

# Diabetes 2005

From the 41st Annual Meeting of the European Association  
for the Study of Diabetes ■ Athens, Greece

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## The Pressure is On: Preserving Renal Function in Diabetes



Important data on diabetes presented at the 41st Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2005**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2005** will be followed by a **Diabetes 2005** booklet (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$25 processing fee to the Yale Office of Continuing Education, 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 2005** 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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Nephropathy is one of the most feared complications of diabetes. The importance of early detection of patients at risk for nephropathy cannot be overemphasized as diabetes is the leading cause of end stage renal disease (ESRD) in the US. Once ESRD becomes established, renal replacement therapy is not only costly but has a significant negative effect on both cardiovascular risk and quality-of-life.

### Estimating Risk

While there are several tools available to estimate cardiovascular risk, none exists to predict the risk of microvascular disease, such as nephropathy, in those with Type 2 diabetes. To address this issue, investigators from Oxford, UK (abstract 79) used the UKPDS database to assess factors that predicted the development of nephropathy (defined as glomerular filtration rate [GFR] <60 ml/min, or the presence of macroalbuminuria or ESRD) in 2,859 patients followed for a mean of six years. They reported 515 (18%) cases of incident nephropathy. The risk factors that proved significantly associated with the development of renal disease are shown in Table 1. Based on these data, another UKPDS "risk engine" may soon be available to estimate the risk of nephropathy, as has already been done for macrovascular disease.

### An Ounce of Prevention

It is also well known that ACE inhibitors (ACE-Is) and angiotensin-II receptor blockers (ARBs) are renoprotective; both reduce the risk and delay the progression of diabetic nephropathy. Rossing and colleagues (abstract 8) from the Steno

Diabetes Centre in Denmark sought to determine whether ultra-high doses of the ARB, irbesartan, would further reduce the progression of microalbuminuria in a cohort of 52 hypertensive Type 2 diabetic patients. Following a two-month wash-out period from prior ACE-I or ARB therapy, patients were randomized to receive irbesartan 300 mg, 600 mg, or 900 mg for two months. The investigators found that all doses of the drug lowered urinary albumin excretion (UAE), blood pressure, and GFR. UAE was reduced significantly further, albeit by a relatively small amount, with higher doses: 300 mg, -52% (95% confidence interval [CI], -46 to -57%); 600 mg, -49% (95% CI, -43 to -54%); and 900 mg, -59% (95% CI, -54 to -63%). All doses of irbesartan were well tolerated. Clearly, additional clinical trials of longer duration are required to confirm the renoprotective effects as well as the safety and dose-response relationship of high-dose ARB therapy.

Emerging evidence showing that aldosterone plays a key role in the pathogenesis of diabetic nephropathy may suggest an additional therapeutic intervention, given that ACE-Is or ARBs do not by themselves sufficiently suppress circulating aldosterone concentrations. Several investigators at the EASD meeting in Athens this week presented promising findings with the use of spironolactone in these patients. Schjoedt *et al.* (abstract 10) from The Netherlands and Denmark conducted a double-masked, randomized, placebo-controlled cross-over trial of spironolactone 25 mg once daily vs. placebo in 21 Type 1 diabetes patients with nephropathy, who were already on antihypertensive therapy including an ACE-I

**Table 1. Risk Factors Associated With Renal Disease in Type 2 Diabetes**

Risk Factor	Hazard Ratio	95% Confidence Interval
Age (per year)	1.12	1.10 - 1.14
Female gender	1.91	1.56 - 2.26
Afro-Caribbean ancestry	1.46	1.01 - 1.92
Asian-Indian ancestry	1.64	1.03 - 2.24
Systolic blood pressure (per 10 mmHg)	1.05	1.01 - 1.10
Duration of diabetes (per year)	1.14	1.09 - 1.18

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## ...Preserving Renal Function

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and/or an ARB. The group was then followed for two months. Spironolactone was associated with a 30% further reduction in albuminuria, a 35% reduction in fractional albumin clearance, and a 10 mmHg reduction in daytime mean blood pressure over placebo. In a similar study from the same group (Jacobsen *et al.*, abstract 11), spironolactone 25 mg once daily in addition to ongoing antihypertensive therapy (including diuretics and maximum doses of ACE-I or ARBs) in 21 Type 1 diabetic patients with established nephropathy, produced a 33% (95% CI, 25% to 41%) further reduction in albuminuria and a 40% (95% CI, 24% to 53%) decrease in fractional clearance of albumin. Based on their findings, the presenters concluded that aldosterone receptor blockade superimposed upon renin-angiotensin system blockade may offer additional renoprotection in Type 1 diabetes patients with nephropathy.

The results with spironolactone are interesting; however, there are obvious safety concerns for hyperkalemia, especially when used in conjunction with RAS blockers. Case in point, van den Meiracker and Dutch colleagues (abstract 12) performed a masked, parallel-group, one-year follow-up trial of 59 Type 2 diabetes patients with established nephropathy taking spironolactone 50 mg daily vs. placebo. They found that, although patients exhibited a marked reduction in UAE, this was at the expense of an actual *faster* deterioration in renal function, and a higher incidence of significant hyperkalemia.

To a large degree, diabetic nephropathy is preventable with glucose and blood pressure control. Microalbuminuria, an early feature of diabetic nephropathy, is strongly associated with

insulin resistance. On this basis, Pistrosch and German colleagues (abstract 185) compared the effects of 12 weeks of the insulin sensitizer rosiglitazone, a thiazolidinedione (TZD), to placebo in a double-blind, cross-over study of 10 patients with Type 2 diabetes. The authors reported that rosiglitazone improved GFR and renal nitrous oxide bioavailability (a measure of endothelial function), and reduced albumin excretion in those patients with microalbuminuria, in comparison to placebo. The results from this small study suggest that insulin-sensitizers may actually prove beneficial in the early stages of diabetic nephropathy. The TZD class of agents has also been found to have small but significant antihypertensive effects. The implications of these modest effects on renal or cardiac outcomes is not yet known.

## A New Approach

New therapies are also emerging based on our increasing understanding of the pathogenesis of diabetic nephropathy. Anderson and colleagues (abstract 182) reported on the results of a double-blind, placebo-controlled trial of ruboxistaurin, a selective protein kinase C (PKC)  $\beta$  inhibitor in 123 Type 2 diabetic patients with established albuminuria on stable doses of ACE-Is or ARBs. At one year, the mean albumin:creatinine ratio decreased significantly with ruboxistaurin (-24%,  $p < 0.05$ ), whereas no change was seen with placebo (-9%,  $p = 0.33$ ). Additionally, no significant change in GFR was detected in the ruboxistaurin-treated patients ( $-2.5 \pm 1.9$  ml/min;  $p = 0.185$ ), whereas placebo patients did experience a small but significant decrement ( $-4.8 \pm 1.8$  ml/min;  $p = 0.009$ ). Importantly, the PKC inhibitor was not associated with any increased reporting

of adverse events. The presenters concluded that ruboxistaurin may prove a useful addition to established therapies for diabetic nephropathy. We note that the authors did not report results from any between-group statistical comparisons, and therefore these data should be considered highly preliminary.

## Looking for Zebras....

Managing hypertension in those with Type 2 diabetes and microalbuminuria or nephropathy is often challenging, with these individuals often requiring more office visits and physician interventions (Mugarza *et al.* abstract 960). In patients failing to attain blood pressure targets despite good compliance with multiple agent anti-hypertensive regimens, secondary causes of hypertension should be considered. Mukherjee and Asian colleagues (abstract 962) screened 90 patients with Type 2 diabetes and poorly controlled hypertension (despite therapy with two to five drugs) for primary hyperaldosteronism, using the plasma aldosterone:plasma renin activity ratio. Eight patients (8.8%) had an elevated ratio; seven of these were found to have abnormal aldosterone levels (i.e., non-suppressible) by an intravenous saline load test. Computed tomography scanning revealed a unilateral adrenal adenoma in four patients and bilateral adrenal hyperplasia in three. Among the four with an adenoma, adrenal venous sampling confirmed hyperaldosteronism, and, in the three patients to date who have undergone surgery, histology was consistent with an adenoma in two and hyperplasia in one. In those found to have primary hyperaldosteronism, the use of spironolactone may be beneficial, as long as it can control blood pressure and the potential for hypokalemia.



## The Pity de Foie Gras



Nonalcoholic fatty liver disease (NAFLD) is commonly observed in patients with metabolic syndrome and therefore frequently encountered in our diabetic and pre-diabetic patients (Table 2). Within the spectrum of NAFLD lies non-alcoholic steatohepatitis (NASH), representing a progression from simple steatosis to inflammatory changes, with the possibility of subsequent fibrosis. Individuals with NASH have high circulating free fatty acid concentrations that likely allow for greater hepatic fatty acid uptake and oxidation, with downstream deleterious effects on insulin action in hepatocytes. The ensuing hepatic insulin resistance results in increased endogenous glucose

production and the well-characterized lipid abnormalities marked by increased VLDL synthesis. Once considered an innocent sequelae of obesity, NAFLD can actually progress to frank cirrhosis.

Simmons and Australian co-workers (abstract 328) evaluated 1,454 adults and found an age-adjusted metabolic syndrome prevalence of 5.3% in men and 20.8% in women that persisted after adjusting for a number of other confounders (e.g., BMI, socioeconomic factors, exercise, smoking). The number of components of metabolic syndrome correlated positively with markers of hepatic function—specifically, with alanine aminotransferase (ALT) ( $r = 0.161$ ,  $p < 0.001$

men;  $r = 0.111$ ,  $p = 0.002$  women), alkaline phosphatase ( $r = 0.100$ ,  $p = 0.013$  men;  $r = 0.083$ ,  $p = 0.20$  women), and gamma glutamyl transferase ( $r = 0.125$ ,  $p = 0.002$  men;  $r = 0.130$ ,  $p < 0.001$  women). For unclear reason, elevated bilirubin correlated among men ( $r = 0.093$ ,  $p = 0.022$ ) but not women ( $r = 0.032$ ,  $p = \text{ns}$ ).

The presence, degree, and pattern of ALT elevation are considered nonspecific in the diagnosis of NAFLD. However, elevated ALT is associated with a significant increased risk of coronary events (Figure 1) according to a study of 1,578 patients without Type 2 diabetes by Schindhelm and European colleagues (abstract 218). This is

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likely merely a reflection of the association between obesity, NAFLD, and insulin resistance.

The management of those with NAFLD or NASH should center around weight reduction and the avoidance of hepatotoxins. There is also obvious interest in the pharmacologic treatment of insulin resistance in these patients. Thiazolidinediones ameliorate insulin resistance and reduce hepatic fat stores in patients with Type 2 diabetes. It has therefore been conjectured that these agents may benefit patients with NASH. Harrison and American colleagues (abstract 770) performed a randomized, double-blind, placebo-controlled trial to examine the efficacy of pioglitazone (45 mg daily for six months) in 47 patients with impaired glucose tolerance or Type 2 diabetes as well as biopsy-proven NASH. As compared to placebo, therapy with pioglitazone improved liver

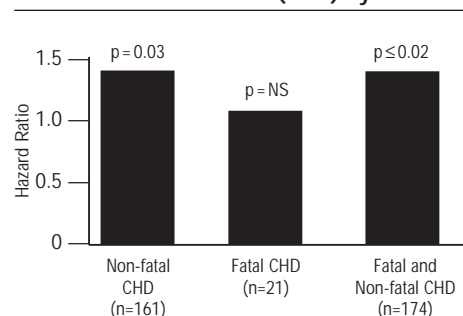
**Table 2. Main Differential Diagnosis of Abnormal Liver Tests in Patients with Diabetes**

■ NAFLD
■ NASH
■ Hemochromatosis
■ Viral hepatitis, especially hepatitis C
■ Drug-associated hepatotoxicity (i.e., statins)

histology with significant reductions in hepatic fat content ( $p < 0.001$ ) and significant improvement in the overall histologic index including inflammation, ballooning necrosis, and fibrosis ( $p < 0.01$ ).

The link between NAFLD, NASH, insulin resistance, and diabetes continues to be defined.

**Figure 1. Hazard Ratio for Coronary Heart Disease (CHD) by ALT\***



\*ALT (3rd vs. 1st and 2nd tertiles) adjusted for age, gender, alcohol-intake, smoking, physical activity, lipids, blood pressure, waist circumference, and HbA1c.

The insights provided by the investigators at this week's meeting will likely pave the way for the development of effective therapeutic options for this increasingly common condition.



## Novel Insulin Delivery Systems: An Update



In the history of medicine, few events were more dramatic than the discovery of insulin. Insulin remains, however, generally underutilized due to perceived barriers related to its mode of administration—namely, subcutaneous (SC) injections. Numerous attempts have been made to develop commercially viable, noninvasive insulin delivery systems, including oral, nasal, transdermal, and inhalation routes of administration, with many of these presented at this year's ADA meeting [see *Diabetes 2005*, Volume 11, Issue 3]. Many of these products are in various stages of development. The pulmonary insulins fall into two main groups: dry powder formulations and solutions, each delivered through different patented inhalation systems.

### Insulin Is in the Air

Exubera® is a widely studied, rapid-acting insulin in powdered form that is delivered to the pulmonary system via a specialized inhaler. The inhaler generates a pulse of compressed air that disseminates the dry powder into an insulin "cloud" and delivers it into a spacer from which it is inhaled. Norwood and North American colleagues compared the glycemia lowering effect of this inhaled product with that of SC human insulin in 226 patients with Type 1 diabetes (abstract 73). Similar effects on HbA1c at 12 weeks (7.1% and 7.0% in the inhaled and SC insulin groups, respectively) were found. Patients treated with inhaled insulin compared with SC insulin experi-

enced a higher overall hypoglycemic event rate (6.8 vs. 5.5 events/patient-month) but a lower rate of severe hypoglycemia (risk ratio 0.52, 90% confidence interval 0.31-0.87), and a higher incidence of cough (30.9% vs. 7.8%), the latter being generally mild and occurring within minutes of dosing. Antibody levels rose with the inhaled insulin to a median of 37.0  $\mu$ U/ml (mean 134.3  $\mu$ U/ml) by week 12 and declined following drug discontinuation.

The Technosphere® system delivers a dry, encapsulated powder formulation of insulin to the pulmonary tree via a small MannKind™ inhaler. In previous investigations, insulin delivered via this system exhibited bioavailability that mimicked normal, meal-related, first- or early-phase insulin release. In an open-label, two-period, cross-over study, Boss of the US and German colleagues (abstract 816) randomized 16 patients with Type 2 diabetes (mean HbA1c 7.3%) to treatment with prandial inhaled Technosphere insulin or SC regular insulin, each combined with the patients' usual dose of basal insulin. The baseline adjusted post-prandial total insulin exposure was comparable between treatments. However, the baseline adjusted post-prandial glucose excursion for inhaled insulin was only about half of that for SC insulin (5,095 vs. 9,851 min · mg/dl, respectively;  $p < 0.008$ ). Post-prandial maximum adjusted blood glucose excursions were lower with the inhaled insulin (49 vs. 82 mg/d,  $p < 0.003$ ). The incidence of hypoglycemia was similar between the treatments.

The effects on HbA1c of add-on therapy with the metered-dose inhaler formulation of short-acting human insulin by KOS Pharmaceuticals were compared with bedtime SC insulin glargine in 24 patients with poorly controlled (mean HbA1c 8.4%) Type 2 diabetes (abstract 817). In addition to their ongoing sulfonylurea and/or metformin regimen, patients received inhaled insulin up to 15 minutes before main meals or SC insulin at bedtime. Both modes of insulin administration produced similar improvements in HbA1c (-1.2% with inhalation and -1.0% with SC). However, inhaled insulin produced significantly ( $p = 0.011$ ) greater improvement in serum triglycerides as compared to SC insulin (-36% [from 249 to 142 mg/dl,  $p < 0.01$  from baseline] vs. -12% [from 258 to 205 mg/dl,  $p = ns$ ]) and significantly ( $p < 0.05$ ) reduced LDL-cholesterol from baseline (from 129 to 113 mg/dl with inhaled vs. no change with SC insulin). Four cases of confirmed hypoglycemia occurred in those treated with SC insulin, and three cases occurred in those treated with inhaled insulin.

### Making Insulin Easier to Swallow

Oralin is a novel oral spray formulation of insulin that is absorbed through the buccal mucosa. In a double-blind study, Raz and Israeli colleagues randomized 26 patients with Type 2 diabetes poorly controlled with SC insulin glargine plus metformin to seven puffs of Oralin

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or placebo three times daily (abstract 820). The puffs were administered 10 minutes before mealtime and patients continued their usual diabetes treatment regimen. After eight weeks of treatment, Oralin-treated patients exhibited a

15.4% reduction in post-prandial glucose level compared to a 3.9% elevation in the placebo group ( $p=0.04$ ). The effect on HbA1c was similar between the treatment groups (6.6% reduction with Oralin and 3.4% reduction with placebo,  $p>0.05$ ).

There is significant interest in the US Food

and Drug Administration's (FDA) approach to these noninvasive formulations. Exubera was recently approved by an FDA advisory board and should be available shortly. It will offer a new option to insulin-requiring diabetic patients. Concerns about cost and long-term safety of these formulations will need to be addressed.



## Stroke of Bad Luck



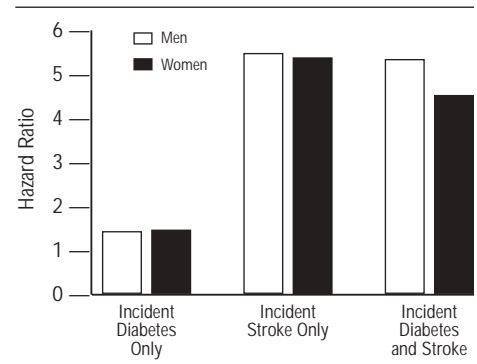
Recently, much attention has been placed on the association between diabetes and myocardial infarction (MI). The same cannot be said, however, for stroke—despite the fact that diabetes remains a major risk factor for cerebrovascular disease. This should come as no surprise, since the fundamental biology of atherosclerosis is the same, no matter the vascular territory involved. Several abstracts concerning the cerebrovascular complications of diabetes were presented this week.

Type 2 diabetes has been associated with cognitive impairment and dementia, especially in elderly patients. Although such deficits have been ascribed to ischemic cerebrovascular disease, there are few data to confirm this. Manschot *et al.* from The Netherlands studied 122 Type 2 diabetic patients (mean age, 66 years) and 59 non-diabetic controls, matched for age, gender, and education level. A comprehensive neurological and neuropsychiatric examination was performed, including brain magnetic resonance imaging (MRI) scans. In addition, a complete cardiovascular risk factor analysis was conducted. Hypertension (73% vs. 32%), MI or coronary artery bypass graft (CABG) (19% vs. 3%), prior stroke (19% vs. 7%), and intermittent claudication or peripheral vascular surgery (15% vs. 0%) were all more prevalent in the diabetic patients. Moderate cog-

nitive dysfunction was also encountered more frequently in those with diabetes, especially within the domains of executive functioning, information processing, speed, and memory. Silent cerebral infarcts (19% vs. 7%) were more common in the diabetic patients, as were cortical and subcortical atrophy and deep (but not periventricular) white matter lesions. Established macrovascular disease was associated with ischemic changes on MRI suggestive of vascular disease and cognitive abnormalities. Diabetes duration and HbA1c were not, however, related to any cerebral deficit. The relationship between cognitive impairment and MRI changes appears to be partly dependent on macrovascular disease, but largely independent of diabetes-related disease variables. These preliminary data suggest that control of cardiovascular risk factors may decrease the risk of stroke and dementia in diabetic patients. We note, however, that this study did not address the potentially important role of hypoglycemia in cognitive impairment in diabetic patients.

The recent CARDS study demonstrated a cardiovascular benefit in reducing normal LDL-cholesterol levels with atorvastatin in Type 2 diabetic patients as a primary prevention strategy (*Lancet*, 2005). Hitman and UK colleagues reported this week on stroke outcomes from this trial in which

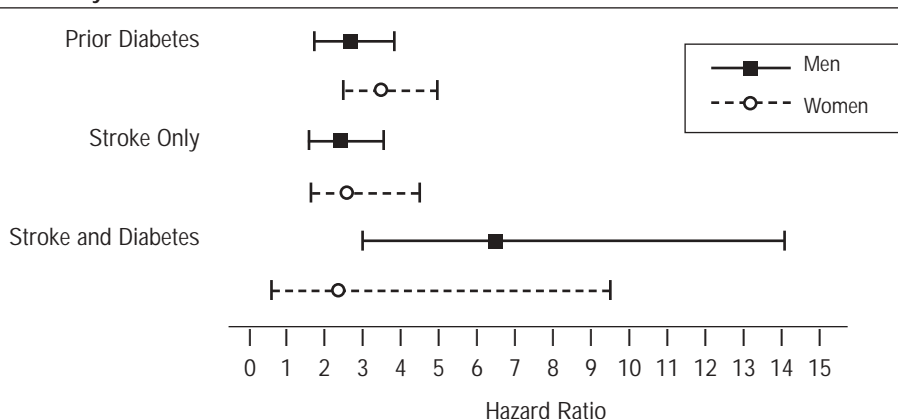
**Figure 3. Hazard Ratios for Stroke Mortality by Baseline Disorder Including Antecedent Diabetes and Stroke Status**



2,838 patients with Type 2 diabetes but no history of coronary heart or macrovascular disease were randomized to atorvastatin 10 mg vs. placebo and followed for a median of 3.9 years. Cox regression modeling was used to compare treatment effect on time to first stroke, which was classified as fatal or non-fatal. Atorvastatin therapy was associated with a 48% relative risk reduction in stroke (21 vs. 39,  $p=0.016$ ). Eight of the strokes were fatal (1 vs. 7) and 52 were non-fatal (20 vs. 32). Predictors of stroke included age ( $p<0.001$ ), longer duration of diabetes ( $p=0.02$ ), and higher systolic blood pressure ( $p=0.04$ ). Baseline HbA1c was of only marginal significance ( $p=0.07$ ), but those with baseline HbA1c  $>10\%$  experienced significantly more strokes (hazard ratio = 2.35,  $p=0.02$ ).

Hu and colleagues (abstract 220) prospectively followed 25,287 Finnish men and 26,537 Finnish women aged 25-74 years to determine the effect of baseline and incident stroke and diabetes on stroke mortality. During nearly 19 years of follow-up, 1,043 stroke deaths occurred. In the multivariate analysis of baseline disorders, hazard ratios for stroke mortality were determined (Figure 2). A second multivariate analysis

**Figure 2. Hazard Ratio and 95% Confidence Interval for Stroke Mortality by Baseline Disorder**



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(similar to the baseline analysis, but including antecedent diabetes and stroke status) was also performed to determine the impact of incident diabetes and/or stroke on stroke mortality (Figure 3). The authors concluded that both diabetes and stroke, present either at baseline or during follow-

up, increase the risk of death from stroke, but that incident stroke had the more powerful effect. These data should not be surprising. They will likely be contrasted to the well-known data (Haffner *et al.*, *N Engl J Med* 1998) showing that both a history of MI or diabetes contributes equally to future MI risk. However, it should be noted that the Hu study deals primarily with mortality from stroke. Data on the contrasting

effects of baseline diabetes and stroke on incident stroke were not reported, but would be of great interest.

These reports and others from the EASD meeting in Athens this week suggest a similar relationship between diabetes and vascular disease whether the latter involves the coronary or the cerebral circulations.



## Facts on Axons



First identified as a clinical entity more than 200 years ago, diabetic neuropathy is now the most common form of neuropathy in the Western world. With an overall prevalence estimated as high as 50%, neuropathy has a clinical course that parallels the duration and severity of hyperglycemia in both Type 1 and Type 2 diabetes patients. For many patients, diabetic neuropathy is both distressing and disabling, and unfortunately, no therapy has proven completely satisfactory. Several presentations at the EASD described potential new therapeutic options for this troublesome complication.

Agrawal *et al.* from India reported on the use of glyceryl trinitrate in a spray form for painful diabetic neuropathy (abstract 213). In a double-blind, placebo-controlled, cross-over study of 48 patients with neuropathy the use of this topical spray resulted in significant improvements in pain, as assessed by several validated pain scoring systems. The drug was also generally well tolerated. The presenters hope to pursue the potential use of this simple therapy in larger, long-term trials. Raskin *et al.* reported on the results from three large clinical trials that have examined the efficacy and safety of duloxetine, a dual reuptake inhibitor of both serotonin and norepinephrine, involving a total of 1,139 patients (abstract 216). Across all three studies, duloxetine in doses of 60 mg once or twice daily demonstrated a significant treatment

effect over placebo. The drug also proved to be well tolerated. In a similar review, Griesing *et al.* provided a combined analysis of six trials (1,346 patients) that had examined the efficacy and safety of pregabalin, a GABA analogue (abstract 965). The investigators reported that pregabalin therapy resulted in small but significant reductions in pain scores. Dizziness and somnolence were the most common adverse events with the drug; 11% of patients withdrew from the trials because of side effects, in comparison to 4% of placebo-treated patients.

Vitamin B12 is important for the synthesis of fatty acids, which help maintain the myelin sheath around neuronal axons. Basat and colleagues compared therapy with vitamin B12 (1,000 mg/day parentally for one week followed by 3,000 mg three times per week) with gabapentin (an established, though off-label therapy for diabetic neuropathy and the forerunner of pregabalin, 1,200 mg/day for one week then 2,400 mg/day) in a randomized, open-label, 12-week trial involving 78 patients (abstract 967). It should be pointed out that all patients included in this study had normal vitamin B12 levels prior to entry. Patients in both the gabapentin and vitamin B12 groups showed significant reductions in pain score (6.8 to 4.1 and 6.7 to 4.3, respectively), with no significant difference between groups. Both groups also reported similar improvements in the McGill

pain questionnaire and a quality-of-life questionnaire.

Serhiyenko *et al.* looked at the use of vitamin B1 (benfotiamine [BET]) and alpha-lipoic acid (ALA) in the treatment of diabetic neuropathy (abstract 969). Sixty-one patients with Type 1 diabetes and moderate-to-severe diabetic peripheral neuropathy were studied. Patients were treated with either ALA 600 mg orally three times daily (n = 18), BET 150 mg orally three times daily (n = 17), the combination of the two (n = 15), or placebo (n = 11). After two months of therapy, all groups showed an improvement in symptom scores in comparison to placebo, with the effect of combination therapy being the most impressive (reduction in pain of 65%, skin tenderness 59%, paresthesia 71%, numbness 74%, and tingling 69%). Biochemically, these changes were accompanied by improvements in antioxidant state and measures of platelet aggregation.

Taken together these reports highlight the fact that diabetic neuropathy is a syndrome encompassing many pathophysiological abnormalities, which may require different therapeutic approaches, perhaps in combination. The advantage of some of these newer agents is that they will avoid the significant adverse effects associated with centrally-acting drugs. They may also be quite cost effective. In the future, as experimental data continue to emerge, we will hopefully be able to offer our patients evidence-based therapies for this distressing condition.



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



Muscle oxidizes glucose to produce the energy required for contraction. It might therefore seem logical that increasing glucose supply to muscles might improve their performance. This hypothesis was tested by Stettler and colleagues from Switzerland (abstract 712). Eight, well-trained

males with Type 1 diabetes performed standard exercise tests under controlled euglycemic (95 mg/dl) or hyperglycemic (220 mg/dl—a state by no means uncommon during exercise in Type 1 diabetes) states. No significant effect on peak power output, rate of perceived exertion, lactate levels, heart rate, or

respiratory exchange ratio was found. The investigators concluded that the increase in extra-cellular glucose availability had not translated into increased oxidation, and that, therefore, hyperglycemia could not be recommended for physical activity enhancement in Type 1 diabetes.

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