

# Diabetes 2006

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## The Super-Sizing of America



Important data on diabetes presented at the 66th Annual Scientific Sessions of the American Diabetes Association come 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 (ACC and ADA 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.

Yale University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education to physicians. Yale University School of Medicine designates this continuing medical education activity for a maximum of 5.5 Category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

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The most recent CDC "obesity maps" ([www.cdc.gov/nccdphp/dnpa/obesity/trend/maps](http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps)) show worrisome trends. In 1990, very few states had an obesity prevalence in excess of 15%. In 2004, 33 states had rates of 20% to 24%, and an additional nine were in excess of 25% (Figure 1). Notably, no state had a prevalence less than 15%. Given these staggering statistics, it is no wonder that there were so many participants attending the symposium entitled "Obesity Treatment: Behavioral vs. Pharmacological vs. Surgical Approaches." In an opening presentation, Dr. Thomas Wadden of the University of Pennsylvania reviewed behavioral studies showing that the greatest weight loss occurs in patients who are given a program of reduced caloric intake with meal replacements (i.e., the use of shakes or portion-controlled meals) and exercise (between 30 to 60 minutes per day). He recommends that patients weigh themselves only a few times a week while they are trying to lose weight (as opposed to daily during weight maintenance), have a structured, goal-oriented group approach to weight reduction (vs. individual counseling), have frequent visits with their clinician, and report regularly on their progress with exercise programs. In those who still can't accomplish substantial weight reduction, enrollment in a commercial program (i.e., Weight Watchers™, Jenny Craig™) is advisable.

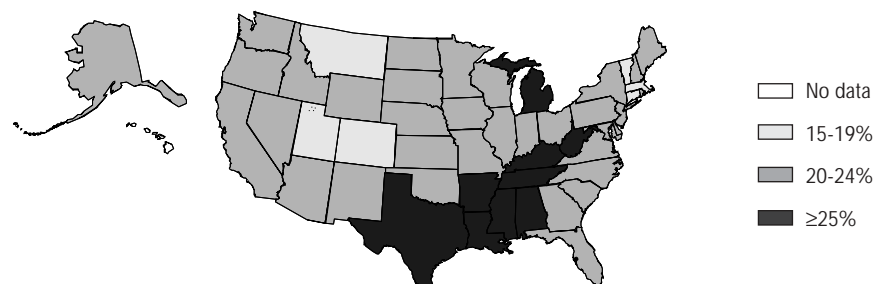
In related presentations made this week, the influence of type of diet on weight loss was discussed. Although low-carbohydrate diets may initially produce greater decreases in weight,

several groups of researchers this week reported that there is no substantial difference in long-term weight loss between low-carbohydrate and low-fat diets. Two independent sets of investigators (332-OR, 1650-P) found that decreased calorie consumption, regardless of the macronutrient balance (carbohydrates and fat), results in weight loss and reduction in cardiovascular risk factors. In the larger and longer of the two studies (1650-P), 80 overweight/obese men and women (mean BMI  $36 \pm 0.4$  kg/m<sup>2</sup>, mean age 56 years, mean HbA1c  $7.3 \pm 0.1\%$ ) with Type 2 diabetes not treated with insulin and with stable weight for at least six months were studied. They were randomly assigned to a high fat (40% of calories from fat, 20% monounsaturated fat) or a high carbohydrate (25% of calories from fat) kilocalorie-restricted diet (mean, 1,416 kcal in females, 1,919 kcal in males). Significant weight loss (-3 to -4 kg) and improvements in blood pressure, HDL-cholesterol, HbA1c, fasting glucose, and insulin sensitivity were observed in both diet groups after one year, with no significant differences between diets.

### Eat Your Breakfast!

Of the four major causes of obesity—genetics, metabolism, behavior, and environment—only the latter two have changed enough within the last two decades to be blamed for the epidemic. Behavioral changes include decreased activity levels, increased portion sizes, and readily available

Figure 1. Obesity Trends\* Among US Adults (BRFSS, 2004)



\*BMI  $\geq 30$  kg/m<sup>2</sup>, or  $\sim 30$  lbs overweight for 5'4" person.

Source: Behavioral Risk Factor Surveillance System (BRFSS), CDC.

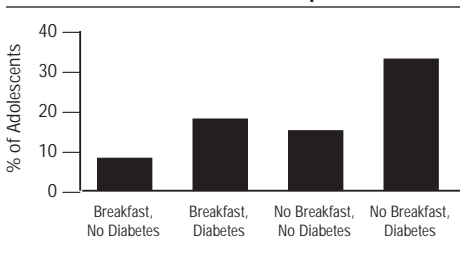
Continued on page 2

## The Super-Sizing of America

Continued from page 1

high calorie food at relatively low cost. In a population of ~2,700 adolescents (aged 13 to 19 years), Wollitzer and California associates (1771-P) also found that regularly skipping breakfast produces a risk for obesity that is as high as having a family history of Type 2 diabetes. Nearly one-third of those with a family history of diabetes and who frequently skipped breakfast (the highest risk category) were obese compared to 8.3% of those with no family history of diabetes and who ate breakfast regularly (Figure 2).

**Figure 2. Obesity Rate by Family History of Diabetes and Breakfast Consumption**



## Pharmacologic Approaches to Weight Loss

The symposium's next speaker, Dr. Louis Aronne of Cornell University, drew an analogy between suboptimal hypertension management in the 1960s and the current strategies for weight control. He presented data supporting a feedback system that hinders further weight loss via a "plateau effect." Leptin may play some role in this compensatory feedback system. Attendees were also advised to carefully review patient's concurrent medications. In the speaker's experience, many patients lose weight following the identification and discontinuation of culprit pharmaceutical agents (i.e., selected antidepressants) and, if necessary, switching to alternative remedies.

Most patients cannot achieve their weight loss target with only behavioral modification, even with an increase in exercise. Therefore, physicians often turn to pharmacotherapy. After reviewing their respective mechanisms of action, Dr. Aronne proposed patient criteria that may assist clinicians in selecting between sibutramine and orlistat (Table 1), the two currently approved agents for weight loss. In addition, he briefly discussed several other drugs and combinations that have been reported to cause weight loss, but are not currently available or FDA-approved for this indication (i.e., rimonabant, pramlintide, topiramate, zonisamide, naltrexone plus bupropion, topiramate plus phentermine, and AOD9604—

**Table 1. Selection Criteria: Sibutramine vs. Orlistat**

| Sibutramine               | Orlistat                  |
|---------------------------|---------------------------|
| Use in patients with/who: | Use in patients with/who: |
| ■ Strong appetite         | ■ Don't feel hungry       |
| ■ Don't feel full         | ■ Are on other meds       |
| ■ Think about food        | ■ Eat out often           |
| ■ Low CVD risk            | ■ High CVD risk           |
| ■ Are younger             |                           |
| ■ GI problems             |                           |

growth hormone fragment that stimulates metabolic rate and is currently in Phase 2 trials).

Aronne stated that rimonabant, the first selective cannabinoid-1 receptor antagonist, may be approved this year by the FDA. There is a lot of interest in the endocannabinoid system, which appears to play a role in the development of obesity, through effects on leptin signaling, appetite, and physiologic components of the metabolic syndrome. In recently published studies rimonabant produced a mean weight loss of approximately 6 kg over one year (*JAMA* 2006; 295:761-775) as well as improved cardiometabolic risk, findings supported by a poster presented at this week's meeting. In a randomized, placebo-controlled trial of 1,047 overweight/obese patients with Type 2 diabetes, Scheen and international colleagues (560-P) reported that rimonabant 20 mg was associated with significantly ( $p < 0.001$ ) greater weight loss compared to placebo (-5.3 kg vs. -1.4 kg) and improvements in HbA1c (-0.6% vs. +0.1%). 43% of those taking rimonabant had a final HbA1c < 6.5% (vs. 21% of those given placebo). Statistically significant improvements with rimonabant as compared to placebo were also observed for waist circumference, HDL-cholesterol, triglycerides, and fasting glucose. The results with rimonabant were comparable regardless of whether patients were receiving metformin or sulfonylureas.

New hormonal targets for anti-obesity therapy was the topic of an entire symposium this week. Brain and gut peptides that regulate appetite and metabolism appear to be garnering the most interest and several are in early stage development at several pharmaceutical houses. During the symposium, the presenters reviewed:

- **Oxyntomodulin**—a gut-derived peptide secreted in response to meals which appears to modulate calorie intake, perhaps through the GLP-1 receptor.
- **GLP-1 and GIP** (see Issue 3, pg 1, and pg 3 in today's issue)—the "incretin hormones," also gut-derived, that decrease calorie intake by slowing gastric emptying and suppress appetite through a central effect.

- **Enterostatin**—a pancreatic peptide that reduces fat intake and may also have peripheral effects to enhance fatty acid oxidation.

- **Granulocyte-macrophage colony-stimulating factor (GM-CSF)**—a pro-inflammatory cytokine that reduces calorie intake probably through central mechanisms.

Several abstracts this week indicated that other hormones—including ghrelin and polypeptide YY—have an important physiological role in modulating satiety via the hypothalamus and have great potential for the design of anti-obesity drugs. The last decade has seen great advances in our understanding of the central and peripheral mechanisms involved in the regulation of body weight. However, we still have a long way to go before we fully understand the exact role of all of these hormones, how they cross-talk to each other to help maintain energy balance.

## A Procedure Not to Be Taken Lightly

The number of patients in the United States undergoing gastric weight-loss surgery rose from approximately 14,000 in 1998 to more than 82,000 in 2002—an increase of more than 600%!—with more than one in five of these individuals having Type 2 diabetes (*Am J Public Health* 2006;96:1-3). While these numbers are staggering, according to the final speaker, Dr. David Flum, a surgeon from the University of Washington, less than 1% of those who could undergo bariatric surgery based on BMI criteria actually undergo the procedure. He added that while lifestyle and pharmacologic therapy are effective management tools in diabetics, the amount of weight reduction typically achieved with these interventions is trivial. Post-surgical weight loss is accompanied by resolution of glucose intolerance and diabetes, as well as improvements in sleep apnea, gastroesophageal reflux, lipid profile, and hypertension.

While the current criteria for bariatric surgery is a BMI > 35 kg/m<sup>2</sup>, with at least two comorbidities or BMI > 40 kg/m<sup>2</sup>, it has been suggested that the threshold be lowered to 33 kg/m<sup>2</sup>. Flum added that this 2 kg/m<sup>2</sup> decrease could result in an exponential increase in the number of people (an estimated 10 million individuals) who would become eligible for the procedure. In addition to lowering the BMI, there is movement afoot for disease-based criteria (with diabetes being an indication) as well as age-based indications. The advent of the less invasive, reversible gastric banding procedures may be more acceptable to patients, whether or not these criteria change.

The suggestion to expand the use of gastric weight-reduction surgery should not be taken

Continued on page 3

## The Super-Sizing of America

Continued from page 2

lightly as these procedures are associated with significant rates of morbidity and mortality. Most of the data are associated with the Roux-en-Y procedure, which is the most common bariatric procedure performed in the US. Mortality rates range from 0.4% to 1.1%, and these procedures may also result in nutritional deficiencies, impaired wound healing, infection, osteoporosis, and cholecystitis.

Newer, less invasive gastric procedures such as gastric banding or implantable devices may be associated with less severe side effects. One such device, the Tantalus™ System (MetaCure, NV), an electrode system that is implanted into the stomach laparoscopically and enhances gastric contractions during meals (1714-P), appeared to reduce weight and improve glycemic control in a study of 24 obese patients with Type 2 diabetes (Table 2).

## Bariatric Surgery: New Mortality Data

With these comments in mind, the first population-based study of cause-specific mortality among Pennsylvania residents who had bariatric surgery performed between 1995 and 2004 was presented by Omalu and colleagues (297-OR). The investigators found mortality rates following bariatric surgery to be *higher* than those in the

**Table 2. Effects of Tantalus™ System**

|                             | Change from baseline at: |                   |                  |
|-----------------------------|--------------------------|-------------------|------------------|
|                             | Week 10<br>(n=11)        | Week 20<br>(n=10) | Month 9<br>(n=8) |
| Weight loss (kg)            | -5.4 <sup>†</sup>        | -7.7 <sup>†</sup> | -8.6             |
| Waist circumference<br>(cm) | -3.6*                    | -3.9*             | -5.7*            |
| Glucose (mg/dl)             | -51 <sup>†</sup>         | -56 <sup>†</sup>  | -61*             |
| HbA1c (%)                   | -1.2 <sup>†</sup>        | -1.2*             | -1.1*            |

\*p<0.05 †p<0.01

general population, even after excluding deaths within the first 30 days or 1 year. The leading causes of post-operative death were coronary heart disease (19%), sepsis (14%), therapeutic complications (11%), pulmonary embolism (12%), and other vascular diseases (8%). Late-stage complications may also develop in these individuals according to a presentation made by Dr. Mary-Elizabeth Patti of the Joslin Diabetes Center during a separate symposium held Sunday morning. She presented the clinical characteristics of an infrequent, unique symptom that has been observed in a small number of patients. Post-bypass hypoglycemia syndrome is characterized by severe postprandial hypoglycemia and hyperinsulinemia that presents two to four years

after gastric bypass. It is often unresponsive to diet intervention, with some patients responding to acarbose, octreotide, or diazoxide. Some patients with severe hypoglycemia required partial and/or total pancreatectomy for control. Pancreatic pathology is negative for insulinoma but high islet cell volume has been reported. Dr. Patti added that metabolic testing of post-bypass patients with, as well as without, the syndrome has demonstrated hypoglycemia and increased insulin in response to mixed-meal challenge, with no difference in counterregulatory hormone secretion or insulin sensitivity. In all post-bypass patients, increased secretion of GIP is observed, but with no correlation to the severity of the syndrome. Increased secretion of GLP-1 is also seen and this does appear to parallel the severity of post-bypass hypoglycemia and its symptoms.

We are clearly still in the "Dark Ages" in the management of obesity. It will be critically important for both our patients and the viability of our healthcare system that we better understand the biological underpinnings of weight regulation. Specifically, we need to better understand the neurohumoral mechanisms that control appetite and the metabolic compensations under conditions of calorie restriction. With this knowledge, we can begin to design more intelligent therapeutic approaches than are currently available today.



## GLP-1: Getting to Know You



Glucagon-like peptide 1, or GLP-1, a gut-derived "incretin" hormone that stimulates insulin secretion and inhibits glucagon release, has been the focus of significant attention from the diabetes community for the past several years. Interest in this therapeutic area was heightened in 2005 with the release of the first GLP-1-related drug, exenatide.

In the opening presentation of a symposium on incretin therapy, Dr. Jens Juul Holst from Denmark reviewed the physiologic effects of GLP-1 (Table 3). He added that there is emerging evidence supporting a central action of GLP-1, as well.

**Table 3. Physiological Effects of GLP-1**

- Stimulates insulin secretion (glucose-dependent)
- Inhibits glucagon secretion
- Regulates appetite and food intake
- May have  $\beta$ -cell, cardiovascular, and neuro-protective effects

Dr. Torsten Vahl of the University of Cincinnati next discussed exendin-4, the GLP-1-like peptide that is found in the saliva of the venomous Gila monster, and is the basis for the drug, exenatide. This lizard consumes large amounts of food, but (unlike humans), it eats very infrequently—usually just four to five times per year. In response to food, exendin-4 in the saliva of the Gila arouses pancreatic  $\beta$ -cell activity with resultant insulin release to promote calorie storage. The characteristics that exendin-4 shares with GLP-1 were reviewed. Both hormones improve glucose tolerance, restore insulin secretion, reduce body weight, and delay gastric emptying. The quantitative differences between exendin-4 and GLP-1 can be explained by their pharmacokinetic differences. The rapid metabolism of GLP-1 (7-36 amide) by the enzyme, DPP-4 (see yesterday's edition), produces a metabolite (9-36 amide) that has no major physiologic effects. Exendin-4 is resistant to this deactivation and therefore has a much longer half-life.

The symposium concluded with a clinical presentation by Dr. Michael Nauck of Germany who presented data on GLP-1 as a clinical drug

target for diabetes and obesity. He reviewed the results of several of the numerous oral and poster presentations involving exenatide and other GLP-1-analogues at this week's meeting. He cautioned that when reviewing data regarding these agents, and especially when comparing across trials, it is critical to know baseline HbA1c levels, since greater effects tend to be observed in patients with HbA1c  $\geq 9\%$ .

Exenatide is effective in lowering HbA1c and decreasing body weight. In an oral presentation (116-OR), Linnebjerg and international colleagues found that exenatide also produced dose-dependent slowing of gastric emptying. While weight loss may be partially attributed to this, central actions of exenatide have also been proposed.

Henry and colleagues presented two-year follow-up data for 283 Type 2 diabetes patients (mean age  $57 \pm 10$  years, BMI  $34 \pm 6$  kg/m<sup>2</sup>, HbA1c  $8.3 \pm 1.0\%$ , baseline fasting glucose  $174 \pm 3$  mg/dl) treated with exenatide 10  $\mu$ g twice daily combined with metformin and/or sulfonylurea (485-P). Significant ( $p < 0.05$ ) improvements were observed in HbA1c (Table 4), with half of patients achieving an HbA1c  $\leq 7\%$  and

Continued on page 4

## GLP: Getting to Know You

Continued from page 3

31% achieving an HbA1c  $\leq$  6.5%, as well as improved fasting glucose. On average, patients lost 4.7 kg with greater amounts (~12 kg) observed in those in the highest baseline weight quartile (104 kg).

Similar findings were reported in a retrospective study of 41 patients receiving insulin plus exenatide for eight weeks by Bhatia and colleagues of New York (442-P). Although 32 patients lost a mean of 3.2 kg, the remaining 9 patients had no change or a slight increase (<1 kg) in weight. Doses of all types of insulin were reduced significantly with the addition of exenatide (Figure 3). Results of a pilot study by Davis and colleagues (456-P) suggest that in some patients with Type 2 diabetes receiving insulin and oral agents, it may be possible to substitute exenatide for insulin, although many of these study patients (38%) experienced a deterioration in glycemic control.

A primary drawback to the use of exenatide is its twice daily injectable route of administration. Kim and colleagues (487-P) evaluated

**Table 4. Glucose Control and Weight Change with Exenatide**

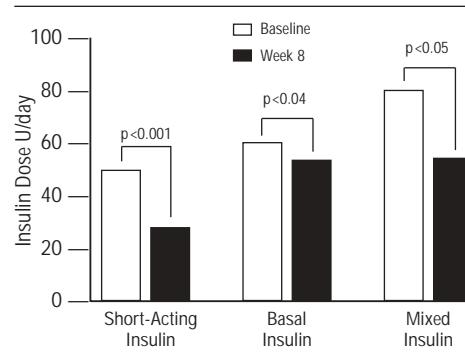
|                        |                             |
|------------------------|-----------------------------|
| Dose                   | 10 $\mu$ g bid<br>x 2 years |
| $\downarrow$ HbA1c (%) | -1.1 $\pm$ 0.1%*            |
| FPG (mg/dl)            | -25.2 $\pm$ 2.8*            |
| Body weight (kg)       | -4.7 $\pm$ 0.3*             |

\*  $p < 0.05$  from baseline

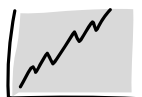
a new microsphere long-acting formulation of this peptide that is administered once weekly. In a population of Type 2 diabetes patients suboptimally responsive to metformin or diet plus exercise, they found improvement in HbA1c levels (86% of those given long-acting exenatide 2.0 mg once weekly had HbA1c  $\leq$  7%) as well as an average 4 kg weight loss at 15 weeks. While provocative, we wonder about the safety of chronically elevated exenatide levels that would be expected to result from this product.

Another GLP-1 agonist presented at this week's meeting was liraglutide (115-OR, 1712-P,

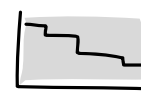
**Figure 3. Insulin Dose Before and After Addition of Exenatide**



1933-P, 2007-PO), an agent that is highly bound to albumin and therefore has a half-life of between 12 and 14 hours, requiring only once daily injection. Like exenatide, liraglutide increases insulin secretion, decreases HbA1c (by approximately 1.8% from baseline of 8.1-8.5%), fasting glucose, and glucagon secretion, while also resulting in weight loss of approximately 2-3 kg (115-OR).



## Progression to Diabetes: The Tipping Point



Impaired glucose regulation—defined and measured as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)—eventually begets Type 2 diabetes in the majority of affected individuals. When, why, and how this progression occurs remains largely unknown.

In an attempt to clarify the “when” part of the question, Nichols and colleagues (952-P) estimated the diabetes progression rates in a large (n=5,452) cohort of subjects with newly developed “pre-diabetes.” Of the 4,548 subjects with fasting plasma glucose (FPG) 100-109 mg/dl, progression to diabetes occurred in 6.7% over an average follow-up of 5.5 years (1.2% per year). Of the 932 with FPG 110-125 mg/dl, progression occurred in 24% over 4.9 years (4.3% per year). The authors concluded that progression occurs much more rapidly in those patients at the higher end of the IFG range.

In a symposium on impaired glucose regulation, several presenters attempted to unravel the “why and how” questions. Thinking of diabetes in stages was a common theme in the first presentation by Dr. Gordon Weir of the Joslin Clinic who defined five stages of blood glucose, ranging from normal to diabetic ketoacidosis

(DKA). The stages are characterized by declining insulin production and  $\beta$ -cell mass. The relative or absolute decline in  $\beta$ -cell mass results in glucotoxicity with the remaining  $\beta$ -cells therefore being exposed to chronically elevated glucose levels. The glucotoxicity further impairs  $\beta$ -cell function setting up a vicious cycle of progressive hyperglycemia. The excellent correlation between glucose levels and  $\beta$ -cell dysfunction supports this hypothesis; however, a molecular basis for glucotoxicity has not been established. This alteration in  $\beta$ -cell function occurs early in pre-diabetes and so Weir feels that efforts should be directed at keeping individuals in this stage as long as possible. He proposed methods to do so, including lifestyle changes, and potentially, drug therapy.

In the second presentation of the symposium, Dr. Ele Ferrannini of Italy reviewed his mathematical model of  $\beta$ -cell function and the role of  $\beta$ -cell glucose sensitivity and insulin sensitivity in the progression to diabetes. Overall, his findings indicate that both  $\beta$ -cell sensitivity and insulin sensitivity interact in a non-linear manner to determine glucose tolerance. There is a *simultaneous* decline of  $\beta$ -cell glucose sensitivity and peripheral insulin sensitivity that marks the

progression to the hyperglycemic state, with obesity and/or genetics possibly being the “tipping point.”

The notion that IFG is a glucose sensing defect rather than an insulin secretory deficit, was supported by data from a small study by Perreault and colleagues (156-OR). Using the glucose step-up method (glucose infused intravenously at 2, 4, 6, 8, and 10 mg/kg/min x 40 minutes each),  $\beta$ -cell glucose sensitivity and insulin secretory capacity in six subjects with IFG but normal 2-hour glucose during oral glucose tolerance test (OGTT) were compared with those of seven normal subjects, matched for age, body fat, and BMI. Neither absolute insulin secretory capacity nor insulin clearance differed between the subject populations. However, C-peptide and insulin increased proportionately to increasing glucose in both populations, until the latter part of the step-up protocol (8 mg/kg/min glucose infusion). At this point, the insulin secretory response to glucose accelerated in those with IFG ( $p = 0.03$ ). In the IFG patients, increased insulin secretion markedly attenuated any further increase in glucose ( $p = 0.007$ )—a more robust response that even in those with normal glucose tolerance ( $p = 0.09$ ).

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## Progression to Diabetes...

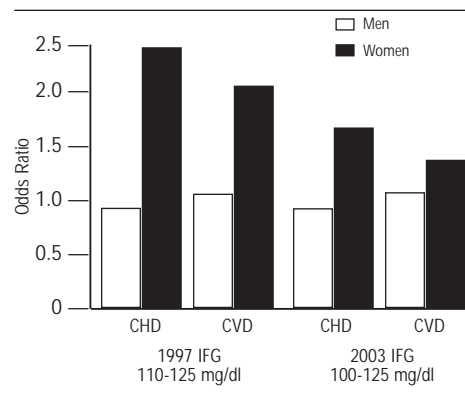
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In a larger study of 29 patients with IFG and 21 subjects with normal fasting glucose (NFG), Bock and colleagues (157-OR) found, instead, very similar rates of insulin secretion with significantly ( $p < 0.05$ ) lower insulin action in the IFG (i.e. insulin resistance) vs. the NFG group.

The identification of patients with impaired glucose regulation may be important for targeted therapies directed at stabilization of  $\beta$ -cell function, to prevent progression to diabetes. Moreover, patients with IFG, and especially IGT, are at increased cardiovascular risk. Earlier in the week's sessions, Levitzky and colleagues (1-OR) found similar odds ratios for coronary heart disease (CHD) and cardiovascular disease (CVD)

using the 1997 and 2003 ADA IFG criteria (Figure 4). However, in the final symposium presentation, Dr. David Nathan from Harvard told the audience that lowering the IFG criteria below 100 mg/dl was being considered. Using the current definition, Nathan found that a substantial percentage (7.6%) of those with IGT and no diagnosis of diabetes already have diabetic retinopathy compared to 12.5% in those with a three-year history of diabetes. Although lowering the IFG definitional threshold would likely capture more patients "at risk" for diabetes development, numerous discussions would be needed amongst experts, and professional and health organizations, since such a change would have broad implications across the healthcare system and society at large.

Figure 4. Odds Ratio for CHD and CVD in Men and Women by 1997 and 2003 ADA IFG Criteria



## Glargine in Pregnancy



Diabetes during pregnancy is associated with increased risk for complications for both mother and baby and therefore requires vigilant blood glucose control. The peakless profile of insulin glargine may be beneficial in controlling glucose during gestation. However, this basal insulin analogue is not approved for use in pregnant women. Two posters this week revealed data from recently completed retrospective analyses in this area. Poyhonen-Alho and Finnish colleagues (1806-P) compared the maternal and perinatal outcomes among 47 pregnant women with Type 1 diabetes who had used glargine prepartum and continued its use during the gestational period. Results were compared to those of 50 pregnant women matched for age, parity, duration of diabetes, and diabetic complications who were using NPH. Both study groups administered short-acting insulin prior to meals. During the first trimester, the mean glycemic control was similar in the two groups (HbA1c

6.9% with NPH vs. 7.4% with glargine), with those in the glargine group having a significantly greater decrease in HbA1c from the first to the third trimester ( $p = 0.04$ ). There was a tendency for a greater number of hypoglycemic episodes with NPH (21 vs. 11 events,  $p = 0.07$ ). Both regimens were safe, with no differences in gestational age at delivery, pregnancy complications, and perinatal outcomes (fetal weight, shoulder dystocia, respiratory distress, infection, first plasma glucose after delivery).

In the second study (1804-P), Gallen and associates of the UK surveyed the maternal and fetal outcomes of 127 pregnancies among 120 women (115 with Type 1 and 5 with Type 2) who used glargine during the gestation. Among the 120 women, 82 (65%) had been treated with glargine prior to the pregnancy. During pregnancy, hypoglycemia requiring assistance occurred in nine women (7%) with 16 women (12%) having two or more episodes. Pre-eclampsia occurred

in 16 (12%) cases. Background retinopathy developed in one woman, progressed in three, and laser photocoagulation was required in seven women. A total of 122 live births (mean gestational age of 37.5 weeks, mean birthweight of 3500 grams, and 24 [20%] births weighing  $\geq 4$  kg) resulted from the 127 pregnancies, with seven cases (6%) of early miscarriage. The malformation rate was 2.5%, occurring as three congenital abnormalities among the 122. Five of the neonates had 1 minute Apgar scores  $< 5$ . There were no neonatal deaths. 51 (42%) babies had neonatal hypoglycemia and 28 (23%) had hyperbilirubinemia. These results were comparable to those in recently published studies, suggesting that glargine does not result in any increase in maternal or fetal adverse outcomes.

These observational data are encouraging, but not conclusive. They indicate the need for larger, randomized clinical trials of the safety of basal insulin analogues in pregnancy.



## Focus on Science



### Gene Therapy

Insulin gene therapy has been hampered on many fronts. One problem has been failure to develop a satisfactory system with tightly regulated glucose-sensing insulin release. Han *et al.* from Chicago (107-OR) developed a liver-specific glucose responsive synthetic promoter (SP) attached to an

insulin-response gene sequence. The investigators generated a recombinant adenovirus-expressing rat insulin under the control of the promoter and administered it into streptozocin-induced diabetic mice. Euglycemia was achieved within a week

and maintained for a month. Insulin expression was observed in hepatocytes only, indicating that this is indeed a liver-specific promoter. This mode of gene therapy may hold promise for future cure of human Type 1 diabetes.

Silvio E. Inzucchi, MD  
Robert S. Sherwin, MD

Editors, Yale University,  
New Haven, Connecticut