

# Diabetes 2006

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## Feeding Behavior: A Tale of Mice and Men

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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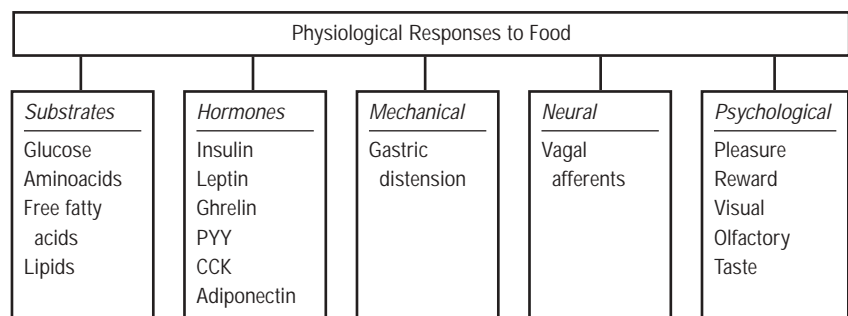
It is highly unlikely that any physician in the US is not caring for individuals who are significantly overweight, and who may even have developed obesity-associated morbidities. Indeed, the obesity epidemic in the affluent West as well as worldwide is driving research into the mechanisms that regulate feeding and feeding behavior. An important symposium on "Central Mechanisms of Metabolic Control" was held this week, providing an update on recent developments in the field.

The first speaker, G. Morton from the US, described the information gleaned from animal studies on the neuroendocrinology of eating. It is becoming clearer that both short- and long-term satiety signals are integrated in the brain and control the balance between food intake and energy expenditure (Figure 1). For instance the adipokine, leptin, the pancreatic hormone, insulin, and the gut hormone, ghrelin, all interact within the hypothalamus, and their relative effects shift this balance toward either food intake (designed to maintain body fat stores) or energy expenditure (designed to burn excess calories mostly through thermogenesis). It has more recently been established that these long-term signals may also modify the physiological response to short-term, meal-related signals. Satiety signals transmitted from the gut through vagal afferents are thought to initially act at the level of the brain-stem, and Dr. Morton presented data showing that manipulation at the level of the hypothalamus can modulate brain-stem responses to these satiety signals, which, at least in animal models, alters meal size.

While the information gleaned from studies in rodents is helping unravel some of the mechanisms involved in the maintenance of energy homeostasis, M. Stumvoll of Germany reminded the audience that our ultimate goal is to understand *human* obesity and the human brain is appreciably different from that of a transgenic mouse! In particular, humans have developed a large, and, frankly, little understood cerebral cortex. Modern neuroimaging techniques such as PET scanning and functional MRI are showing the major role played by other brain regions such as the insular cortex, prefrontal cortex, and the limbic system. It is patently obvious that eating is not a purely biological act. Regretably, few of us react consistently to satiety signals, consciously or unconsciously. Dr. Stumvoll presented data showing the importance of visual imagery in determining satiety, and, conversely, how, in "force-fed" volunteers, the visual cortex no longer "lights up" during subsequent feeding. The individual literally no longer wants to look at food.

Next was a very intriguing presentation from L. Reed of the UK. Dr Reed, a psychiatrist with an interest in addictive behavior, has been working closely with Dr. S. Amiel, an expert in brain metabolism. They've discovered that other regions of the brain, such as the limbic system, appear to become activated following glucose ingestion. The limbic system is involved in many aspects of body homeostasis such as energy and water balance, as well as sexual, reproductive, and antagonistic behavior. Thus, it is crucial to many

**Figure 1. Factors Involved in Physiological Response to Feeding**



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## Feeding Behavior...

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fundamental human functions and apparently interacts at some level to determine feeding behavior. Their work, using PET, shows interesting parallels between addictive behavior and feeding, especially in the involvement of the reward circuitry of the limbic system. Preliminary data suggest that insulin-resistant individuals may also be resistant to the "reward" aspect of feeding and therefore need to eat more in order to experience the same pleasurable effect when eating. Of greatest intrigue is the observation that this system is additionally activated by hypoglycemia, leading to the somewhat controversial possibility that recurrent hypoglycemia may actually be, in part, a manifestation of addictive behavior. Most practicing diabetologists are aware of those intensively treated Type 1 patients who experience recurrent hypoglycemia and yet seem very reluctant

to consider a period of looser glycemic control. Is this just a fear of microvascular complications or something much more complex?

The intricacies of feeding behavior highlighted by Drs. Stumvoll and Reed were also apparent in the discussion on its pharmacological management by F. Rodriguez de Fonseca of Spain. The data derived from animal studies focuses very much on the hypothalamus, but it is clear that there is far more to feeding behavior than this region alone. The implication is that any pharmacological intervention must be able to affect many different brain (and peripheral) sites if it is to have any significant benefit. Conversely, any intervention may affect many other neural processes that tap into these same centers. The most recent example of this is rimonabant, an endocannabinoid receptor antagonist. The endocannabinoid system has been shown to play a major role, both centrally and peripherally, in energy balance, glucose homeostasis, feeding

behavior, adipose metabolism, as well as other physiological systems. The ability of rimonabant to interact with cannabinoid receptors is providing important insights into the physiology of weight loss and insulin sensitivity. However, the effect of this weight loss drug, is modest, suggesting that other systems are compensating. Moreover, this therapy carries with it a significant risk of neuropsychiatric side effects—testament to its action in some of the processes detailed above.

Clearly, the central regulation of peripheral metabolism and feeding behavior is a fascinating and complex area of research, but the epidemic of obesity and diabetes in the world will ensure that it is a very active area over the next few years. The data emerging from rodent models and human imaging studies will hopefully lead to a much greater understanding of physiological processes underlying these increasingly common conditions.



## Controlling Glucose in the Hospital



Inpatient glucose management has been receiving increased attention from physicians, nurses and hospital administrators for several years. This interest was piqued following the publication of several studies showing a reproducible association between hyperglycemia and adverse outcomes in a variety of clinical settings. In selected studies, mainly in the critically ill, intensive glucose control regimens have led to improved outcomes, including mortality. Controlling glycemia in the hospital, especially outside of the ICU, is challenging due to the various forces at play that tend to increase blood glucose levels in patients who are ill. At this week's meeting, several groups from around the world reported on their quality improvement projects in this arena.

Some hospitals have tackled the problem of inpatient hyperglycemia by hiring nurse specialists to monitor and recommend management changes in groups of diabetic patients. Stanisteert *et al.* from the UK reported on just such a plan (abstract 878). Their diabetes special-

ist nurse evaluated inpatients upon referral. To date, more than one in three of these consultations uncovered an adverse incident. Of these, almost two-thirds were attributable to an error in insulin prescribing or administration, resulting in preventable hypo- or hyperglycemic events and/or the inappropriate treatment of same.

The Glucommander™ is a computer-based insulin infusion control system demonstrated to improve glucose control in patients in both ICUs and general wards. Davidson and US associates reported on their preliminary experience with the Glucommander™ following cardiac surgery (abstract 964). The specific protocol employed in this setting involved a glucose goal of 106 mg/dl. To date, 182 patients have been studied, with 31% having an established diagnosis of diabetes. Patients were placed on IV insulin if their post-operative glucose exceeded 140 mg/dl or if two glucose measurements exceeded 110 mg/dl. Using this threshold, more than 90% of patients required IV

insulin. Blood glucose <120 mg/dl was attained at a mean of 3.2 hours, and IV insulin was continued for 29 hours on average. Overall, 96% of patients were controlled with no glucose level over 200 mg/dl in the 48 hours after surgery. A minority (8%) of patients had a glucose <60 mg/dl; no one experienced a glucose <50 mg/dl. Based on historical controls, the length of stay in this patient population was 6.2 days versus 7.3 days in the year prior to the protocol. This translated to a cost savings of \$2.1 million for a single 450-bed hospital. We'd point out that historical controls are difficult to assess in such studies, since the goal of reducing length of stay is a frequent target of many quality improvement efforts—most of which occur simultaneously in our hospitals.

It is encouraging to see such reports from institutions taking inpatient management of hyperglycemia seriously. The data would suggest that such efforts may have significant downstream benefits on patient outcomes.



## Diabetes and CVD: One and the Same?



A recently issued joint statement by the American Diabetes Association (ADA) and the American Heart Association (AHA) calls for a renewed effort by healthcare providers to prevent both cardiovascular disease (CVD) and diabetes by identifying and treating a core set of risk factors such as prediabetes, hypertension, dyslipidemia, and obesity (Eckel, *et al. Diabetes Care* 2006;29:

1697-1699). As in prior EASD as well as ADA meetings, the links between diabetes and CVD were reviewed in much detail.

### Diabetes and Risk of CVD

In 2003, the ADA lowered the threshold for the definition of impaired fasting glucose (IFG)

in order to increase the sensitivity of identifying those who will convert to diabetes within 10 years. Rijkijkhuizen and associates from The Netherlands assessed how this cut-point change impacted the risk of CVD mortality in a population of 1,428 subjects administered a 75-g oral glucose tolerance test (OGTT) in 1989 and then again in 1996

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(abstract 92). Compared to those with normal fasting glucose (NFG), the conversion from IFG to diabetes was associated with an at least two-fold higher risk of CVD mortality whether assessed using the 1997 cut-point (Hazard Ratio [HR] 2.47, 95% confidence interval [CI] 1.17-5.19) or the 2003 cut-point (HR 2.14, 95% CI 1.12-4.10). Those with IFG in 1989 who remained IFG or converted to NFG had a nonsignificant increase in CVD mortality (HR 1.50, 95% CI 0.72-3.15 by ADA 1997 threshold; HR 1.15, 95% CI 0.69-1.93 by ADA 2003 criteria). These findings indicate that the risk for CVD mortality is primarily related to the conversion to diabetes.

## CVD and Risk of Diabetes

While the risk of CVD in patients with diabetes is well established, the converse also appears to be true. That is, in a population of patients with established CVD, the prevalence of diabetes and other abnormalities of glucose tolerance are significantly increased. Some have proposed that diabetes itself should be considered a cardiovascular disease, one of whose manifestations happens to be hyperglycemia. In an oral presentation, Birkeland and Norwegian colleagues presented the results of a case-control study of 149 Caucasian patients (mean age 68 years) hospitalized for coronary artery disease (CAD, n=51), peripheral artery disease (PAD, n=47), or cerebrovascular disease (CeVD, n=51) and 59 control subjects with no CVD (abstract 88). Using the WHO/ADA criteria for dysglycemia (i.e., IFG, impaired glucose tolerance [IGT], or diabetes) as assessed by a 75-g OGTT, the investigators found dysglycemia in significantly higher percentages of CAD, PAD, and CeVD patients compared with controls. As summarized in Table 1, the inflammatory marker of total leukocyte count was significantly higher in all patient groups compared to placebo, while soluble tumor necrosis factor receptor type 1 (sTNF-R1) was significantly higher in those with CAD and PAD, and C-reactive protein (CRP) significantly higher only in those with PAD, each compared to placebo. The markers of inflammation tended to parallel increasing blood glucose levels in all groups.

## CVD in Diabetes: Pathophysiological Insights

Several poster presentations provided insight into the pathophysiology of CVD in those with obesity and diabetes. In a study of 81 men between 22 and 55 years, stratified by BMI quartiles, Perseghin and Italian colleagues performed

**Table 1. Dysglycemia Prevalence and Inflammatory Marker Values in Patients With CVD vs. Controls**

Parameter	CAD	PAD	CeVD	Controls
Dysglycemia* (%)	49%	55%	57%	29%
Odds ratio for dysglycemia (95% CI)	1.7 (1.04-2.77)	1.9 (1.19-3.06)	2.0 (1.25-3.19)	1.0
Total leukocyte count (10 <sup>9</sup> /l)	6.9 ± 2.0 <sup>†</sup>	7.2 ± 1.8 <sup>‡</sup>	6.8 ± 1.9 <sup>†</sup>	5.9 ± 1.4
CRP (mg/dl) (95% CI)	3.7 (2.2-5.2)	4.8 (3.3-6.4) <sup>§</sup>	3.7 (2.3-5.1)	2.8 (1.8-3.7)
sTNF-R1 (pg/ml)	999 ± 493 <sup>§</sup>	1036 ± 376 <sup>†</sup>	965 ± 539	850 ± 283

sTNF-R1 = soluble tumor necrosis factor receptor type 1; CRP = C-reactive protein; CAD = coronary artery disease, PAD = peripheral artery disease, CeVD = cerebrovascular disease.

\*Dysglycemia includes diabetes, impaired fasting glucose, or impaired glucose tolerance. †p<0.01, ‡p<0.001, §p<0.05, vs. control group.

cardiac MR imaging and <sup>31</sup>P-MR spectroscopy (abstract 535). Morphologically, the investigators found that left ventricular mass increased across increasing BMI quartiles (r=0.39, p<0.002), with no difference in chamber volume. Parameters of left ventricular systolic (i.e., ejection fraction, stroke volume) and diastolic (i.e., early/atrial peak ratio and deceleration time) function were not different among the BMI quartiles. In contrast, the phosphocreatine/ATP ratio (a measure of left ventricular energy metabolism) was reduced across increasing quartiles of BMI (i.e., 2.25 ± 0.52, 1.89 ± 0.26, 1.99 ± 0.38, and 1.79 ± 0.29; p<0.006) in association with insulin resistance. This relationship was independent of age, blood pressure, HDL-cholesterol, triglycerides, smoking habits, and metabolic syndrome. These findings support prior hypotheses that perturbations in cardiac energy metabolism may be among the earliest cardiovascular alterations in those with diabetes and suggest that metabolic remodeling in insulin-resistant states precedes the functional and structural changes in the heart before the onset of frank hyperglycemia. Such findings may have a profound impact upon our understanding of insulin resistance, diabetes, and heart disease.

## OHAs and the Diabetic Heart

Data suggests that "older" sulfonylureas (SUs) block not only ATP-sensitive potassium channels in the β-cell but also in the heart. This may prevent a self-protective mechanism known as ischemic preconditioning in which these channels are opened during ischemic stress. Newer SUs, such as glimepiride and gliclazide (available overseas only), are more highly selective for the islet and may therefore be safer agents, especially in a group of patients at risk for ischemic heart disease. To clarify these effects, Thisted

and Danish colleagues examined the 30-day mortality rates among diabetic patients with a first-time hospitalization for acute myocardial infarction (MI) between 1996 and 2002 by the type of antidiabetic treatment prior to the MI, adjusted for prognostic factors of duration of diabetes, use of cardiovascular drugs, and level of comorbidity (abstract 91). Among the 54,835 MI patients, 6,644 were diabetic with 1,636 receiving no pharmacotherapy, 1,526 receiving an older SU, and 579 receiving a newer SU. The adjusted mortality rate ratios were lower among those treated with glimepiride (0.84, 95% CI 0.66-1.06) or gliclazide (0.75, 95% CI 0.47-1.17) compared to glibenclamide (similar to glyburide) (1.08, 95% CI 0.90-1.30), glipizide (1.15, 95% CI 0.92-1.43), or tolbutamide (1.10, 95% CI 0.87-1.38). Others have shown similar trends, but without a prospectively designed study, it is unclear whether these data are indicative of a true increased risk or simply the result of unmeasured confounders.

## Screening for CVD

In 2004, the French Societies of Diabetology and Cardiology recommended screening for silent myocardial ischemia (SMI) in:

- 1) diabetic patients with nephropathy, known carotid disease, or PAD;
- 2) those with two or more CVD risk factors with Type 1 diabetes for at least 10 years or older than 45 years; or
- 3) two or more CVD risk factors and Type 2 diabetes for more than 15 years or older than 60 years.

Valensi and French colleagues retrospectively analyzed the charts of 362 diabetic patients screened prior to these recommendations (1997 to 2000) and determined the prevalence of SMI (defined as abnormal myocardial scintigraphy), coronary stenosis on angiography, and cardiac events (cardiac death, myocardial infarction, cardiac failure,

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coronary revascularization, or unstable angina) in those who met the screening criteria versus those who did not (abstract 1166). The prevalence of SMI was similar in both groups (35% among those meeting the screening criteria and 33% among those who did not). However, the positive predictive value for SMI identifying those with actual coronary stenosis was higher in the 134 who met the criteria compared to the 228 patients who did not ( $p < 0.02$ ). SMI was also predictive of cardiac events (Kaplan Meier log rank 9.1,  $p < 0.005$ ), with the incidence of cardiac events being nearly three-fold greater in those meeting the criteria versus those who did not (11% vs. 4%; OR 2.8, 95% CI 1.2-6.8;  $p < 0.02$ ). Follow-up of the 128 of 134 patients meeting the criteria revealed that cardiac events were more likely to occur within three years in patients with SMI (18%, 8/45) than in patients without SMI (7%, 6/83). In those who met the criteria without SMI, cardiac events occurred between three and five years after screening. The rate of cardiac events during the five years of follow-up was similar between the two groups (23%). Based on their findings, the investigators suggested that diabetic patients meeting screening criteria but having no SMI might need to undergo repeat screening after three years. SMI identifies a higher risk group and the screening criteria from the French seem reasonable. Of note, however, others have found

**Table 2. Adjusted Predictors of Peripheral Artery Disease In Type 2 Diabetes Patients**

Risk Factor	Odds Ratio	95% CI	p-value
Current Smoking	1.50	1.07-2.20	<0.05
HbA1c >7%	1.45	1.07-2.08	<0.05
High pulse pressure	2.00	1.46-2.75	<0.001
Reduced GFR	2.16	1.40-3.30	<0.0001
Microalbuminuria	1.62	1.11-2.36	0.001
Fibrinogen	1.78	1.29-2.47	<0.001
Uric acid	1.50	1.03-2.19	<0.05

surprisingly little effect of classical CVD risk factors on the discovery of SMI in diabetic patients (Wackers *et al*, *Diabetes Care* 2004.)

Screening for another manifestation of atherosclerosis, PAD, is an uncommon practice in diabetic patients. However, according to the findings of Bianchi and Italian investigators, this may need to change (abstract 1216). In a cross-sectional study of 1,610 patients with Type 2 diabetes (mean age  $61.6 \pm 7.0$  years), ankle-brachial pressure index (ABPI) was measured with PAD defined as an ABPI  $< 0.9$ . Overall, the investigators found a PAD prevalence of 17%, with the prevalence increasing significantly with age ( $< 40$  years: 2% vs.  $> 70$  years: 45.5%,  $p < 0.001$ ) as well as diabetes duration ( $p < 0.001$ ). Those with PAD were found to have significantly higher levels of fibrinogen ( $370 \pm 79$  vs.  $347 \pm 76$  mg/dl,  $p < 0.001$ ), a greater prevalence of microalbuminuria (21.3 vs. 13.7%,  $p < 0.05$ ), and lower renal function

(GFR  $80.7 \pm 24$  vs.  $89.9 \pm 22$  ml/min/1.73 m<sup>2</sup>,  $p < 0.001$ ) compared to those without PAD. In age- and gender-adjusted analyses, there were significant correlations between PAD and several risk factors (Table 2) including poor glycemic control. PAD was more common among patients with a history of CVD (37% vs. 15%,  $p < 0.0001$ ). Among the 15% without a history of CVD but considered at high coronary heart disease (CHD) risk (using the UKPDS Risk Engine), the risk of PAD was significantly higher than in those not at high CHD risk (OR 2.5, 95% CI 1.47-4.2,  $p < 0.001$ ).

It is widely agreed that because of the frequency with which cardiac disease is encountered in diabetes, we must aggressively manage risk factors in all our diabetic patients. Whether screening for SMI (or PAD) is a worthwhile undertaking in this high-risk group is a more complex question and remains quite controversial.



## Gestational Frustration



During normal pregnancy, insulin secretory response increases up to four-fold. This compensates for very prominent insulin resistance, which is caused by a variety of circulating factors, mainly of placental origin, in addition to increased adiposity. Similar to Type 2 diabetes, gestational diabetes mellitus (GDM) results from the inability of the mother's pancreas to provide the required augmentation in insulin secretion.

Women with a history of GDM are at markedly increased risk for developing permanent Type 2 diabetes, and also, potentially, cardiovascular disease (CVD). Prikozovich and European investigators studied 119 women (mean age  $31.6 \pm 0.9$  years) with prior GDM and measured markers of endothelial activation (vascular cell adhesion molecule [VCAM] and intercellular adhesion molecule-1 [ICAM-1]), inflammation (i.e., C-reactive protein), and coagulation/fibrinolysis

(i.e., plasminogen activator inhibitor type 1 [PAI-1]) at baseline (approximately 14 to 16 weeks post-delivery) and after one year (abstract 105). All of these markers, which have previously been correlated with increased CVD event rates, were significantly ( $p < 0.05$ ) higher at baseline as well as at one year in women with a history of GDM vs. those with previously normal pregnancies.

### Like Mother, Like Daughter?

Studies indicate that children of women with GDM tend to be at greater risk for obesity and Type 2 diabetes, themselves. In a longitudinal follow-up of a case-control cohort of women that delivered a daughter between 1989 and 1991, Egeland and Canadian investigators assessed the anthropometric, behavioral (i.e., diet, physical activity), and metabolic (i.e., glucose tolerance,

insulin resistance, and dyslipidemia) outcomes in 103 (48 case- and 55-control) consenting mother-daughter pairs (abstract 103). Those born of mothers with GDM were significantly younger than control-daughters ( $14.6 \pm 0.7$  vs.  $15.1 \pm 0.6$  years,  $p < 0.001$ ). As compared to control-group mothers, GDM mothers were of similar age, but had significantly ( $p \leq 0.05$ ) greater BMI, body fat, and triglycerides and lower HDL-cholesterol (Table 3). Both GDM mothers and their daughters were found to have greater waist circumferences ( $p < 0.01$ ) and lower insulin sensitivity ( $p < 0.01$ ), as compared to their control counterparts. In both case- and control-pairs, the mothers' intake of saturated fat as a percent of total energy ( $r = 0.42$ ,  $p < 0.001$ ) and leisure time physical activity scores ( $r = 0.24$ ,  $p = 0.017$ ) were positively and significantly correlated with their daughters'.

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At the time of the analysis, no daughter in either group had developed diabetes.

## Glycemic Control During Pregnancy

Vigilant blood glucose control is required to reduce the risk for maternal as well as fetal complications during diabetic pregnancies. At this week's EASD meeting, Heller and European associates reported on glycemic control and maternal and perinatal outcomes with the rapid insulin analogue, aspart, compared with human insulin (abstract 948). Pregnant women ( $\leq 10$  weeks gestation) with Type 1 diabetes aged 19 to 43 years with an HbA1c  $< 8\%$  at confirmation of pregnancy were randomized to insulin aspart ( $n=157$ ) or regular human insulin ( $n=165$ ). There was a consistent trend towards lower rates of major (24-hour, nocturnal, and daytime) hypoglycemia in women treated with insulin aspart compared to those treated with regular insulin. The relative risk (RR) for all major hypoglycemic episodes was 28% lower with insulin aspart vs. regular (RR 0.72, 95% CI 0.36-1.46,  $p=0.36$ ), with that of nocturnal hypoglycemia being 52% lower (RR 0.48, 95% CI 0.20-1.14,  $p=0.10$ ). Post-prandial glucose increments (mean after breakfast, lunch, and dinner) were

**Table 3. Characteristics of GDM and Non-GDM Mothers and Daughters**

Characteristics	Daughters Born of Mothers with:			Mothers		
	GDM	Non-GDM	p-value	GDM	Non-GDM	p-value
Age (years)	14.6 $\pm$ 0.7	15.1 $\pm$ 0.6	<0.001	46.9 $\pm$ 4.0	46.8 $\pm$ 4.8	NS
BMI (kg/m <sup>2</sup> )	23.5 $\pm$ 4.6	22.1 $\pm$ 3.3	0.07	29.4 $\pm$ 6.2	26.4 $\pm$ 4.5	<0.01
Waist Circumference (cm)	79.9 $\pm$ 10.8	74.9 $\pm$ 8.3	<0.01	95.6 $\pm$ 14.1	87.8 $\pm$ 12.3	<0.01
Body Fat, %	30.6 $\pm$ 6.7	28.8 $\pm$ 7.0	NS	37.9 $\pm$ 7.2	34.3 $\pm$ 7.3	<0.01
HDL-cholesterol (mg/dl)	46.8 $\pm$ 11.7	46.8 $\pm$ 7.8	NS	46.8 $\pm$ 11.7	58.5 $\pm$ 15.6	<0.01
Total cholesterol (mg/dl)	156.0 $\pm$ 23.4	167.7 $\pm$ 27.3	0.07	210.6 $\pm$ 39.0	206.7 $\pm$ 50.7	NS
Triglycerides (mg/dl)	62.3 $\pm$ 26.7	62.3 $\pm$ 35.6	NS	133.5 $\pm$ 106.8	97.9 $\pm$ 80.1	0.05
HOMA-IR	2.2 $\pm$ 1.3	1.7 $\pm$ 0.7	<0.01	3.4 $\pm$ 3.6	1.5 $\pm$ 1.0	<0.001
Activity (hrs/week)	60.6 $\pm$ 37.1	74.2 $\pm$ 49.2	0.09	18.0 $\pm$ 22.7	26.1 $\pm$ 22.1	0.07
Saturated Fat Intake (% total energy)	11.1 $\pm$ 2.8	11.2 $\pm$ 2.1	NS	11.2 $\pm$ 2.8	11.3 $\pm$ 2.5	NS

GDM = gestational diabetes mellitus; NS=not significant.

significantly lower with insulin aspart in both the first (+13 vs. +27 mg/dl,  $p<0.01$ ) and third (+20 vs. +27 mg/dl mg/dl,  $p=0.04$ ) trimesters, but with no differences between the insulins in the average 24-hour plasma glucose or HbA1c. Studying the same population, Kaaja *et al.* found no difference in median gestational age, percentage of macro-

somic or large-for-gestational-age births, fetal mortality, or major congenital malformations between the insulin aspart and regular insulin groups (abstract 949). Similar safety data with another rapid acting insulin analogue, lispro, in diabetic pregnancies was reported by Lapolla and Italian colleagues (abstract 950).



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



### Sweet Dreams?

The association between severe sleep apnea and nocturnal hyperglycemia was evaluated by Pallayova *et al.* from Slovakia in a study of 30 Type 2 diabetes patients with near-normal glucose treated with oral hypoglycemic agents (abstract 241). All patients were monitored with continuous glucose monitoring system (CGMS) for an average of 98 hours, and the eight study patients with sleep apnea also underwent concurrent polysomnographic evaluation. Nocturnal blood glucose increased immediately (within one hour) and significantly following apneic episodes (up to 221 mg/dl). The nocturnal increment in blood glucose was highly correlated with severe oxygen desaturation ( $r=0.72$ ,  $p<0.01$ ). Morning fasting glucose level was significantly higher in those with vs. without sleep apnea (144 vs. 118 mg/dl, respectively;  $p<0.05$ ), with no difference between groups in glucose levels measured thereafter during the day. These findings underscore the need to address sleep apnea to optimize overnight and fasting hyperglycemia in our diabetic patients.

### The "Adipovascular Axis"

Tsiakou *et al.* from Greece measured adiponectin and resistin levels, two adipocyte-derived cytokines, and C-reactive protein (CRP) in the first 24 hours after the onset of stroke in 60 Type 2 diabetes patients and determined their association with stroke severity and outcomes (abstract 689). The investigators found that low adiponectin and high resistin plasma levels on admission for first ischemic stroke in diabetic patients, which suggested a more insulin resistant state, were correlated with the extent of brain injury, clinical stroke severity, and the five-year mortality risk. These findings were independent of the impact of the acute inflammatory response, as revealed by the CRP concentration. Almost half the study population ( $n=28$ , 47%) died within five years after stroke. There was a statistically significant inverse correlation of adiponectin with resistin ( $r=-0.72$ ), CRP ( $r=-0.61$ ), BMI ( $r=-0.39$ ), mean arterial pressure

( $r=-0.43$ ), infarct volume ( $r=-0.34$ ), and stroke severity as measured by National Institute of Health Stroke Scale (NIHSS) score ( $r=-0.41$ ). Resistin was inversely associated with HDL-cholesterol ( $r=-0.33$ ) and positively associated with CRP ( $r=0.61$ ), BMI ( $r=0.59$ ), fasting insulin ( $r=0.38$ ), fasting glucose ( $r=0.42$ ), and insulin sensitivity as assessed by HOMA ( $r=0.55$ ). According to a multivariate Cox's proportional hazards model, the risk of death within five years after the index stroke was significantly associated with the presence of coronary heart disease (HR 8.7, 95% CI 3.6-20.4), NIHSS score in the highest (i.e. most impaired) tertile (HR 7.1, 95% CI 3.2-18.4), CRP in the highest tertile (HR 5.6, 95% CI 3.1-16.2), age  $>70$  years (HR 4.4, 95% CI 2.2-14.3), adiponectin in the lowest tertile (HR 3.5, 95% CI 1.5-9.8), and resistin in the highest tertile (HR 2.1, 95% CI 1.2-6.9).

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