

# Diabetes 2005

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## Metabolic Syndrome: To Be or Not to Be?

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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After nearly 4,000 published human studies on the "metabolic syndrome" (AKA "syndrome X" or "insulin resistance syndrome") and its established, unique ICD-9 code (277.7), the *American Diabetes Association* and the *European Association for the Study of Diabetes* jointly issued a statement earlier this month (*Diabetes Care* 28:2289) that raises some doubts over the syndrome's actual existence. One of the major criticisms had to do with its variable description between professional societies and organizations, without any unifying definition. Of even greater concern, according to these authoritative bodies, "There is no combination of risk factors that boosts a person's cardiovascular disease (CVD) risk beyond the sum of the parts, or constitutes a separate disease." They went on to point out that, "The metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVD risk factor." They outlined areas of necessary research and suggested that clinicians should evaluate and treat all known CVD risk factors without regard as to whether a patient meets the criteria for diagnosis of metabolic syndrome.

In the face of these well-grounded concerns, this constellation of risk factors continues to be explored by numerous investigators worldwide. We summarize for you the results of several such studies presented during this year's EASD Scientific Sessions.

### **Insulin Resistance**

Insulin resistance and its markers clearly serve to identify individuals at increased risk of Type 2 diabetes. Shand *et al.* from New Zealand compared the biological variation over 30 days of several established surrogate markers of insulin resistance in 10 subjects with metabolic syndrome vs. 10 age- and gender-matched healthy controls (abstract 685). Samples for testing glucose, insulin, sex hormone binding globulin (SHBG), and adiponectin were taken every 10 days and HOMA-IR was used to calculate insulin sensitivity. Measures of plasma adiponectin (12-19% variation) and SHBG (10-18% variation) showed the least variability, and, as a result, are likely to be the most reliable for serial assessment of insulin sensitivity.

Kwon *et al.* from the Republic of Korea reported the results of a cross-sectional study of 5,330 participants over 40 years old in whom insulin resistance was analyzed using HOMA-IR and by presence of the metabolic syndrome (defined by NCEP ATP III) and its component risk factors (abstract 603). Only about a third of the subjects who met the criteria for metabolic syndrome was classified by this group as insulin resistant (arbitrarily defined as the highest quartile of HOMA-IR levels). Moreover, 55% of the insulin-resistant group did not satisfy metabolic syndrome criteria (56.8% sensitivity, 67.9% specificity, 33.1% positive predictive value [PPV], 84.9% negative predictive value [NPV]). According to stepwise multiple linear regression analysis, body mass index (BMI) was the best factor for determining the presence of insulin resistance, more so than other factors or the composite metabolic syndrome designation.

Patwardin *et al.* of the ongoing US ADOPT (A Diabetes Outcome Prevention Trial) Group reported findings consistent with those of Kwon *et al.* They assessed the ability of various clinical parameters to identify insulin resistance in recently diagnosed, drug-naive Type 2 diabetes patients (abstract 605). BMI and triglyceride (TG):HDL-cholesterol ratio most strongly correlated with insulin resistance. A simple algorithm that utilized BMI and lipids predicted severe insulin resistance (defined by HOMA-S) with 75% sensitivity and 65% specificity. The algorithm was: non-obese (BMI < 29 kg/m<sup>2</sup>) with TG:HDL-cholesterol > 8; overweight or obese (BMI = 29-35 kg/m<sup>2</sup>) with TG:HDL-cholesterol > 3; or, severely obese (BMI > 35 kg/m<sup>2</sup>) with any TG:HDL-cholesterol ratio.

### **Nephropathy**

Insulin resistance and other components of the metabolic syndrome have been implicated in the pathogenesis of diabetes complications. In an ongoing, single-center, clinic-based cohort study being conducted in Italy, Miccoli *et al.* assessed the prevalence of metabolic syndrome (according to NCEP ATP III criteria) and its relationship to

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## Metabolic Syndrome...

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renal dysfunction in 1,314 Type 2 diabetes patients (abstract 1030). The prevalence of microalbuminuria and overt nephropathy increased directly with the number of metabolic syndrome components, and was uncommon in the few Type 2 diabetes patients who did not meet metabolic syndrome criteria (Figure 1).

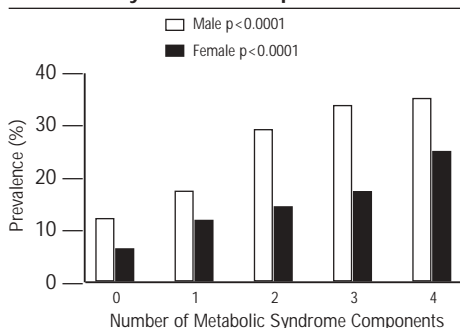
## Coronary Heart Disease

Individuals who meet various definitions of metabolic syndrome have, in general, a two-fold or higher risk of coronary heart disease as well as coronary mortality (see below). Gutt *et al.* from the US examined 144 patients who were approximately two months post-MI for the prevalence of metabolic syndrome and its component risk factors (abstract 1107). In this population, 54 patients (38% of the total population) met the NCEP ATP III criteria for metabolic syndrome. Over a third of the post-MI patients had undiagnosed glucose intolerance and this group of patients had higher levels of coronary heart disease risk factors (i.e., total cholesterol, triglycerides, LDL-cholesterol, C-reactive protein, fibrinogen) than the normoglycemic post-MI patients.

## Cardiovascular Mortality

Perret *et al.* from Switzerland retrospectively evaluated the incidence of mortality during

**Figure 1. Prevalence of Raised Albuminuria\* by Gender and Number of Metabolic Syndrome Components**



\*Both microalbuminuria and overt nephropathy.

hospitalization by patients' metabolic status in a retrospective study of 529 acute coronary syndrome patients admitted to an ICU during 2002-2003 (abstract 1106). About a third (36%) of patients presented with metabolic syndrome (WHO definition, excluding microalbuminuria). Two- and three-vessel disease was more common in these patients (odds ratio [OR] 1.4,  $p=0.01$ ). Metabolic syndrome was also predictive of early mortality (OR 5.9,  $p<0.0001$ ) and independently associated with premature death ( $p=0.01$ ) in a multivariate model matched for age, gender, and CK levels.

Presentations made by the DECODE Study Group provide further evidence of the association

between metabolic syndrome and cardiovascular mortality. Following CVD mortality over 10 years in over 6,000 non-diabetics between ages 50 and 69 years, Balkau *et al.* found that, among those with low CVD risk (<5% 10-year risk by European SCORE [including age, total cholesterol, systolic blood pressure, and smoking status]), men, but not women, meeting the NCEP ATP III definition of metabolic syndrome had a significantly higher risk of fatal CVD. Waist size proved to be equally discriminatory (Table 1) (abstract 315). For those with a 10-year risk of fatal CVD over 5% (high risk), the metabolic syndrome did not provide additional discrimination. In a separate poster presentation from the same group, Qiao *et al.* used Cox regression analysis to study the gender difference in CVD mortality in diabetic subjects with and without metabolic syndrome (abstract 331). They found that the relative risk (RR) of CVD mortality was higher in women as compared to men with diabetes in the absence of metabolic syndrome (RR 4.31 vs. 0.86, respectively), but not in its presence (RR 2.00 vs. 2.05, respectively). The interaction of gender with diabetes was significant (Chi-square = 6.62,  $p=0.01$ ), but the interactions between gender and metabolic syndrome and between diabetes and metabolic syndrome were not, suggesting that metabolic syndrome was itself an important confounding factor.

Given the recent call by the ADA and EASD for critical appraisal, research projects focused on the metabolic syndrome are likely to increase—specifically those addressing the investigative agenda set forth by these organizations. These include the clinical importance of varying numbers and clusters of risk factors; varying cutpoints for existing factors in the definition; the value of adding other (or replacing) CVD risk factors to the definition, such as inflammatory markers; quantifying CVD risk in subjects with intermediate phenotypes only (e.g., impaired fasting glucose/impaired glucose tolerance, mildly elevated triglycerides) and who are not necessarily insulin resistant/hyperinsulinemic; and identifying the underlying mechanism for clustering of CVD risk factors. We look forward to continuing to provide you these emerging data next year!

**Table 1. Hazard Ratios for Cardiovascular Mortality Among Persons With Metabolic Syndrome\* at Low CVD Risk**

	Males	Females
Waist circumference >102 cm men / 88 cm women	2.2 <sup>†</sup>	2.3
SBP/DBP ≥130/85 mmHg	2.7 <sup>‡</sup>	1.1
Glucose ≥110 mg/dl	1.7	1.4
HDL-cholesterol <40 mg/dl men / 50 mg/dl women	2.7 <sup>‡</sup>	3.0 <sup>†</sup>
Triglycerides ≥150 mg/dl	1.3	1.6
Metabolic syndrome (by NCEP ATP III)	2.7 <sup>†</sup>	1.4
Waist circumference with SBP/DBP ≥130/85 mmHg	3.5 <sup>§</sup>	1.3
Waist circumference with triglycerides ≥150 mg/dl	1.9	3.0

\*vs. 1.0 for subjects without metabolic syndrome; <sup>†</sup> $p < 0.05$ ; <sup>‡</sup> $p < 0.01$ ; <sup>§</sup> $p < 0.001$ .



## Glucose: A Critical Factor in the ICU



Tight glucose control is now considered the standard in our intensive care units (ICU), particularly for post-surgical patients, and especially following cardiothoracic procedures. Diabetic and non-diabetic patients appear to benefit from normalization or near-normalization of circulating

glucose levels. Insulin infusion protocols have become very popular to expeditiously and tightly control glycemia in this setting. One of the obvious risks of intensive insulin infusion is hypoglycemia. This was the topic of an abstract by Vriesendorp *et al.* from The Netherlands who

explored predisposing risk factors for hypoglycemia in the Leiden University Medical Center ICU over a two-year period (abstract 100). For purposes of this study, hypoglycemia was defined as any glucose reading under 45 mg/dl. Records from a total of 2,272 patients were analyzed; 6.9% (156)

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## ...ICU

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experienced at least one hypoglycemic episode. This portended adverse outcomes, with a hazard ratio for death of 2.8 (95% confidence interval [CI] 1.7-4.6.). Charts and a patient database were queried to identify clinical features that might predispose to hypoglycemia; the data were adjusted for length of time the patient spent in the ICU. After univariate analysis, several risk factors for hypoglycemia were determined, as shown in Table 2.

Adjustment for clinical variables, including gender, age, and APACHE II (severity of illness) score did not substantially alter the odds ratios. The investigators concluded that several well-defined clinical features are associated with the risk of hypoglycemia during intensive insulin infusion in the ICU. In addition, they felt that the relationship between hypoglycemia and mortality was not cause-and-effect, but simply a reflection of the effects of grave illness on glucose metabolism.

The success of intensive insulin infusion is predicated upon the availability of frequently determined blood glucose values. Unfortunately, this requires frequent venous or arterial blood sampling or frequent finger punctures for capillary blood testing. Each has its obvious disadvantages, including the significant added work for the critical care nursing staff. Two abstracts this week explored new modalities in glucose monitoring, adapted for ICU use. In the first, by Schaller and colleagues of Austria and Germany, interstitial glucose measurements were performed continuously in 20 post-surgery patients using both

**Table 2. Risk Factors for Hypoglycemia in an ICU Setting**

	Odds Ratio	95% CI
Continuous venovenous hemofiltration (CVVH) with bicarbonate-based exchange fluid	14.0	1.8-106
Decreasing nutrition without adjusting infusion	6.6	1.9-23.0
Diabetes mellitus	2.6	1.5-4.7
Sepsis	2.2	1.2-4.1
Inotropic / vasopressor use	1.8	1.1-2.9

microdialysis of interstitial fluid and compared to standard arterial blood glucose measurements (abstract 827). The investigators tested the accuracy of a new continuous glucose monitoring system under development (SCGM1, Roche Diagnostics). The mean duration of monitoring was 36 ± 15 hours and the mean blood glucose during this time was 128 ± 25.2 mg/dl. The mean Pearson correlation coefficient between blood and interstitial glucose (r) as measured by SCGM1 was 0.81. Interstitial glucose sampling via a continuous monitor therefore appears to be a promising alternative to periodic measurement by phlebotomy or finger punctures. Further validation, particularly at the extremes of blood glucose, will obviously be of great importance.

An even more attractive option—totally non-invasive continuous glucose monitoring—was the subject of a second abstract by Cohen and Israeli colleagues, who tested the NBM-100, a finger-based sensor that uses red/near-infrared spectroscopy to measure blood glucose (abstract 121). Fifteen ICU patients were tested for between two and 12 hours. The NBM-100

took measurements every 10-15 minutes—these were then compared to those obtained using conventional arterial blood samples every 30-60 minutes. A total of 432 data points were analyzed; the glucose range was 57-256 mg/dl. The mean absolute relative difference between the modalities was 8.3%, with a mean absolute difference of 11.5 mg/dl. On Clark Error Grid analysis (which assesses agreement between two blood glucose measurement techniques and the clinical decisions that would have resulted from any deviation), an impressive 98.6% of the measurements fell within zone A (similar readings) or zone B (different readings, but no change in clinical decision making.) This very preliminary study introduces a possible new option for continuous monitoring of blood glucose for our ICU patients. Its application in the clinical setting will of course require further studies, including larger numbers of patients, wider glucose ranges, and in a variety of clinical scenarios often encountered in the critical care setting (e.g., sepsis, hypotension, and vasopressor use).



## Pre-Diabetes: Below the Tip of the Iceberg



Type 2 diabetes results from the slow (estimated at 5-10% per year) loss of β-cell function over a period of a decade or more in the face of insulin resistance. Affected individuals progress from normal glucose tolerance to impaired glucose regulation to overt Type 2 diabetes. Patients with impaired glucose regulation—either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (Table 3)—are now classified as having “pre-diabetes,” reflecting their relatively high risk for developing diabetes. In addition, it is now clear that individuals with pre-diabetes are at increased risk of cardiovascular disease (CVD). Accordingly, it is important to identify these individuals so that diabetes prevention strategies can be pursued and coexisting CVD risk factors might be aggressively treated. A number of presentations made this week addressed how to best identify the pre-diabetic patient.

**Table 3. ADA Diagnostic Criteria for Impaired Glucose Regulation**

	Fasting Plasma Glucose	“Casual” Plasma Glucose	2-Hour OGTT* Plasma Glucose
Normal	<100 mg/dl		<140 mg/dl
Impaired Glucose Regulation	100 to 125 mg/dl (IFG)		140 to 199 mg/dl (IGT)
Diabetes	≥126 mg/dl	≥200 mg/dl with symptoms	≥200 mg/dl

OGTT= 75-gram Oral Glucose Tolerance Test.

Source: *Diabetes Care* 2005.

### Impaired Fasting Glucose

Witte *et al.* of the United Kingdom assessed the value of an isolated fasting glucose level in the IFG range in predicting the future development of incident diabetes over a 10-year period in 5,914 participants in the Whitehall II study

(abstract 44). Cardiovascular risk assessments, including OGTT, were conducted at five-year intervals. At baseline, the prevalence of IFG was relatively low (3.2% according to WHO classification [110-125 mg/dl] and 14.7% according to ADA classification [100-125 mg/dl]). The predictive

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## Pre-Diabetes...

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value of an isolated IFG assessment, expressed as the area under the receiver operator characteristics (ROC) curve, was 0.58 according to WHO classification and 0.62 according to the ADA classification (perfect prediction, area under ROC = 1.00). Of note, however, a multivariate model that included BMI, hypertension, family history of diabetes, total cholesterol, HDL-cholesterol, and physical activity level, but not IFG, predicted the incidence of diabetes significantly better (area under ROC = 0.69) than did the isolated IFG value. Including the IFG value in the multivariate model further increased the predictive value (area under ROC = 0.73 for both WHO and ADA classifications). Thus, for the majority of the population, a fasting glucose value may be used as a component of a group of risk factors rather than an isolated risk indicator. The WHO and ADA classifications yielded an equal level of prediction.

Similarly, Wojcik *et al.* from Poland assessed IFG as a risk factor for diabetes in a cohort of 108 individuals with IFG, IGT, or both, who were compared to an age- and gender-matched control group of 36 persons, all having completed a five-year follow-up period (abstract 680). IFG resolved in about half of study subjects without a specific intervention, and was a risk factor for diabetes, but not for IGT.

## Insulin Resistance

Since hyperinsulinemia pre-dates impaired glucose regulation, Lawler *et al.* from the US assessed the ability of insulin resistance (by HOMA-IR) to predict incident diabetes among 971 subjects without diabetes (abstract 724). Approximately 10% of the cohort developed diabetes during a mean follow-up of nine years. According to multivariate Cox proportional hazards analysis (adjusted for age, smoking status, exercise, hypertension, triglycerides, HDL-cholesterol, total cholesterol, and BMI), higher HOMA values were predictive of diabetes in those with normal fasting glucose (RR 2.1 for second tertile and RR 3.9 for third tertile of HOMA values with test for trend,  $p < 0.001$ ). HOMA was not, however, additionally predictive of time to diabetes among subjects with IFG, although the confidence intervals were large due to small numbers ( $p > 0.2$ ). These data suggest that HOMA may potentially be used to identify a group of subjects with normal fasting glucose but significant insulin resistance who are at an increased risk of diabetes and as such might benefit from diabetes prevention strategies.

## Metabolic Syndrome

In a cohort study of 1,325 subjects over 50

**Table 4. Odds Ratio\* (95% CI) for Diabetes (Adjusted for Age and Duration of Follow-up)**

	Men (n = 601)	Women (n = 724)
Fasting glucose	10.19 (5.47-18.97)	6.84 (3.95-11.85)
2-hour glucose	1.63 (1.39-1.91)	1.99 (1.68-2.35)
HbA1c	2.08 (1.16-3.71)	6.13 (3.19-11.79)
BMI	1.02 (0.92-1.13)	1.14 (1.06-1.22)
Waist circumference	1.03 (0.99-1.06)	1.08 (1.05-1.10)
ADA Risk Score	1.00 (0.92-1.08)	1.09 (1.00-1.18)
Cambridge Risk Score (per 0.10 increase in probability)	1.18 (1.05-1.34)	1.31 (1.16-1.47)
Metabolic syndrome (NCEP ATP III)	2.93 (1.67-5.15)	6.02 (3.48-10.42)
Number of metabolic syndrome components	1.94 (1.54-2.44)	2.44 (1.93-3.08)
Modified metabolic syndrome criteria <sup>†</sup>	2.35 (1.17-4.75)	5.75 (3.32-9.96)

\*Per unit increase in algorithm.

<sup>†</sup>Required waist circumference and at least two other components + fasting glucose cutpoint = 100 mg/dl.

years of age followed for six years, Girman *et al.* from The Netherlands used logistic regression analysis to estimate the risk of incident diabetes, with metabolic syndrome (NCEP ATP III criteria) (abstract 45). The risk of diabetes was significantly higher in both men and women with metabolic syndrome, as compared to those without (Table 4). Each component of the metabolic syndrome predicted an additional two-fold increased risk. A gender difference was also found. Metabolic syndrome and the number of risk factor components present significantly predicted diabetes in women with and without IFG. However, the number of components present was significant in men only with normal, but not IFG.

## Pre-Diabetes & CVD

The risk of diabetes and CVD in patients with the pre-diabetic state was also explored by Timar *et al.* of Romania (abstract 357). These investigators enrolled 1,024 individuals, aged 40-70 years, without a diagnosis of diabetes and performed OGTT. Those with IFG were then followed for six years and their CVD risk was assessed longitudinally. In this cohort, lowering the cutpoint for IFG from  $\geq 110$  to  $\geq 100$  mg/dl increased the prevalence of IFG a dramatic three-fold (from 8% to 23%). The new lower IFG criterion identified 58.5% of all subjects with IGT, as compared to 26.3% with the older criterion. Progression to diabetes was different depending on which criterion was used: in subjects with fasting glucose between 110-125 mg/dl, the progression was 34% over the observation period. It was somewhat lower (21%) in those whose fasting glucose was between 100-109 mg/dl. Of the 234 adults with IFG, the age- and gender-adjusted incidence of major cardiovascular events (i.e., fatal and non-fatal MI and

**Table 5. Risk Factors for Diabetes**

- Habitually inactive
- First-degree relative with diabetes
- Member of a high-risk ethnic group (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Delivered a baby weighing >9 pounds or diagnosed with gestational diabetes mellitus
- Hypertension ( $\geq 140/90$  mmHg)
- HDL-cholesterol < 35 mg/dl and/or a triglyceride level > 250 mg/dl
- Polycystic ovary syndrome
- IGT or IFG on previous testing
- Other clinical condition associated with insulin resistance (acanthosis nigricans)
- History of valvular disease

Source: *Diabetes Care* 2005.

stroke) was 9.9/1,000 person-years in subjects with fasting plasma glucose values between 100-109 mg/dl and 14.2/1,000 person-years in subjects with fasting plasma glucose values between 110-125 mg/dl ( $p = 0.465$ ). Thus, lowering the cutpoint for IFG captured more individuals with an increased risk of progression to diabetes and of CVD.

## Pre-Diabetes & All-Cause Mortality

Barr *et al.* from Australia used Cox's proportional hazards model to evaluate all-cause mortality by glucose tolerance status in a population-based survey of 11,247 adults (abstract 330). The median follow-up was 4.2 years. After controlling for age, gender, fasting lipids, blood pressure, waist-hip ratio, smoking, and previous cardiovascular disease, all-cause mortality was increased in persons with IFG (HR 1.9) as well as IGT (HR 1.6).

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## Diabetes Prevention

The ADA now recommends screening for pre-diabetes in individuals  $\geq 45$  years of age, particularly in those with a BMI  $> 25$  kg/m<sup>2</sup>. Screening should also be conducted for people who are  $< 45$  years old and are overweight if they have another risk factor for diabetes (Table 5). Testing should be repeated every three years.

Earlier identification of the pre-diabetic state could lead to interventions that potentially delay the onset of diabetes. Various prevention strategies have been or are currently under inves-

tigation, among them diet, exercise, and treatment with thiazolidinediones, metformin, alpha-glucosidase inhibitors, meglitinides, and anti-obesity agents. Interestingly, blockade of the renin-angiotensin system by an angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) has also been suggested as an approach to Type 2 diabetes prevention. In an abstract by Drs. Alkhenizan and Elswes data from 10 randomized, controlled trials ( $>77,000$  subjects) were reviewed showing that ACE-I/ARB therapy significantly prevented the development of new-onset diabetes (RR=0.79; NNT= 50 vs. other antihypertensive agents). The authors recommended use of these agents, especially for

high-risk patients (abstract 691). Of note, diabetes prevention was not the primary endpoint in any of the studies in their review. There are now three ongoing prospective, randomized, double-blind studies of IFG/IGT patients in which diabetes prevention is the primary endpoint: DREAM (rosiglitazone and/or ramipril), ACT NOW (pioglitazone), and NAVIGATOR (nateglinide and/or valsartan). Until information from these trials is available, we would reiterate that the clinical standard for pre-diabetic patients should involve lifestyle changes and weight reduction, as well as the assessment and treatment of other established CVD risk factors, such as lipids and blood pressure.



## Hypoglycemia: Awareness of Unawareness



Hypoglycemia remains the principal limiting factor to the achievement of near-normal glycemic control in Type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) firmly established that intensive insulin therapy, while markedly reducing the risk of microangiopathy, increases the risk of severe hypoglycemic episodes. Fortunately, experiencing an episode of severe hypoglycemia is relatively unusual for most patients with Type 1 diabetes. On the other hand, newer Continuous Glucose Monitoring Systems (CGMS) are showing how common episodes of mild to moderate hypoglycemia may actually be.

Pedersen-Bjergaard and Danish colleagues (abstract 807) prospectively studied a cohort of 119 Type 1 diabetic patients with disease duration  $22 \pm 12$  years and HbA1c  $8.3 \pm 1.1\%$  using the Medtronic MiniMed CGMS continuously for six days. They reported that the total number of hypoglycemic episodes (defined as a CGMS value  $< 40$  mg/dl) was 3.9 per week. Comprised in this figure are: silent hypoglycemia of 3.0 episodes per week, symptomatic hypoglycemia of 0.8 episodes per week, and severe hypoglycemia of 0.06 episodes per week. In common with many other trials, these investigators found no significant relationship between the episodes of hypoglycemia and risk factors such as HbA1c, hypoglycemia awareness, and disease duration. Intriguingly, they did note that individuals taking ACE-I or ARB treatment were less likely to experience symptomatic hypoglycemia. The suggested benefits from drugs that modulate the renin-angiotensin axis has been observed by others, as reported in *Diabetes 2005* from the 65th Scientific Sessions of the American Diabetes Association.

It is well recognized that exercise increases the risk of hypoglycemia, both during exercise and in the recovery period. Ferreira and colleagues

from Australia looked indirectly at hypoglycemia risk during the post-exercise period in a group of adolescents with Type 1 diabetes by measuring the glucose infusion rates required to maintain euglycemia (abstract 97). They reported that glucose infusion rates after 45 minutes of cycling increased abruptly for one hour after exercise then fell to baseline for the next five to six hours. Interestingly, glucose infusion rates then increased again at six to seven hours post-exercise at a time that coincided with the onset of sleep. This is a phenomenon not infrequently reported by our exercising patients. These findings would suggest that individuals with Type 1 diabetes have both an immediate and delayed risk of hypoglycemia after exercise. They should be advised to monitor more regularly during both these times, and be especially careful to avoid nocturnal hypoglycemia.

Hypoglycemia impairs cognitive function in most patients with Type 1 diabetes. How quickly their cognitive function recovers after an episode of hypoglycemia remains unclear. Zammitt and colleagues from Edinburgh (abstract 808) addressed this question in a study of 36 Type 1 diabetic patients (20 with self-reported normal hypoglycemia awareness and 16 with impaired hypoglycemia awareness). A cognitive test battery that assessed general cognitive performance was given to patients at baseline, twice during hypoglycemia, and every 10 minutes following recovery from hypoglycemia. They found that patients with normal hypoglycemia awareness showed significant cognitive impairment during hypoglycemia and that recovery of cognitive function on the more complex tasks took up to 40 minutes following restoration of euglycemia. Interestingly, the patients with impaired awareness showed no deterioration in

cognitive performance during hypoglycemia or recovery, suggesting that they had adapted to this condition. It is currently thought that recurrent hypoglycemia might improve glucose transport or increase the use of alternate fuels such that cognitive function is maintained during subsequent episodes of hypoglycemia.

In a related presentation Warren *et al.* from the same Edinburgh group looked at memory function and learning during acute hypoglycemia (abstract 810). Again patients with ( $n=20$ ) and without ( $n=15$ ) hypoglycemia awareness were studied. Patients completed various learning and memory tasks during hypoglycemia and were then asked to recall the information at the end of the hypoglycemic period (immediate recall) and one hour after the restoration of euglycemia (delayed recall). Hypoglycemia impaired both immediate and delayed recall in the majority of tasks assessed in the patients with normal hypoglycemia awareness, but only delayed recall on the auditory verbal learning test was impaired in the unaware patients. These findings are consistent with the literature showing that recurrent hypoglycemia and/or intensive insulin therapy alters the threshold for cognitive dysfunction such that individuals are better able to tolerate moderate hypoglycemia. They also have important practical implications for clinicians in that information or instructions on care provided to a patient when they are hypoglycemic may not be remembered on recovery of euglycemia. For those with impaired awareness, any problem with delayed memory may have significant repercussions. Frequent monitoring and hypoglycemia avoidance are essential for such individuals.

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