

Diabetes 2008

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From Triumvirate to Ominous Octet



Important data on diabetes presented at the 68th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2008**, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of **Diabetes 2008** will be followed by a **Diabetes 2008** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, 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 2008 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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The Banting Medal, the highest honor bestowed by the American Diabetes Association, was presented to Dr. Ralph DeFronzo of the University of Texas, San Antonio for his four decades of scientific achievement in the pathogenesis and treatment of insulin resistance and Type 2 diabetes. Following the presentation of the award, Dr. DeFronzo proceeded to deliver the Banting Lecture, entitled "*From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes.*"

In 1987, Dr. DeFronzo presented the Lilly Lecture at the ADA Scientific Sessions, in which he discussed the pathobiological 'triumvirate' of Type 2 diabetes—with metabolic defects in muscle, liver, and pancreas. The intervening two decades have led to many new discoveries concerning other tissues involved in the development of hyperglycemia. Dr. DeFronzo first reviewed some of his pivotal work from the 1970s and 1980s in which he, along with others, described the cardinal features of Type 2 diabetes, beginning initially with severe resistance to insulin action, first in skeletal muscle, and later in liver. These result in, sequentially, decreased peripheral glucose uptake and augmented endogenous glucose production. The abnormal intracellular signaling defects involved in insulin resistance were described, involving the insulin receptor substrate (IRS)-1 and phosphoinositol (PI)-3

kinase pathway, which are linked to the movement of glucose transporters to the cell surface, their site of action. In contrast, the insulin-stimulated mitogen-activated protein (MAP)-kinase pathway is spared, which may trigger inflammatory and pro-atherogenic events.

Dr. DeFronzo next described the major pancreatic β -cell defects involved in the progression from insulin resistance to Type 2 diabetes. This series of experiments employed the disposition index, a quantitative measure describing the relationship between β -cell secretion and insulin sensitivity. These studies demonstrated that by the time a patient develops impaired glucose tolerance—and certainly by the time they progress to diabetes—up to 80% of β -cell function has been lost. Such β -cell defects appear to result from both environmental and genetic influences. The recent discovery of polymorphisms within the TCF7L2 gene that predict the development of β -cell failure is an exciting, related area of clinical investigation.

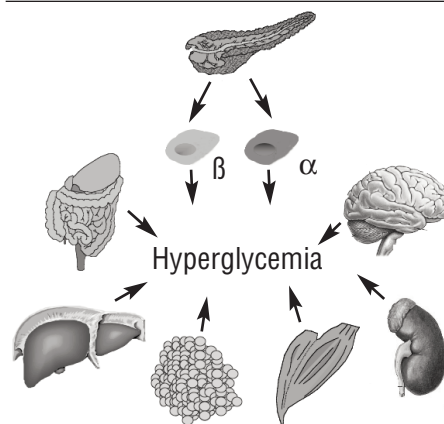
Another component of the pancreatic islets, namely the α -cell, responsible for glucagon secretion, also appears to be abnormal in patients with Type 2 diabetes. As a result, post-prandial secretion of glucagon is increased, further driving hepatic glucose production.

The important role of the adipocyte was also discussed. Increased lipolytic activity from fat stores results in higher circulating free fatty acid levels. 'Lipotoxicity' results, with downstream deleterious effects on both insulin secretion and action. A variety of other adipocytokines have also more recently been described, further altering metabolic processes that maintain euglycemia.

The incretin axis was next described. These gut peptides serve to modulate pancreatic insulin and glucagon secretion to lower post-prandial blood glucose concentrations. In some recent work from the DeFronzo lab, mimetics of glucagon-like peptide (GLP)-1 appear to additionally augment splanchnic (mainly hepatic) glucose extraction, further minimizing postprandial glucose excursions.

The kidney, not usually thought of in the pathogenesis of diabetes, was introduced to the

Figure 1. The "Ominous Octet" of Defects in Diabetes



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From Triumvirate to Ominous Octet

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audience as an important player in the maintenance of glucose homeostasis. This organ filters some 162 grams of glucose each day, reabsorbing essentially 100 percent of this load in euglycemic patients. Two sodium-glucose co-transporters in the nephron are responsible for this metabolic feat. These 'SGLTs' are now emerging diabetes drug targets for a possible next generation of anti-hyperglycemic therapies

(see "Not Yet Ready for Prime Time...")

Finally, derangements at the level of the hypothalamus seem to play a pivotal role in appetite dysregulation and the genesis of obesity—clearly a major risk factor for the development of diabetes.

So, the original three defects have now grown to eight—muscle, liver, β -cell, α -cell, gastrointestinal tract, fat, kidney, and brain (Figure 1). In Type 2 diabetes, these can easily be described as an "ominous octet."

Dr. DeFronzo concluded his comments by encouraging a new paradigm for the therapy of Type 2 diabetes, with early and simultaneous treatment involving metformin, thiazolidinediones, and GLP-1 agonists. Each in its own way targets the major metabolic defects of the disease. Such aggressive therapy, he feels, holds the best promise for the preservation of β -cell function and the durable optimization of glycemic control.



Not Yet Ready for Prime Time...



In a symposium entitled "New Classes of Pharmacologic Agents for the Treatment of Hyperglycemia on the Horizon," standing-room only attendees were introduced to a number of novel classes of antihyperglycemic drugs currently under investigation (Table 1). These agents all appear to reduce glucose levels through novel mechanisms, but their future role in diabetes care is unclear.

Since the inception of this newsletter, we've consistently kept our readers updated on emerging therapies for diabetes and related conditions. While some have indeed come to market, most have not. It is important to recognize the significant hurdles these compounds will encounter during drug development. The regulatory environment is getting increasingly challenging and drugs approved for the treatment of diabetes, must, at a minimum, be proven to be both efficacious and safe in large, randomized clinical trials. With increasing scrutiny of drug safety, the US Food and Drug Administration also may soon require long-term outcomes/safety trials either prior to or soon after drug approval.

Sodium-Glucose Co-transporter-Type 2 (SGLT-2) Inhibitors

Dr. Robert R. Henry of the University of California, San Diego opened the symposium by presenting information on a novel class of compounds—the renal SGLT-2 inhibitors, which are currently in development. The kidney plays a major role in glucose homeostasis, both in the filtration and ultimate reabsorption of glucose. In the proximal tubule, glucose reabsorption is mediated by two sodium-glucose co-transporters—with type 1 (SGLT-1) contributing approximately 10% and type 2 (SGLT-2) contributing approximately 90%. The rationale behind the development of SGLT-2 inhibitors is that if one can inhibit this transporter, glucose reabsorption in the nephron will be blocked, leading to glucosuria, decreases in blood glucose, and a net energy deficit. The latter

Table 1. New Classes of Pharmacologic Agents for the Management of Diabetes

<i>Compound Class</i>	<i>Mechanism of Action</i>
SGLT-2 Inhibitors	■ Partial inhibition of glucose reabsorption in proximal renal tubules
Glucokinase Activators	■ Augment insulin secretion and hepatic glucose extraction
Glucagon Receptor Antagonists	■ Reduce hepatic glucose production
Sirtuins	■ Mimic effects of caloric restriction and exercise

SGLT = sodium-glucose co-transporter.

might also result in weight loss. The concern is obviously polyuria, potential urinary tract infections, and fluid/electrolyte losses. Dr. Henry listed several SGLT-2 inhibitors currently in various stages of development, with dapagliflozin appearing to be the farthest along (Phase 2/3 trials).

In a separate session, List and colleagues from North America reported on the glucose-lowering effects of dapagliflozin (abstract 329-OR). After a two-week lead-in phase, 389 treatment-naïve patients with Type 2 diabetes were randomized in equal ratios to once-daily dapagliflozin (2.5, 5, 10, 20, or 50 mg), metformin XR 750 mg titrated to 1,500 mg, or to placebo, each administered for 12 weeks. As compared to placebo, treatment with all doses of dapagliflozin was associated with significant reductions from baseline in HbA1c (ranging from -0.55 to -0.90% across the dapagliflozin dosages compared with -0.18% with placebo, $p < 0.01$ for all comparisons). The investigators did not statistically compare the changes in HbA1c of dapagliflozin with that produced by metformin (mean HbA1c change from baseline of -0.73%), but these appeared comparable. Laboratory analyses of patients treated with the SGLT-2 inhibitor revealed 0.1 to 0.2 mEq/l increases from baseline in mean serum magnesium across all doses and a 0.2 mg/dl increase from baseline in mean serum phosphate at the higher doses. Decreases in serum uric acid of approximately 1.0 mg/dl were also observed in all dose groups. The most common adverse

events in dapagliflozin-treated patients were urinary tract infection, nausea, dizziness, headache, fatigue, back pain, and nasopharyngitis. The rate of hypoglycemic events with dapagliflozin was similar to that with metformin, but greater than that observed in placebo-treated patients.

Glucokinase Activators

In the second presentation of the symposium, Dr. Daryl Graner of Vanderbilt University in Nashville discussed the mechanism of action of glucokinase activators, currently in Phase 1/2 trials. Glucokinase is the smallest member of 4 hexokinase family compounds. This enzyme plays a key role in glucose regulation, acting as a glucose sensor in both the β -cell as well as the liver. Studies of Type 2 diabetes patients have found levels of glucokinase activity to be approximately 50% lower than that of non-diabetic individuals. These reduced levels may result in the impaired hepatic glucose uptake and reduced insulin secretion seen in Type 2 diabetes. Therefore activating glucokinase may result in improved β -cell function, insulin secretion, and net reduction in hepatic glucose output. Pharmacologic activators of this enzyme represent an interesting therapeutic strategy.

In a later presentation, the acute glucose lowering effects of a glucokinase activator currently under development (RO4389620) was discussed by Bonadonna and colleagues of Italy, Germany, America, and Switzerland (abstract 332-OR). In a

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randomized, double-blind, three-period crossover study, 15 patients with diet-treated Type 2 diabetes (age 51 ± 2 years, BMI 29.2 ± 0.9 kg/m²) were given a single oral dose of R04389620 25 mg or 100 mg, or placebo at 120 minutes prior to an oral 75 gram radio-labeled glucose load. In the R04389620 phases of the study, glucose concentrations during the oral glucose tolerance test (OGTT) were lower (mean difference over five hours and corrected for fasting glucose as compared to placebo were -19 ± 5 mg/dl with the lower dose and -42 ± 5 mg/dl with the higher dose, $p < 0.001$). Using mathematical modeling of the OGTT plasma glucose and C-peptide concentration curves, the investigators observed that the sensitivity of β -cells to both glucose levels ($p < 0.01$) and their rate of change ($p < 0.02$) was significantly higher with the glucokinase activator as compared to placebo. Potential hypoglycemia would be one concern with this compound.

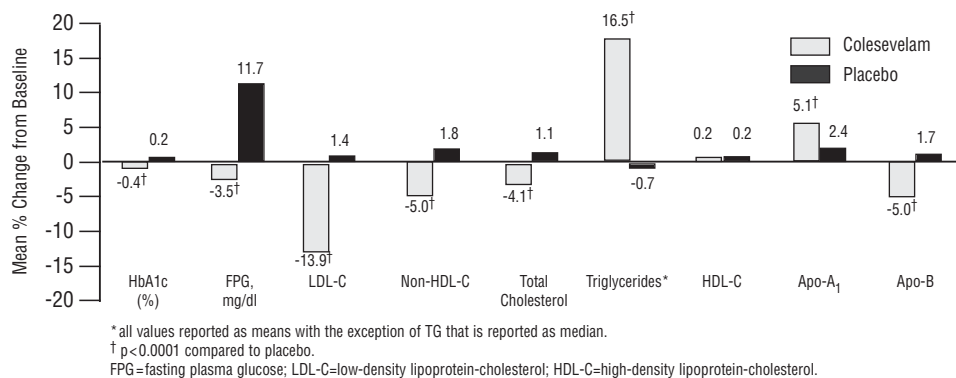
Glucagon Receptor Antagonists

The third presentation of the symposium was by Dr. Kitt Petersen of Yale University who described the glucagon receptor antagonist class of antihyperglycemic agents. Like the glucokinase activators, the glucagon receptor antagonists are currently in Phase 1/2 trials. Through a review of studies, Dr. Peterson established that increased hepatic gluconeogenesis is responsible for increased glucose production in those with Type 2 diabetes. In these patients, glucagon production, which stimulates both glycogenolysis and gluconeogenesis, is relatively increased. Therefore, glucagon receptor blockade may decrease the actions of glucagon and theoretically lower serum glucose concentrations. To date, however, these compounds have only been studied in animals (*ie*, diabetic rodents) and healthy male subjects.

Sirtuins

In the final presentation of the symposium, Dr. David Sinclair of Harvard Medical School discussed the sirtuins. It has been known for quite some time that caloric restriction and exercise are associated with an increase in lifespan. This effect appears to require a family of proteins known as sirtuins. There are seven sirtuins in humans and their concentrations have also been associated with increased lifespan and improved metabolic efficiency. As many an oenophile may recall, approximately five years ago, the compound resveratrol—which activates endogenous sirtuins—was isolated from red wine. Since that time, over

Figure 2. Mean Percentage Change in Glycemic and Lipid Measures



500,000 sirtuin-like or sirtuin-stimulating compounds have been screened, with one currently in Phase 2 trials. In animal models, the administration of resveratrol was found to have strikingly favorable effects on lifespan as well as on several metabolic and cardiovascular (CV) parameters. These compounds may have a future role in the treatment of patients with Type 2 diabetes and other metabolic conditions.

Binding Resins

In a pilot study, oral administration of the bile-acid sequestrant colesevelam HCl, either once- or twice-daily, improved lipid profiles and reduced HbA1c and fasting plasma glucose (FPG) levels in patients with Type 2 diabetes. These findings have recently been confirmed in three double-blind, placebo-controlled studies, with results of a pooled analysis presented by Jaiil and US colleagues (abstract 459-P). In the study endpoint analysis, the administration of colesevelam either to a current regimen of metformin-, insulin-, or sulfonylurea-based therapy was associated with significant reductions in HbA1c and FPG as well as improvements in several lipid parameters, including LDL-cholesterol, as compared to placebo ($p < 0.0001$ for all comparisons except HDL-cholesterol, Figure 2). Of note, however, colesevelam was associated with significant increases in triglycerides as compared to placebo. This drug, which has been on the market for years as a lipid lowering binding resin, was recently approved to lower glucose in patients with Type 2 diabetes.

11 β -Hydroxy-steroid Dehydrogenase Inhibitors

A novel, selective inhibitor of 11 β -hydroxy-steroid dehydrogenase Type 1 (11 β HSD1) was studied by Hawkins and US colleagues (abstract 344-OR). Activation of this enzyme in fat cells, which locally converts cortisone (which has little glucocorticoid activity) to the more active cortisol,

has been implicated in the pathogenesis of the metabolic syndrome and Type 2 diabetes. Following a 14-day washout of prior anti-hyperglycemic medications, the investigators administered 100 mg of the 11 β HSD1 inhibitor twice daily for 28 days to 30 overweight/obese patients between the ages of 40 and 68 years with Type 2 diabetes. Insulin sensitivity and fasting metabolic status were assessed at the end of the washout and at the end of the 28-day treatment period. Stepped hyperinsulinemic, euglycemic, pancreatic clamp studies were used to optimally assess hepatic and peripheral insulin sensitivity under fixed hormonal conditions. From a baseline insulin-suppressed endogenous glucose production of 0.924 mg/kg/min in evaluable subjects, 11 β HSD1 inhibitor treatment enhanced the ability of insulin to suppress glucose production and to increase insulin-stimulated glucose uptake. Lipid profiles also improved with treatment (LDL-cholesterol decreased 20.1 mg/dl, total cholesterol decreased 24.7 mg/dl). These results suggest that this novel pharmacologic agent enhances hepatic and peripheral insulin sensitivity, with a potential role in insulin-resistant patients. Effects on the hypothalamic-pituitary-adrenal axis will need to be further investigated.

Addressing the Neurochemistry of Obesity

The control of appetite is enormously complex, involving multiple, redundant neural circuits that are just beginning to be understood. It is apparent that the development of effective pharmacological weight-loss medications will likely involve combinations of therapies to simultaneously address several of these. Trevaskis and California colleagues characterized the metabolic effects of dual and triple peptide treatment regimens in diet-induced obese rats (abstract 192-OR). The dual therapies were: amylin + leptin, amylin + pancreatic polypeptide (PPY)(3-36), and leptin +

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PPY(3-36); the triple therapy regimen consisted of all three peptides. After four weeks, the greatest weight loss was observed in animals administered the triple regimen. In their analysis of hepatic genes involved in energy utilization, the investigators found reduced levels of several lipogenic genes, suggesting that improvements in certain hepatic metabolic factors may be in part responsible for the favorable weight changes observed.

Anti-inflammatory Agents

Evidence suggests that the CV complications associated with diabetes may be due to, in

part, abnormalities in inflammatory response and oxidative signaling. Investigators at this week's meeting offered information on newer agents that may address some of these abnormalities. Emerging evidence seems to indicate that abnormalities in the inflammatory response may also play a role in the progression from the dysmetabolic state to Type 2 diabetes. Tardif and international colleagues reported potentially promising findings on the use of anti-inflammatory/anti-oxidative therapy on the development of Type 2 diabetes (abstract 355-OR). In the ARISE (Aggressive Reduction of Inflammation Stops Events) trial, 6,144 patients (37% with confirmed Type 2 diabetes at baseline) who had acute coronary syndrome within the prior year were randomized

to a novel anti-inflammatory/anti-oxidant compound (succinobucol) 300 mg/day or placebo, each in addition to their standard treatment. For the patients without diabetes, those randomized to succinobucol had a significantly lower incidence of new Type 2 diabetes (1.6% [30/1923] vs. 4.2% [82/1950]; hazard ratio [HR] = 0.37, 95% CI 0.32,0.42; $p < 0.0001$). Of note, the investigators also found that succinobucol treatment was associated with a reduced rate of CV death, cardiac arrest, myocardial infarction (MI), and stroke (-19%, $p = 0.029$) compared to placebo. However, higher rates of atrial fibrillation were seen with active therapy, which also resulted in diarrhea in nearly one in four patients.



Micro-Trends



The effects of hyperglycemia on the microvasculature of patients with diabetes are well established. According to widely reported statistics, nearly all patients with Type 1 diabetes for 20 years have at least some degree of retinopathy and up to 20% of those with Type 2 diabetes already have retinal involvement at the time of diagnosis. Patients' susceptibility to retinopathy is clearly linked to the duration of diabetes and the quality of blood glucose control. Several studies presented at this week's Scientific Sessions expand our understanding of the microvascular complications of diabetes.

In a study of 624 patients with Type 2 diabetes for 20 to 30 years, Wong and colleagues of Australia found that earlier age at Type 2 diabetes diagnosis was associated with increased risk for retinopathy when stratified by mean HbA1c level and controlled for duration of diabetes (abstract 833-P).

Hypertension has previously been associated with retinopathy. Blood pressure (BP) fluctuations may be particularly injurious, according to Brazilian investigators, specifically during the late afternoon/evening period (4 to 8 pm). In a cross-sectional study Kramer *et al.* found that diabetic patients with, as compared to those without, retinopathy had higher incremental systolic BP (11.3 ± 12.7 vs. 1.0 ± 11.4 mmHg, $p=0.006$) and diastolic BP (6.7 ± 8.6 vs. -0.73 ± 10.0 mmHg, $p=0.017$) (abstract 830-P). After adjustments for HbA1c, diabetes duration, age, renal function, and current smoking status, each 1 mmHg increase in late afternoon/evening BP was associated with a striking 10.2% increase in the prevalence of diabetic retinopathy (odds ratio [OR] 1.1, [1.011, 1.202], $p=0.027$). The underlying mechanisms of this association remain nebulous.

Diabetes is also the most common cause of renal failure, accounting for nearly one-half of new cases. While microalbuminuria has long been considered the initial, clinically measurable sign of renal disease, there are a multitude of factors that contribute, not necessarily manifesting with increased urinary protein excretion. In a study of 562 Korean patients with Type 2 diabetes by An and colleagues of the Republic of Korea, the prevalence of normoalbuminuria among 151 patients with renal insufficiency (defined as glomerular filtration rate [GFR] <60 ml/min/1.73m²) was 29% (abstract 743-P). Normoalbuminuric renal insufficiency was associated with female gender, lower HbA1c, lower prevalence of hypertension, and diabetic retinopathy. Increasing duration of diabetes was actually associated with decreased prevalence of normoalbuminuric renal insufficiency ($p=0.014$). One might speculate that atherothrombotic disease may play a role in this form of chronic kidney disease. These interesting data need to be further explored in a Western population.

The importance of progressive renal disease as a risk factor for CV complications is now well accepted. As a measure of mortality, Hoefield and coworkers of the United Kingdom found estimated GFR (eGFR) and albumin:creatinine ratio (ACR) to be independent predictors of MI and mortality in diabetic patients (mortality OR 2.4 in those with eGFR >60 ml/min and ACR >3.5 mg/mmol; OR 2.2 in those with eGFR <60 ml/min and ACR <3.5 mg/mmol, and OR 4.8 in those with eGFR <60 ml/min and ACR >3.5 mg/mmol, $p < 0.001$ as compared to those with eGFR >60 ml/min and ACR <3.5 mg/mmol) (abstract 740-P).

On the brighter side, intensive therapies for BP and glucose control appear to delay the

onset and progression of renal complications. This may in part be responsible for some encouraging trends towards decreasing percentages of Americans with end-stage renal disease (ESRD) attributable to diabetes. Rutledge and American colleagues analyzed data from the Epidemiology of Diabetes Intervention and Complications (EDIC) study (the observational extension of the Diabetes Control and Complications Trial [DCCT]) (abstract 311-OR). They specifically examined the effect of prior intensive diabetes treatment on the incidence of kidney disease 11 to 12 years following completion of the DCCT. Those assigned to intensive glycemic therapy continued to enjoy a reduced overall incidence of renal disease at the end of follow-up; however, the protective effects of intensive therapy as compared to conventional therapy occurred only during years 1 to 8 of EDIC (relative risk [RR] reduction 53% for microalbuminuria), with no additional benefit during years 9 to 12 of follow-up (RR increase of 35% for microalbuminuria). This may be a manifestation of worsening glucose control over time in the initially aggressively treated DCCT cohort once they were transitioned into EDIC. Logically, good glucose control needs to be continued for sustained microvascular protection.

The reports of a decreasing incidence of ESRD in patients with diabetes were confirmed in an analysis of data from the United States Renal Data System by Burrows and colleagues from Georgia (abstract 266-OR). The investigators found that between the years of 1990 and 1996, the crude incidence increased significantly (from 285.4 to 421.8 per 100,000 persons, $p < 0.001$). An increase was also observed in the age-adjusted incidence, although it was not statistically significant.

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This incidence, however, dropped between 1996 and 2005 (from 343.0 to 201.1 per 100,000 persons with diabetes, $p < 0.001$), at a rate of approximately 4.3% per year. When analyzed by age categories, the data indicated that the incidence of



ESRD in diabetic patients 75 years of age or older increased between 1990 and 1999, and then was stable between the years 1999 and 2005 ($p = 0.34$). More importantly, the incidence of ESRD attributed to diabetes in all other age categories declined between 1996 to 2005 with annual rates

of decline of: 4.1% in those less than 45 years of age ($p < 0.001$), 4.4% in those 45 to 64 years ($p < 0.001$), and 3.0% in those 65 to 74 years ($p = 0.02$). Accordingly, it is quite likely that our (and our patients') concerted efforts to control BP and glycemia is paying off substantially.



What the Dickens?

The name, Pickwickian Syndrome, describing patients with obesity and sleep disordered breathing, was based on a historical reference to a character in Charles Dickens' *Pickwick Papers*. This very common condition has received a significant amount of recent attention especially for its metabolic and CV implications. A task force of the International Diabetes Federation (IDF) was recently convened to evaluate the literature in this area as it applies to the diabetic patient and to make recommendations for treatment and future research initiatives. During the ADA Scientific Sessions this week, Dr. Paul Zimmet of Australia presented the findings of the task force, which resulted in a consensus statement on links between obstructive sleep apnea (OSA)—the most common form of sleep-disturbed breathing—Type 2 diabetes and cardiovascular disease (CVD) (Shaw *et al.*, *Diabetes Res Clin Pract* 2008).

By way of background, Zimmet began his talk by defining OSA for the audience: a sleep disorder characterized by interruptions of airflow (apneas) or by a decrease in airflow (hypopneas) of at least 10 seconds associated with either arousal from sleep or a blood oxygen desaturation. He mentioned that many patients affected by OSA

are unaware of their breathing difficulties, which often come to light only when habitual snoring and/or episodes of apnea (Table 2) are witnessed by another person (*ie*, sleep partner) or suspected because of residual effects, such as daytime sleepiness and fatigue.

Zimmet then emphasized that OSA is commonplace, especially among individuals with Type 2 diabetes, CVD, and/or obesity. While obesity, particularly central obesity, is the strongest risk factor, emerging evidence suggests OSA may be independently associated with Type 2 diabetes, insulin resistance, and metabolic syndrome (independent of obesity). Several biological mechanisms may be involved (Figure 3) (Zimmet ADA 2008).

The IDF task force recommended that persons with OSA be evaluated for a co-existing metabolic disorder. The screening tests include measurements of waist, BP, fasting lipids, and glucose. Likewise, patients with diabetes should be screened for OSA, especially those who present

with the primary symptoms (Table 2). Diagnosis can be confirmed in a sleep laboratory or by simpler home monitoring devices where facilities are limited. On the treatment front, available therapies include weight loss in those who are overweight or obese, reduction in alcohol intake, Continuous Positive Airway Pressure (CPAP), and/or dental appliances. Treatment of OSA has beneficial effects on quality of life and BP control; favorable results on glucose control, obesity, and other risk factors have not been consistently observed.

The task force also recommended that all healthcare professionals caring for patients with diabetes and/or OSA be educated about associations between the conditions and trained in their care. They also made specific recommendations for research in the areas of: epidemiology, effects of OSA on insulin resistance/secretion and complications of Type 2 diabetes, intervention studies (CPAP, weight loss, etc) and, resource development (*eg*, reliable and inexpensive diagnostic tool for use in a primary care setting).

Table 2. Symptoms of Sleep Apnea

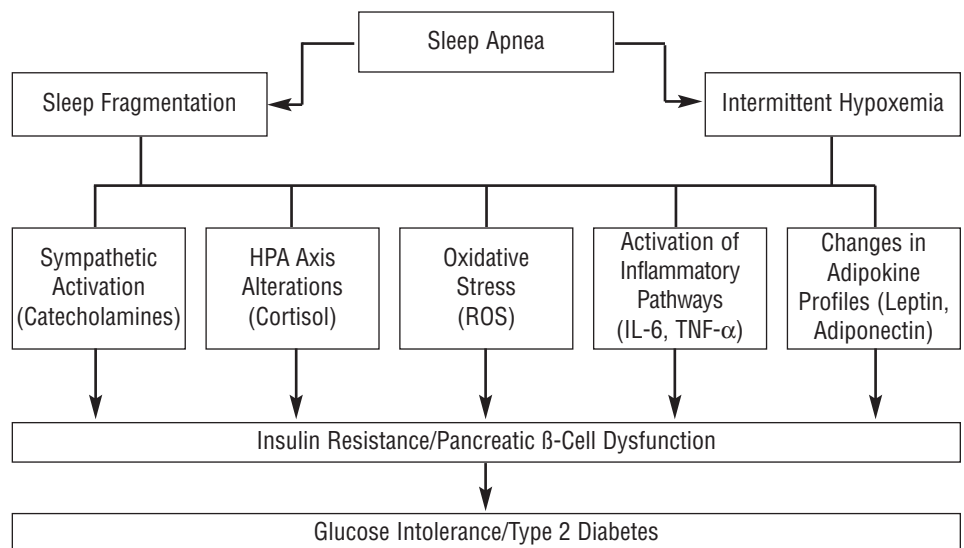
Primary Symptoms

- History of habitual snoring
- Witnessed apneas
- Excessive daytime sleepiness

Other Symptoms

- Fatigue, loss of energy
- Irritability
- Poor memory
- Depression
- Mood changes
- Morning headaches
- Sexual dysfunction
- Nocturia

Figure 3. Potential Mechanisms Linking Sleep Apnea to Glucose Intolerance



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