;  $p = 0.025$ ). In the longitudinal sub-group, fibrate and statin use increased to 10.4% and 36.5%, respectively, during the five years of follow-up. In Cox proportional hazards analysis of time to new peripheral neuropathy, time-dependent fibrate (OR 0.52 [0.27-0.98]) and statin (OR 0.65 [0.46-0.93]) use were significant determinants ( $p < 0.05$ ) of incident neuropathy. These observational data suggest that statin or fibrate therapy may protect against the development of nerve damage. We note, however, that the use of lipid lowering medications may define a group of patients with more aggressive control of other risk factors for neuropathy, including diabetic management over time.

**Table 3. Characteristics of Patients With or Without Diabetic Polyneuropathy**

	With Diabetic Polyneuropathy	Without Diabetic Polyneuropathy
Age (yrs)	64±11	53±16
Duration of diabetes (yrs)	16±10	13±10
BMI (kg/m <sup>2</sup> )	30±6	28±6
Waist circumference (cm)	103±15	97±16
Systolic blood pressure (mmHg)	137±17	133±18
Triglyceride (mg/dl)	152±99	133±94
HDL-cholesterol (mg/dl)	53±19	59±19
Micro-Macroalbuminuria (%)	42.2	23.3
Moderate to severe renal failure (%)	24.8	14.1
Retinopathy (%)	39	25
Foot complications (%)	12.1	0.9

Therefore, it is difficult to ascribe the improved neuropathy outcomes to the lipid therapy alone.

Atkin *et al.* from the UK evaluated the role of subject height on the development of neuropathy among Type 1 patients in the DCCT (800-P). 149 of the 1245 patients assessed at five years developed neuropathy. Baseline height was significantly related to the development of neuropathy (OR=1.032 per each cm increase in height,  $p = 0.029$ ), after adjusting for age, sex, disease duration, prevention

cohort, intervention group, blood pressure, lipids, smoking, and baseline HbA1c. This relationship was stronger in the conventionally-treated group (OR=1.040,  $p = 0.025$ ) than in the intensively-treated patients (OR=1.014,  $p = 0.54$ ). There was, however, no significant relationship between height and retinopathy or nephropathy. This phenomenon has been ascribed to longer neuronal paths in taller patients, allowing more opportunities for metabolic, vascular, or compressive injuries.



## So Many Posters, So Little Time....



### Basal-Bolus in the Hospital

Smiley *et al.* from Atlanta, GA and Miami, FL reported preliminary data from the RABBIT 2 Trial (Randomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes.) This prospective, randomized, multicenter study compared the efficacy and safety of a "basal-bolus" insulin regimen with regular insulin sliding scale (RISS) in patients with Type 2 diabetes admitted to a general medical ward. A total of 130 patients were randomized to receive either glargine + mealtime glulisine started at a total daily dose of 0.4 units/kg/day for those with blood glucose 140-200 mg/dl and 0.5 units/kg/day for blood glucose 201-400 mg/dl. The insulin dose was equally divided between the basal and prandial components. RISS was given four times per day for blood glucoses >140 mg/dl. Patients administered the basal-bolus regimen experienced greater improvement in their glycemic control than did RISS patients. The blood glucose target of <140 mg/dl was achieved in 66% vs. 38% in these respective groups. The difference in mean blood glucose between the groups ranged between 23 and 58 mg/dl during second to the

sixth hospital day. No differences in hypoglycemia, mortality, or length of stay were demonstrated. So, in this trial, basal-bolus insulin appeared to provide a significant metabolic advantage to the more traditional RISS and is likely the preferred insulin option in many hospitalized diabetic patients.

### Pumps over MDI

Continuous subcutaneous insulin infusion (CSII), or the insulin pump, is being widely used for management of Type 1 diabetes. But how do results compare with an intensive insulin injection regimen? Hovarth *et al.* from Austria (464-P) performed a systematic meta-analysis comparing CSII with multiple daily injections (MDI). There were 17 randomized controlled trials, with a total of 680 patients randomized to CSII. Patient mean age was 18-44 years, mean diabetes duration was 6-24 years, and HbA1c ranged from 7.5-13.2%. Overall, an HbA1c treatment difference of -0.63% favoring CSII was demonstrated. The CSII group also had a lower 24-hour blood glucose profile, lower incidence of severe hypoglycemia, and lower total daily insulin requirements as compared to MDI. The median rate of overall hypoglycemic

events per patient per week was 1.9 (0.9-3.1) for CSII and 1.7 (1.1-3.3) for MDI therapy. Thus CSII may be a better option to achieve glycemic control in Type 1 diabetes patients who are on MDI, without higher risk of hypoglycemia.

### Niacin in Diabetes...Safe?

While niacin reduces concentrations of triglyceride-rich and small low-density lipoprotein particles and increases HDL-cholesterol levels, there have been concerns about potential worsening of glycemic control due to an increase in insulin resistance. In an open-label study, Elrishi *et al.* from the UK observed a decrease in HbA1c, from 8.06 % vs. 7.40 % ( $p = 0.010$ ) in a cohort of 59 patients with Type 1 or 2 diabetes treated with extended-release niacin (750-2,000 mg daily) for six to >12 months (2446-PO). HbA1c improved in 51% of patients, no significant change in 14%, and worsened in 35%. Eight patients (13%) required a change in their insulin regimen; none commenced insulin as a result of niacin. Nonetheless, we feel that the potential impact of this lipid-lowering drug on diabetic control must be considered.

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