

# Diabetes 2006

From the 42nd Annual Meeting of the European Association  
for the Study of Diabetes ■ Copenhagen, Denmark

2002 2003 2004 2005 **2006** 2007 2008

Sponsored by Yale University School of Medicine,  
Department of Internal Medicine, Section of Endocrinology

Volume 14 ■ September 14, 2006 ■ Issue 1



## Yikes! Those Spikes!



Important data on diabetes presented at the 42nd Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2006**, 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. E-mail or fax delivery to your office of **Diabetes 2006** will be followed by a **Diabetes 2006** 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 2006** 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 interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, 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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Supported through an unrestricted educational grant from Takeda Pharmaceuticals North America, Inc.

For years, there's been considerable controversy as to the importance of post-prandial glucose (PPG) in the management of patients with diabetes. Historically, we as clinicians have mainly focused upon fasting (or pre-prandial) glucose levels to guide therapy, in conjunction with the more long-term indicator of glycemic control, HbA1c. However, epidemiological studies, including DECODE and the Honolulu Heart Study, have determined that PPG spikes may be more closely aligned with cardiovascular risk, the leading cause of mortality in our diabetic patients. Moreover, this risk appears to be present even before the development of diabetes *per se*. Accordingly, various professional organizations have proposed guidelines in managing PPG. For example, the American Diabetes Association recommends that PPG, typically measured two hours after the start of the meal, be maintained at less than 180 mg/dl. Admittedly, however, there is a general paucity of data from clinical trials that the control of PPG actually results in improved clinical outcomes. Also, testing PPG presents an added challenge for many of our patients, who sometimes find it difficult to check fingersticks regularly. Nonetheless, most persons find themselves in the post-prandial phase (generally regarded as the three to four hours after a meal)

for the majority of their waking hours. Therefore, it is likely that control of PPG has a significant impact upon HbA1c, and as such is important to target therapeutically. Anti-hyperglycemic agents with a major post-prandial effect are listed in Table 1. Several abstracts presented at this week's EASD meeting further explored the implications of PPG in diabetic patients.

Major-Pedersen and Danish collaborators (abstract 132) sought to determine whether addressing postprandial hyperglycemia using the rapid-acting non-sulfonylurea insulin secretagogue, nateglinide, could improve endothelial dysfunction, one of the earliest markers of atherosclerosis. The investigators measured post-oral glucose load endothelial function in 56 insulin-resistant subjects with impaired glucose tolerance (IGT). Baseline characteristics of the group included an age of  $57.5 \pm 7.3$  years, body mass index (BMI)  $34.4 \pm 5.68$  kg/m<sup>2</sup>, Homeostasis Model Assessment (HOMA)  $6.4 \pm 0.7$  (values above 3 are generally seen in insulin-resistant individuals), HbA1c  $6.4 \pm 0.8\%$ , and fasting plasma glucose (FPG)  $112 \pm 18$  mg/dl. One-half of the subjects were randomized to the intervention group, receiving an individually-adjusted dose of nateglinide, 10 minutes before the glucose load. The flow-mediated dilation (FMD) technique (by ultrasound) was used to

**Table 1. Anti-hyperglycemic Agents with a Major Effect on PPG**

<i>Class</i>	<i>Mechanism of Action</i>	<i>Examples</i>
Alpha-glucosidase inhibitors	Retards intestinal carbohydrate absorption	Acarbose Miglitol
Non-sulfonylurea secretagogues (meglitinides)	Increases islet cell insulin output	Repaglinide Nateglinide
GLP-1 agonists	Increases glucose-dependent insulin secretion Decreases glucagon secretion Slows gastric emptying	Exenatide
Amylin analogues	Slows gastric emptying Decreases glucagon secretion	Pramlintide
Rapid insulin analogues	Increases insulin levels	Lispro Aspart Glulisine

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assess endothelial function. Typically, in normal individuals, FMD increases in the post-prandial setting, in part due to the vasodilatory effects of insulin. FMD is known to be attenuated in those with low insulin sensitivity. To underscore the difference between normal and insulin-resistant subjects in this study, the investigators also measured post-oral glucose load endothelial function in nine healthy, insulin-sensitive individuals (age  $41.1 \pm 3.0$  years, BMI  $23.2 \pm 2.1$  kg/m<sup>2</sup>, HOMA  $0.7 \pm 0.1$ , FPG  $74 \pm 5$  mg/dl). In both the intervention and the control IGT groups, the delta post-prandial FMD (fasting FMD subtracted from post-prandial FMD, expressed as a percentage) were negative values ( $-3.42 \pm 1.67\%$  and  $-2.20 \pm 1.19\%$ , respectively). In contrast, in the healthy group, the delta FMD was  $+4.80 \pm 1.41\%$ ,  $p=0.009$ . On day 2 of the study, after receiving nateglinide prior to the glucose load, the intervention group's delta FMD values increased by  $+2.32 \pm 1.45\%$  ( $p=0.02$ ). The investigators concluded that endothelial function deteriorates after an oral glucose load in insulin-resistant individuals but that, by decreasing post-load hyperglycemia with nateglinide, vasodilatation is enhanced to the extent that it mimics the endothelial response in healthy individuals. Furthermore, they conjectured that these findings could potentially impact upon the prevention of cardiovascular disease in insulin-resistant individuals with pre-diabetes or even early Type 2 diabetes.

In another abstract involving nateglinide, Lambadiari and Greek colleagues compared its effects on PPG and lipids to that of a traditional secretagogue—the sulfonylurea, glibenclamide, a European version of our glyburide (abstract 560). Twenty-four newly-diagnosed patients with Type 2 diabetes (age  $54 \pm 2$  years, BMI  $25 \pm 1$  kg/m<sup>2</sup>, HbA1c  $7.5 \pm 0.3\%$ ) were first kept euglycemic with intravenous insulin and then studied on two separate occasions, first after ingesting a standard mixed meal without any drug administration, and then after the same meal, but preceded by a single dose of either 120 mg nateglinide ( $n=12$ ) or 5 mg glibenclamide ( $n=12$ ). The overall glucose response to the meal was reduced to the same degree by nateglinide and glibenclamide. The overall insulin secretion (from baseline to 360 minutes) was better after glibenclamide ( $337 \pm 30$  mU/l/hr) than after nateglinide ( $264 \pm 20$  mU/l/hr,  $p<0.05$ ). However, insulin secretion during the first 30 minutes was more prominent in the nateglinide ( $13 \pm 1$  mU/l/hr) than in the glibenclamide group ( $9 \pm 1$  mU/l/hr,  $p<0.05$ .) Post-prandial triglyceride levels were similar between groups, but free fatty acid concentrations were less after nateglinide. The

investigators concluded that the more physiological insulin secretory profile, with a near-reestablishment of first-phase insulin secretion, achieved with nateglinide was more efficient in suppressing lipolysis in the post-prandial state than with glibenclamide. The impact of either of these effects on long-term outcomes, is, of course, debatable.

Another drug that improves post-prandial glucose metabolism is the recently available amylin analogue, pramlintide, currently approved for use in Type 1 and in insulin-requiring Type 2 diabetes. This injectable agent reduces PPG excursions by slowing gastric emptying and also, presumably, by suppressing glucagon secretion by pancreatic  $\alpha$ -cells, thereby decreasing hepatic glucose production. A physiological study was conducted by Woerle and colleagues from Germany and the US in which nine healthy subjects were studied (age  $41 \pm 3$  years, BMI  $27.8 \pm 1.1$  kg/m<sup>2</sup>) (abstract 572). After three hours of a primed continuous isotopic glucose infusion, 30 g of pramlintide or placebo were injected subcutaneously, and subjects then proceeded to consume a mixed meal consisting of 50 g glucose, 25 g fat, and 20 g protein, enriched with a dideuterated glucose tracer. The meal itself was also radio-labelled to further measure gastric emptying by scintigraphy. PPG excursions were larger over the initial 120 minutes in placebo-treated subjects versus pramlintide ( $94 \pm 2$  vs.  $86 \pm 0.2$  mg/dl,  $p<0.001$ ). Of note, however, no significant differences in post-prandial glucagon were found between the groups ( $53.7 \pm 4.7$  vs.  $52.8 \pm 5.2$  pg/ml, respectively,  $p=NS$ ). Post-prandial insulin concentrations were greater and hepatic glucose production trended lower with placebo. Despite lower post-prandial insulin, PPG excursions were reduced with pramlintide, corresponding to significant reduction in overall glucose appearance ( $24.6 \pm 1.3$  vs.  $18.5 \pm 1.4$  mol/kg/min,  $p=0.007$ ).

Modestly lower gastric emptying in the active therapy group ( $67.6 \pm 3.1$  vs.  $78.2 \pm 2.7\%$  retention at 120 minutes,  $p<0.05$ ) was associated with a reduction in the rate of appearance of oral glucose ( $18.4 \pm 1.2$  vs.  $9.9 \pm 1.5$  mol/kg/min,  $p<0.05$ ). The researchers concluded that pramlintide reduced PPG excursions predominately by slowing gastric emptying, leading to greater splanchnic glucose sequestration.

Tan and international colleagues assessed the effects of PPG on the inflammatory marker, C-reactive protein (CRP), which is known to increase after meals (abstract 989), further fueling concerns about the importance of PPG control as regards to cardiovascular outcomes. The collaborators compared the effects of the basal insulin glargine with a mixed insulin product consisting of 50% lispro and 50% neutral protamine lispro (NPL) (50/50 lispro mix), both in combination with metformin on PPG, serum insulin, and highly sensitive (hs)-CRP after 24 weeks of treatment in a prospective, open-label, randomized study. After a six-week lead-in treatment period with 75/25 lispro mix (75% NPL, 25% lispro) and metformin, patients were randomized to receive either metformin + glargine (at bedtime) or metformin + 50/50 lispro mix (tid with meals). Insulin doses were titrated to achieve a fasting glucose  $<120$  mg/dl and, in the lispro mix group, a two-hour PPG  $<144$  mg/dl. A subgroup of patients then underwent single mixed meal testing. These individuals, ate dinner and then received their assigned insulin. After an overnight fast, lispro mix patients were then given a dose five minutes prior to the meal, which consisted of a standardized McDonald's breakfast (fat 39 g, carbohydrate 78 g, protein 24 g). Prior to randomization, the changes in glucose, insulin, and hs-CRP levels before and after the test meal were similar between groups. Table 2 shows the corresponding levels between the two groups during the mixed meal.

**Table 2. Changes in Glucose, Insulin, and hs-CRP Between Insulin Treatment Groups**

Time (hrs)	Glucose (mg/dl)		Insulin (mcU/ml)		hs-CRP (mcg/ml)	
	Lispro Mix	Glargine	Lispro Mix	Glargine	Lispro Mix	Glargine
0	124	104	27	26	1.95	1.80
1	164*†	171†	73*†	41†	2.86†	2.98†
2	149*†	173†	69*†	43†	2.64*†	3.18†
3	128*	162†	55†	45†	2.38*†	3.40†
4	106*†	139†	41†	37†	1.95*	2.74†
6	95*†	108	27	29	1.74	2.07
8	99*†	95	24	24	1.60	1.90

Lispro Mix=50% lispro and 50% neutral protamine lispro.

\*between-group changes from 0-hour significantly different ( $p<0.05$ ).

†within-group significantly different from 0-hour ( $p<0.05$ ).

Note: In both insulin groups patients also received metformin.

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The investigators concluded that in insulin-requiring Type 2 diabetics, PPG is associated with a significant increase in hs-CRP, a change which appears to be partly dependent on the type of insulin therapy used. In general, there was less post-prandial hs-CRP increase in patients taking the pre-mixed insulin, which has a major component of the rapid-acting analogue, lispro. Interestingly, the peak hs-CRP occurred at one hour with lispro mix, corresponding to the

peak PPG. With the basal insulin glargine, the peak hs-CRP occurred at three hours and corresponded to the peak in insulin concentration. The impact of these changes on cardiovascular risk is speculative at this point.

Clearly, there continues to be extensive interest in the causes, treatment, and implications of PPG in patients with diabetes. While these investigations are noteworthy and of some interest, the long-term impact of PPG control in diabetic patients will remain elusive until large, randomized clinical trials can confirm its importance on clinical

outcomes, such as vascular complications. Until then, it would appear prudent to concern ourselves with PPG control mainly in those patients in whom the fasting/pre-prandial glucose is at target, yet the HbA1c is not. It is in this population that a PPG-focused approach to anti-hyperglycemic therapy may be most important. We'd also point out that, in addition to optimizing pharmacological therapy to control PPG, the total caloric intake at the meal, particularly the percent calories from carbohydrates, has a major effect on these post-meal glucose spikes.



## But I Didn't Inhale!



Delivering insulin via pulmonary inhalation will soon be a viable treatment option in patients with diabetes. Given the expected higher cost over injectable insulin, its precise role is apt to be controversial. At a minimum, inhaled insulin will provide an opportunity for those Type 2 diabetes patients not achieving adequate control with oral agents and who've been reluctant to start injections. With the first inhaled insulin product (Exubera®, Pfizer) recently approved by the FDA and about to be released onto the market, there was significant interest about this delivery method at the 2006 EASD meeting. Published studies to date have demonstrated that inhaled insulin delivered before meals is quite effective in reducing HbA1c. Safety concerns have arisen however, including potential immunogenicity and the possibility for direct toxic effects on the lungs. Most of these appear to have been adequately addressed. While long-term studies will be needed, in the short-term, inhaled insulin seems to be reasonably safe. Many of the abstracts at this week's meeting dealt with some of these very issues.

Teeter *et al.* from the US (abstract 183) studied the absorption of inhaled insulin (Exubera®) in 67 non-diabetic asthmatic subjects both alone, and then in conjunction with either the aerosolized bronchodilator, albuterol, or the inhaled steroid, fluticasone. Systemic insulin levels were then measured. Before bronchodilator use, mild-to-moderate asthma was associated with a reduced pulmonary absorption of inhaled insulin. Administration of a bronchodilator 30 minutes before insulin improved the hormone's bioavailability such that its pharmacokinetics mimicked that in non-asthmatic volunteers. Accordingly, the investigators recommended that, to ensure normal inhaled insulin bioavailability, asthmatic patients should administer bron-

chodilators in a consistent sequence before inhalation. There was no apparent drug-drug interaction with fluticasone.

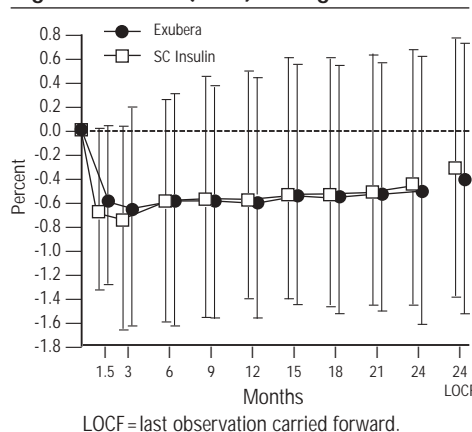
Another inhaled insulin product (AIR®) is being developed by Eli Lilly and Company, in conjunction with Alkermes Inc. Its pharmacokinetic and glucodynamic response in non-diabetic COPD patients was studied by Rave and international colleagues (abstract 184). Compared to healthy subjects, insulin exposure (as estimated by the area-under-the-curve [AUC] for insulin) after insulin inhalation was reduced by 22% ( $p=0.13$ ) in subjects with emphysema and by 44% ( $p<0.001$ ) in those with chronic bronchitis. Glucose infusion rates (used to maintain euglycemia) were correspondingly reduced in both COPD groups (emphysema: -33%,  $p<0.01$ ; chronic bronchitis: -40%,  $p<0.01$ ). Also, the intra-subject variability of insulin exposure, while comparable between healthy subjects and emphysemics (coefficient of variation [CV]: 29% and 28%, respectively), was quite high in those with chronic bronchitis (CV, 52%). One implication from this pair of studies is that underlying lung

disease may significantly effect both the efficacy and safety of inhaled insulin and that the agents should be used cautiously, if at all, in these individuals. The final FDA-approved prescribing information for Exubera™ is still pending.

Hollander and US collaborators (abstract 1003) studied body weight changes associated with inhaled insulin (Exubera®) versus subcutaneous regular insulin in pooled data from five controlled phase 3 trials. Although HbA1c reduction and hypoglycemia rates were similar between the groups, less weight gain occurred after six months of inhaled insulin versus insulin injections. In a total of 1,048 Type 1 patients, weight gain with inhaled insulin was 0.2 kg vs. 1.1 kg with subcutaneous insulin (difference, -0.87 kg in favor of inhaled [95% CI, -1.23, -0.50]); in 912 Type 2 patients the corresponding figures were 0.7 and 1.6 kg, respectively (difference -0.93 kg in favor of inhaled [-1.39, -0.48]). Although the differences are small and of questionable clinical significance, the trends are interesting. The researchers proposed that one explanation might be the more physiological pharmacokinetic profile of inhaled versus injectable insulin. Notably, regular insulin has a very unphysiological onset and duration of action. Therefore, a comparison to one of the more popular rapid-acting injectable analogues (lispro, aspart, or glulisine) would have been a more meaningful comparison.

Cefalu *et al.* from the US provided an overview of the sustained efficacy and tolerability of Exubera® therapy versus subcutaneous insulin over two years in a study involving 635 patients with Type 2 diabetes. Glycemic control was maintained equally, with HbA1c ultimately reduced to 7.3% in both groups (Figure 1). Moreover, the percentage of patients reaching a HbA1c of <7% was statistically equivalent (47.5% with inhaled and 45.2% with injections). The incidence of

Figure 1. Mean ( $\pm$  SD) Change in HbA1c



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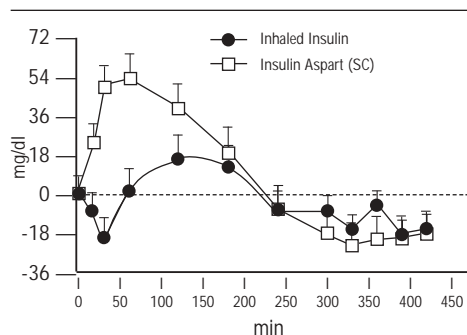
## But I Didn't Inhale!

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hypoglycemia was lower with inhaled insulin (0.8 vs. 1.0 events per patient-month) as was weight gain (1.7 ± 4.7 vs. 3.0 ± 5.2 kg). There was no difference between groups in FEV<sub>1</sub> or DLCO, as measures of pulmonary function, with both groups experiencing minimal decreases over time. Cough was encountered more frequently in the inhaled insulin group (23% in the first three months, decreasing to 4% at 24 months). Other adverse events were similarly distributed.

Finally, Boss and colleagues (abstract 181) from the US and Russia studied a novel version of inhaled insulin in 110 patients with Type 1 diabetes, focusing upon post-prandial glucose control. The investigational pulmonary insulin, called Technosphere® (MannKind), which has an action profile that includes a faster onset and shorter duration of action than seen with any other existing insulins, and so might be ideally suited for prandial dosing. Enrolled patients already on basal-bolus insulin regimens were

**Figure 2. Post-Prandial Glucose Excursions at Week 12**



randomized to receive inhaled insulin or injectable aspart before meals. All patients were followed for three months and doses were individually adjusted. A standardized liquid mixed meal was administered at 0, 8, and 12 weeks of therapy, with post-prandial glucose excursions measured. The mean age of the group was 34 years, and the mean BMI was 24.4 kg/m<sup>2</sup>, without statistical difference between groups. HbA1c was reduced in

both groups: -0.83 ± 1.11% (p < 0.001) with inhaled insulin and -0.99 ± 1.07% (p < 0.001) with aspart (between groups, p = 0.49). Body weight decreased by 0.4 ± 2.2 kg with inhaled insulin and increased by 0.9 ± 1.9 kg in the group receiving aspart (between groups, p = 0.002). Patients receiving inhaled insulin experienced lower post-prandial blood glucose excursions as compared to those on injections (Figure 2). The total post-prandial glucose elevations (AUC) were 1,741 and 7,211 mg/dl/min, respectively. Also, no change in lung function was seen after three months of treatment (ΔFEV<sub>1</sub>: -0.064 ± 0.189 L with inhaled insulin and -0.072 ± 0.193 L with aspart [p = 0.82]; ΔDLCO: -1.62 ± 3.29% and -1.09 ± 3.08%, respectively [p = 0.39]). The researchers concluded that this specific inhaled insulin product provided better control of post-prandial glucose excursions than even the rapid acting insulin analogue, aspart.

We will need to learn more about this emerging area of insulin therapy. Where and when these inhaled products will fit into our therapeutic armamentarium is not yet clear.



## Pre-DM: Pathophysiology, Prognosis, and Prevention



Impaired glucose tolerance (IGT; two-hour glucose 140-199 mg/dl during oral glucose tolerance test [OGTT]) and impaired fasting glucose (IFG; glucose 100-125 mg/dl) defines a group of individuals at high risk for the future development of diabetes. Accordingly, these states (Table 3) are now termed "pre-diabetes." With increasing realization of the benefits of exercise and weight loss, and with the availability of several drug categories that improve insulin sensitivity, either directly or indirectly through weight reduction, there has been increasing interest in identifying these individuals so that diabetes prevention strategies might be undertaken. Further study in this area has also revealed that prediabetes, especially IGT, identifies a group of patients at high risk for cardiovascular disease. Many abstracts at this week's meeting focused upon the identification of individuals with abnormal glucose regulation and its related implications.

Khunti *et al.* from the UK (abstract 759) presented a meta-analysis of Type 2 diabetes prevention trials. In all, 13 trials comprising almost 8,000 patients with IGT were included. Compared to standard advice, the pooled hazard ratio (HR) for lifestyle interventions was 0.50 (95% CI: 0.42 - 0.59), indicating a marked 50% reduction in the risk of diabetes. Compared to placebo, the HR

for oral hypoglycemic agents was 0.66 (95% CI: 0.53 - 0.81) and for anti-obesity agents, 0.44 (95% CI: 0.28 - 0.69). Therefore, both lifestyle and pharmacological therapies significantly reduce the rate of progression to diabetes in individuals with IGT. The researchers seemed to imply that the effect size is similar between the modalities, but such a conclusion is difficult to make within the context of a meta-analysis, given the highly variable baseline characteristics and interventions in many of these trials.

**Table 3. Hyperglycemic States: Current ADA Definitions (in mg/dl)**

	FPG	2-hr PG*	"Casual" PG†
Diabetes	≥126	≥200	≥200‡
Pre-diabetes			
■ Impaired Fasting Glucose	100-125	—	—
■ Impaired Glucose Tolerance	—	140-199	—

PG=plasma glucose, FPG=fasting plasma glucose.

\*Refers to the 2-hr plasma glucose during a 75-g OGTT.

†Casual is defined as without regard to meals.

‡If accompanied by classical hyperglycemic symptoms.

Tuomilehto and international colleagues (abstract 725) explored risk factors for developing diabetes among 1,160 subjects with IGT in the STOP-NIDDM database. (STOP-NIDDM was a diabetes prevention trial using acarbose, the alpha-glucosidase inhibitor). Using a Cox regression model, several readily available clinical parameters were found to be important in determining diabetes risk. The 2.5 year risk of developing diabetes for each combination of factors was then calculated based on the model (Table 4). The researchers concluded that a simple evaluation taking into account gender, height, waist circumference, and the presence of hypertension provides a simple, low-cost screen to identify those IGT patients at the greatest risk of diabetes.

Nakagami *et al.* from Japan (abstract 319) wondered whether measurement of HbA1c alone would be an appropriate initial screening test for diabetes. Using population-based data, the researchers identified 1,904 individuals aged 35-89 years who had a HbA1c measured together with plasma glucoses during an OGTT. In this group, the prevalences of previous diabetes, undiagnosed diabetes, and impaired glucose regulation (including either IFG and/or IGT) by WHO criteria were 5.5%,

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**Pre-DM...**

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5.8%, and 18.8%, respectively. The area under the receiver operating curve (ROC) for undiagnosed diabetes was actually similar between HbA1c (0.849 [95% CI: 0.814-0.895]) and fasting glucose (0.899 [0.864-0.933]). A HbA1c of 5.6% yielded a sensitivity of 54.9%, a specificity of 94.9%, a positive predictive value of 41.5%, and a negative predictive value of 97.0%. The investigators concluded that HbA1c may be a useful diabetes screen, with an absolute value of 5.6% seeming to be an appropriate threshold. We would point out, however, that despite its high specificity, the low sensitivity presents obvious concerns about missing large percentages of patients who are actually diabetic by OGTT. On the other hand, HbA1c behaved similarly to fasting glucose, which is actually now the preferred screening test in the US. One take-home message from this investigation is surely that fasting glucose itself is not a very sensitive test for identifying patients with diabetes, at least if we compare it to the gold-standard two-hour OGTT glucose. Outside of the research arena, however, whether the inferior performance of fasting glucose has a significant impact in clinical practice is not known.

Halimi *et al.* from France (abstract 322) tested the utility of using microalbumin as a predictor of diabetes. Non-diabetic subjects (n=3,252) between 30 and 64 years of age had baseline laboratory studies and were followed for nine years, at which point 4.6% had been diagnosed with diabetes. The relative risk (RR) of diabetes in patients with baseline microalbuminuria was 2.00 [1.29-3.10], p=0.002. The impact was greater in men (RR 2.11 [1.29-3.44], p=0.003) than in women (RR 1.44 [0.50-4.19], p=0.50). The risk of diabetes persisted after multiple adjustments. Microalbuminuria, which is not uncommonly detected in non-diabetic individuals with metabolic syndrome, may therefore identify a group that is highly predisposed to diabetes.

Del Prato and Italian collaborators (abstract 617) presented some provocative baseline data from the GENFIEV study, describing insulin secretion and action in individuals across different categories of glucose tolerance. This multicenter investigation is recruiting individuals with IFG and/or IGT to identify phenotypic and genotypic features that increase the risk of developing Type 2 diabetes. To date, 1,017 subjects have undergone a two-hour 75-g OGTT; 50% were

**Table 4. The 2.5-Year Risk of Developing Type 2 Diabetes, by Gender, Height, Waist Circumference, and Presence/Absence of Hypertension**

Height (cm)	Women											
	>168 (5' 6")			≤168 (5' 6")								
	≤88	89-102	>102	≤88	89-102	>102						
Waist circumference (cm)	no	yes	no	yes	no	yes	no	yes	no	yes		
Diagnosed hypertension	no	yes	no	yes	no	yes	no	yes	no	yes		
<b>2.5-year-risk (%)</b>	<b>15</b>	<b>19</b>	<b>17</b>	<b>23</b>	<b>24</b>	<b>31</b>	<b>22</b>	<b>29</b>	<b>27</b>	<b>34</b>	<b>36</b>	<b>44</b>
Height (cm)	Men											
	>168 (5' 6")			≤168 (5' 6")								
	≤88	89-102	102	≤88	89-102	>102						
Waist circumference (cm)	no	yes	no	yes	no	yes	no	yes	no	yes		
Diagnosed hypertension	no	yes	no	yes	no	yes	no	yes	no	yes		
<b>2.5-year-risk (%)</b>	<b>17</b>	<b>22</b>	<b>20</b>	<b>26</b>	<b>28</b>	<b>35</b>	<b>26</b>	<b>33</b>	<b>31</b>	<b>38</b>	<b>41</b>	<b>50</b>

found to be normal, 15% were diabetic, 4% had IFG, 23% had IGT, and 8% had both IFG and IGT. The insulinogenic index, a calculated marker of insulin secretion based on early glucose and insulin parameters during the OGTT, declined as a function of glucose tolerance (ANOVA, p<0.0001). Those with IFG, IGT, or IFG+IGT all had lower insulinogenic indices than normal individuals but, not surprisingly, higher than the diabetics. The researchers then further explored the relationship between glucose tolerance, insulin secretion, and insulin sensitivity, analyzing the population based on 20 mg/dl glucose increments from 100 mg/dl at the two-hour mark of the OGTT. Insulin sensitivity and secretion declined in a linear fashion across the different categories of glucose tolerance, including those well within the normal range (i.e. 100 to 120 mg/dl at two hours). These data emphasize that early changes in β-cell performance occur in conjunction with insulin resistance even with very modest increases in two-hour glucose within the normal glucose tolerance category.

Vergès and French collaborators (abstract 46) studied the implications of the degree of IFG in 2,353 patients with acute myocardial infarction. Fasting glucose was measured four to five days after admission to the hospital. Patients were classified as diabetic (FPG>126 mg/dl), 'high' IFG (110-125 mg/dl), 'low' IFG (100-109 mg/dl), or normal (<100 mg/dl). In all, 41.1% had diabetes, 11.1% high IFG, 14.1% low IFG,

and 33.7% were normal. As compared to those with normal glucose, in-hospital cardiovascular mortality was increased in high IFG patients (5.3 vs. 1.8%, p=0.002) but not in those with low IFG (1 vs. 1.8%). In-hospital heart failure was also increased in high IFG patients as compared to normal individuals (42 vs. 20%, p<0.0001) but, again, not in low IFG (21 vs. 20%). After multivariate adjustments for age, gender, history of hypertension, anterior infarction, Killip class of ejection fraction, heart rate and blood pressure at admission, and reperfusion therapy, high IFG (but not low IFG) was an independent risk factor for inpatient mortality (OR 2.33 [1.55-3.47], p=0.03) as well as for heart failure (OR 1.70 [1.36-2.07], p=0.01). Based on these data, it appears that those with higher fasting glucose, in the current IFG range, four to five days post-MI comprise a higher risk group. Whether their identification and possible treatment will improve outcomes is not known.

These presentations provide further insights into the pathogenesis, progression, and prognosis of the pre-diabetic states. The data have stimulated even more excitement among the EASD attendees at the Bella Convention Center in Copenhagen, where, on Friday, the long-awaited results of the DREAM diabetes prevention trial will be announced. We will highlight these results in tomorrow's edition of *Diabetes 2006!*