Diabetes2007

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Important data on diabetes presented at the 43rd Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2007**, 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., Merck & Co., Inc., Novo Nordisk Inc., and Amylin Pharmaceuticals, Inc./Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2007** will be followed by a **Diabetes 2007** booklet (EASD and AHA 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 2007 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 Heart of Diabetes

The vast majority of the excess mortality associated with diabetes is the result of cardiovascular diseases (CVD). As a result, the association between diabetes and atherosclerosis and its outcomes continues to garner much interest at international medical meetings.

HbA1c as Prognosticator

van't Riet *et al*. from the Netherlands examined the relationship between HbA1c and CVD in non-diabetic patients followed in the population-based Hoorn Study (abstract 31), which involves 2,484 participants examined initially between 1989-90. This investigation focused on the 1,674 individuals without diabetes at baseline. Using Cox survival analysis, associations were assessed using HbA1c as a continuous variable. The age- and sex-adjusted hazard ratios (with 95% CIs) for all-cause mortality, CVD morbidity, and CVD mortality ranged between 1.37 and 2.00 for every 1% increase in HbA1c (Table 1). After adjustment for traditional cardiovascular risk factors, the association between non-fatal CVD and the composite of fatal and non-fatal CVD and HbA1c remained significant, with 60% increase in risk for each 1% increase in HbA1c.

In a related presentation, Foody *et al*. from the US performed a retrospective analysis of an integrated healthcare database involving 69,418 patients with diabetes and at least one HbA1c level (abstract 97). Demographic, comorbidity, and health utilization information were collected during the six month period prior to the index HbA1c level. Survival analysis was conducted to examine the first occurrence of acute myocardial infarction (AMI), coronary artery bypass graft (CABG) surgery, or stroke. The cohort was 54% male, with a mean age of 57 years and a mean HbA1c of 7.6%. Four groups were created for the analysis, based on HbA1c: <6.0%, 6.0-7.0%, 7.0-9.0%, and ≥9.0%. With a mean follow-up of 27 months, unadjusted incidence rates in the four groups were 76.5, 80.5, 81.7, and 65.2 per 1,000 patient/years, respectively. After adjustment for comorbidities, diabetes medications, selected lipid lowering and blood pressure control agents, and laboratory values at baseline, high HbA1c remained a significant predictor of macrovascular events. In a Cox proportional hazards regression model, compared to the <6% group, hazard risk for AMI/CABG/stroke was 8% higher in the HbA1c 7-9% group ($p<0.01$) and 15% higher in the ≥9% group ($p<0.001$). Therefore, HbA1c appears to predict increased cardiovascular risk in both diabetic and non-diabetic patients.

Glycemic Therapy and CVD Outcomes

The relationship between antihyperglycemic therapy and cardiovascular risk is an area of great interest. Sun and American colleagues examined the prevalence of CVD and the use of insulin among patients with Type 2 diabetes in a retrospective, observational study using a managed care database involving in excess of 70 million covered lives

Table 1. Risk of Morbidity and Mortality in Relation to Each 1% Increase in HbA1c

	*Model 1**	*Model 2†*
All-cause mortality	1.37 (1.05-1.80)	1.20 (0.91-1.57)
Fatal CVD	1.62 (1.09-2.41)	1.26 (0.84-1.88)
Non-fatal CVD	2.00 (1.56-2.57)	1.66 (1.28-2.13)
Fatal and non-fatal CVD	1.94 (1.54-2.43)	1.60 (1.27-2.01)

Note: Data presented as Hazard Ratio (95% CI).

* Adjusted for age and sex.

†Adjusted for age, sex, hypertension, smoking, LDL-cholesterol, triglycerides, and waist-to-hip ratio.

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(abstract 99). The study population included 357,655 patients with Type 2 diabetes who continuously enrolled in health plans for at least one year during a seven-year period between 1998 and 2004. A diagnosis of CVD encompassed unstable angina, myocardial infarction, stroke, other cardiac events, and other cerebrovascular events, all identified based on ICD-9CM codes. A logistic regression model was used to examine the odds ratio of having CVD between insulin users and non-users, controlling for age, gender, income, race, residential regions, provider specialties, various co-morbid conditions, medication history, baseline HbA1c level, and the length of observation. The odds ratio (OR) for CVD events was lower in insulin users (0.66 [95% CI 0.62, 0.72], p<0.0005). The investigators concluded that the risk of having any CVD among Type 2 diabetes patients using insulin was 34% lower than that among these patients not using insulin. These are provocative results, given the anticipation that insulin therapy would denote a more advanced group of patients who would have an increased risk of vascular disease.

In a matched case-control study, Sadikot *et al.* from India explored the risk of coronary artery disease (CAD) associated with sulfonylurea therapy in 2,733 patients with Type 2 diabetes free of CAD at baseline (abstract 341). This has always been a controversial area, beginning with the UGDP study in the 1970s. That randomized clinical trial found increased cardiovascular mortality in patients treated with sulfonylureas versus insulin and resulted in a "black box" warning for all members of this class. These agents bind to ATP sensitive potassium channel receptors in pancreatic beta cells, thereby stimulating insulin release. Binding to similar receptors in the heart could prevent ischemic preconditioning, a self-protecting mechanism of the myocardium to reduce energy requirements during ischemic injury. However, newer sulfonylureas don't bind as avidly to cardiac potassium channels. Moreover, in the UKPDS, and more recently in the ADOPT study, the use of sulfonylureas was *not* associated with increased cardiovascular events. The purpose of the Sadikot study was to assess the association between different initial sulfonylurea treatment and the subsequent development of CAD in patients with Type 2 diabetes. From the original cohort, 76 developed clinical CAD; 152 matched controls were identified from the remaining patients, based on the UKPDS cardiac risk engine score. The hazard of developing CAD increased by 2.4, 2.0, and 2.9 fold with glibenclamide, glipizide, and either of these older sulfonylureas, respectively, but was

Table 2. Risk of Developing Coronary Artery Diseases According to Initial Oral Hypoglycemic Treatments in Type 2 Diabetes

Initial drug		*Cases with CAD (n=76)*	*Controls without CAD (n=152)*	*OR (95% CI)*	*p-value*
Glibenclamide	Yes	31	34	2.4 (1.3-4.3)	0.004
	No	45	118		
Glipizide	Yes	12	13	2.0 (0.9-4.6)	0.099
	No	64	139		
Glimepiride	Yes	7	20	0.7 (0.3-1.7)	0.385
	No	69	132		
Gliclazide	Yes	11	33	0.6 (0.3-1.3)	0.192
	No	65	119		
Older agents (Glibenclamide or Glipizide	Yes	43	47	2.9 (1.6-5.1)	0
	No	33	105		
Newer agents (Gliclazide or Glimepiride)	Yes	18	53	0.6 (0.3-1.1)	0.09
	No	58	99		
Metformin	Yes	19	37	1.0 (0.5-2.0)	0.913
	No	57	115		

CAD = coronary artery disease.

decreased by 30-40% with glimepiride, gliclazide, and either of these newer sulfonylureas, respectively (Table 2). Such dramatic differences are surprising. We wonder whether they may reflect other factors not adequately captured by the matching methodology (e.g., site of care, years of diabetes, concurrent medications used, lipid and blood pressure treatment results over time, etc.).

However, Danchin and French collaborators asked a similar question using the nationwide FAST-MI registry (abstract 874) and came to a similar conclusion as Sadikot. The impact of sulfonylurea type on six-month mortality was assessed in Type 2 diabetes patients presenting with myocardial infarction. In the 1,316 patients, three groups were defined according to their antidiabetic treatment before admission: no sulfonylurea (SU) (n=851), glibenclamide (a drug very similar to glyburide in the US) (SU1, n=120), and newer SUs (glimepiride/gliclazide, n=339) (SU2). Age, cardiac risk factors, time from symptom onset to admission, and time to reperfusion were similar among the three groups. Five-day mortality was 5.3% in those on no SU, 2.5% in SU1, and only 0.9% in SU2 (p<0.001). Six-month mortality was also significantly higher in no SU (18.3%) and in SU1 patients (13.4%), as compared to SU2 (8.7%) (p<0.001). Mortality was the lowest in SU2, both in those on metformin or insulin and in those not receiving these medications. Using Cox multivariate analysis, with adjustments for other baseline diabetes drugs, the odds ratio for six-month mortality versus patients without SU was 0.82 (95% CI 0.47-1.43, p=NS) for SU1, and 0.42 (95% CI 0.27-0.65, p<0.001) in patients on SU2.

A Comprehensive Strategy

The Steno Diabetes Center trial demonstrated that a comprehensive approach to risk factor management could reduce vascular disease risk by more than 50%. The original study was conducted in 160 patients with Type 2 diabetes and microalbuminuria followed for a mean of 7.8 years. At the end of the randomized trial, the 130 surviving patients were offered intensified multitherapy and followed until the end of 2006. During the entire 13.3 year follow-up period, 24 patients in the intensive therapy group died compared to 40 patients originally assigned to conventional therapy. Intensive therapy reduced the risk for total mortality by 46% (95% CI, 11 to 68%; p=0.015), corresponding to an absolute risk reduction of 30%. Cardiovascular mortality was reduced by 57% (6 to 81%, p=0.036), a 13% absolute risk reduction. The composite of CVD mortality, myocardial infarction, stroke, CABG, revascularization, or amputation was reduced by 59% (37 to 75%, p=0.0003) with an absolute risk reduction of 29%. These differences were demonstrated despite significant improvements in metabolic parameters in the original conventional therapy group. By the end of the study, the two groups were essentially identical in risk factor goal attainment. These data are similar to those reported by the Diabetes Control and Complications Trial (DCCT) study group in Type 1 diabetes patients.

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Heart Failure

From Spain, Flores *et al*. conducted a prospective study of 410 patients admitted to a heart failure unit, comparing their five-year mortality outcomes based on their diabetic status (abstract 1229.) Patients were distinguished into three groups—those without diabetes, those with known diabetes, and those whose diabetes was detected during the hospitalization (undiagnosed diabetes). Overall the prevalence of diagnosed diabetes was 37% and undiagnosed diabetes, 16%.The proportion of patients treated with ACE inhibitors, ARBs, beta-blockers, spironolactone, diuretics, and anti-thrombotic agents was similar among the three groups. All patients with diabetes (i.e., both diagnosed and undiagnosed) were more likely to be readmitted for CVD during the one year period (43.0% and 41.8% vs. 33.2% p<0.01). One-year mortality rate in all diabetic patients trended higher as compared to non-diabetics (19.3-21.8% vs. 13.1%, p=NS). Five-year mortality rates were higher in the undiagnosed diabetes group (66.7%) than non-diabetics (40.7%, p<0.01). Mortality in the former group was also numerically higher when compared with the diagnosed diabetics, but the difference was not statistically significant. The investigators concluded that undiagnosed diabetes occurs in one out of every six patients hospitalized for heart failure and is associated with a five-year mortality that is nearly two-fold that in non-diabetic patients. Further study of this population is clearly warranted.

Stroke: The Other Cardiovascular Disease

Stroke is a cardiovascular outcome not as well studied as myocardial infarction. Nonetheless, many of the same factors that increase coronary heart disease (CHD) risk do the same for stroke (hypertension, diabetes, hyperlipidemia, smoking). Impaired glucose tolerance (IGT) is now a well-established risk factor for CAD. Oizumi and Japanese collaborators asked whether the same relationship applied to stroke (abstract 288).This is an important question, since a high prevalence of IGT has been reported in recent stroke patients. The investigators conducted a cohort study consisting of the participants of the Funagata study, a community-based study, to determine whether or not IGT is a risk factor for stroke.

The prevalence of stroke and CHD in the original Funugata participants (1990-1997) was assessed by studying questionnaires, death certificates, and residence transfer documents through 2002. Glucose tolerance at baseline was classified using conventional criteria. 2,189 were found to have normal glucose tolerance (NGT), 320 had IGT, and 286 had diabetes. The cumulative incidences among the groups were compared using the Kaplan-Meier method and Cox's proportional hazard models. During a mean follow-up duration of 116.5 months, stroke or CHD was diagnosed in 158 and 94 participants, respectively. Stroke risk was significantly higher in those with IGT (adjusted hazard ratio [HR] 1.51, 95% CI 1.02-2.24; p=0.039) and tended to be higher in those with diabetes (HR 1.47, 95% CI 0.96-2.25; p=0.079) than it was in those with NGT. In this cohort, there was no significant association between IGT and the risk of CHD (HR 1.21, 95% CI 0.69-2.13; p=0.509), while diabetes was a significant risk factor (HR 1.97, 95% CI 1.18-3.28; p=0.010). Thus, in a Japanese population, IGT appears to be an independent risk factor for stroke, an association that appears as strong as that for diabetes. This study did not distinguish ischemic from hemmorhagic stroke, which would have been interesting.

Our improved understanding of the interrelationships between diabetes and atherosclerosis will hopefully lead to new and better treatment strategies. All of our diabetic patients, particularly those at the highest cardiovascular risk, will likely benefit as a result.

"DM Bones, DM Bones..."

The primary organs mentioned in any discussion of diabetes include the pancreas, liver, skeletal muscle, adipose tissue, and the heart. But the skeleton? There is actually increasing interest in the fascinating interface between bone and intermediary metabolism. For example, it is now recognized that insulin has anabolic effects in bone, although clearly to a lesser degree than the structurally similar peptide, insulin-like growth factor (IGF)- 1, which is under the control of pituitary growth hormone secretion. Receptors for both main incretins—glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)—have been demonstrated in bone cells. These intestinal peptides function mainly to reduce post-prandial glucose excursions, but there is emerging evidence that they may have a anti-resorptive effect in the skeleton as well. The risk for both Type 1 and Type 2 diabetes is associated with deficiency in vitamin D, which is essentially a hormone, having major effects on maintaining calcium homeostasis, and as a result, bone health. PTHrP, the peptide responsible for most cases of humoral hypercalcemia of malignancy and which has a significant role in developing bone, appears also to regulate pancreatic islet cell growth. Osteocalcin, an osteoblast-derived peptide, was recently shown (at least in an animal model) to affect glucose levels. Thus, at a basic science level, there is increasing interest in these apparently pervasive, although previously unrecognized, relationships.

At a clinical level, the effect of diabetes on bone health has been controversial, with some studies suggesting no significant impact but others revealing increased fracture rates. Obese individuals are known to have increased bone mineral density (BMD)—an association previously thought to offer bone protection in patients with Type 2 diabetes. It is now clear, however, that while BMD is a major predictor of fracture risk, other patient features including age, physical conditioning, and neuromuscular status also play important roles. In patients with diabetes, sedentary lifestyle, deconditioning, peripheral neuropathy, hypoglycemic episodes, and even nocturia may each increase fall risk. In addition, the degree of bone turnover, especially in postmenopausal women, and the somewhat elusive skeletal feature referred to as "bone quality" are both critical determinants of facture risk. In poorly controlled patients, increased urinary calcium losses (with resultant secondary hyperparathyroidism) and hypogonadism may increase bone turnover; microvascular disease and increased glycosylation of collagen, related to hyperglycemia, may worsen bone quality. So, a comprehensive assessment of the diabetic patient would suggest an overall increased fracture risk. Several prospective series have confirmed this, at least in older women. Fracture rates are particularly higher at the hip, humerus, and foot.

The recent finding that thiazolidinediones (TZDs) may confer further increased fracture risk in diabetes has raised some concern. Kahn *et al*. (abstract 77) examined the incidence of fractures in women who received rosiglitazone, metformin, or glyburide in ADOPT (A Diabetes Outcome Progression Trial), a clinical trial of initial monotherapy in subjects with newly diagnosed Type 2 diabetes (median follow-up=4 years). The investigators reported at least one fracture in 111 (of 1,840) women (rosiglitazone, n=60: 9.3% incidence, 2.74/100 patient-years; glyburide, n=21: 3.5%, 1.29/100 patient-years; metformin n=30: 5.1%,

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1.54/100 patient-years). The HR ratio (95% CI) for rosiglitazone vs. glyburide was 2.13 (1.30, 3.51) and for rosiglitazone vs. metformin was 1.81 (1.17, 2.80). The cumulative incidence in each therapy group appeared similar for approximately one year post-randomization with divergence in the rosiglitazone-treated women (but not men) beyond that point. The majority of fractures observed in women who received the TZD during ADOPT were in the upper arm (humerus, n=5), hand (n=8), or foot (n=22)—not typically osteoporotic fracture sites. Among all women in ADOPT, those with fracture were older (58.8±9.6 years vs. 56.2±10.3 years, $p=0.01$) and more were post-menopausal (84.7% vs. 76.1%, $p=0.04$) than those without fracture. No other differences were apparent in other baseline characteristics (ethnicity, HbA1c, fasting glucose, blood pressure, weight, BMI, smoking status) between women with or without fracture. No prior medical history or prior/concomitant medication use could be identified as a potential risk factor for fracture in this cohort.

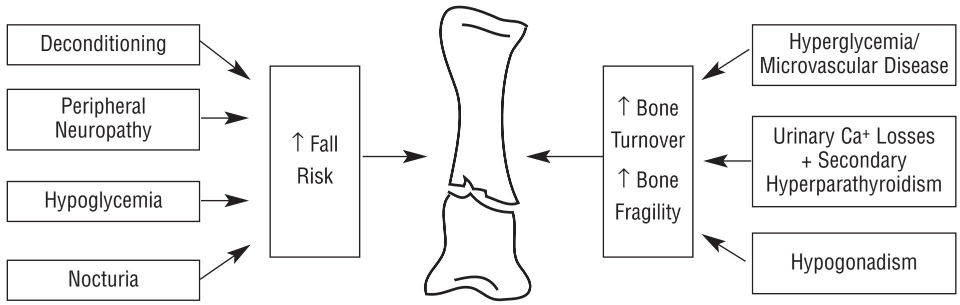
Soon after the announcement of the ADOPT fracture data, a composite analysis of patients in pioglitazone studies reported to the FDA revealed similar trends in women (1.9 vs. 1.1 fractures per 100-patient years of therapy). Clearly, this issue needs to be explored further, but it seems reasonable to advise cautious use of TZD therapy in elderly post-menopausal women with a history of osteoporosis. In addition, any woman on a TZD should follow national recommendations to preserve bone health (calcium, vitamin D intake, daily physical exercise, bone density measurement at age 65.)

In another recent twist in the curious relationship between diabetes and bone, it has emerged that markers of bone remodelling may provide an index of the risk for silent myocardial ischemia (SMI). Osteoprotegrin (OPG) is a member of the tumor necrosis factor family and a key factor in bone remodelling. OPG has recently been shown to be an independent predictor of angiographically diagnosed, but yet asymptomatic CAD. Extending these findings, Avignon *et al.* (abstract 1240) examined 465 consecutive diabetic patients with ≥ one additional risk factor for SMI using stress myocardial perfusion imaging. Of the patients screened 92/465 patients had a positive stress test, indicating SMI. Of six novel biomarkers measured, OPG was the only one to be associated with SMI; the relative risk (RR) of SMI for patients above the 75th percentile for OPG levels was an impressive 3.19 (95% CI, 1.99 to 5.18) in comparison to those below that percentile. In univariate analysis, the other plasma markers significantly associated with SMI were higher triglyceride levels ($p=0.04$) and lower levels of HDL-cholesterol ($p=0.02$). The association of OPG with SMI remained significant after correcting for other variables associated with CAD in the univariate analysis (RR 3.59; 95% CI 1.95-6.60; $p<0.0001$). This association of OPG with SMI was seen in men ($p<0.0001$), women ($p=0.03$), and in patients with Type 1 ($p=0.002$) or Type 2 ($p=0.0004$) diabetes. The investigators concluded that measurement of OPG may provide an improved method of identifying diabetic patients who might benefit from SMI screening.

In a related presentation Hopkins *et al.*, UK, followed a prospective cohort of subjects with Type 2 diabetes to determine factors that affect the progression of coronary artery calcium (CAC) (abstract 1241). CAC scores on electron beam computed tomography (EBCT) studies predict both abnormal myocardial perfusion and incident CVD, and has an increased prevalence in Type 2 diabetic subjects with no symptoms or history of CAD. The investigators examined 398 asymptomatic patients (mean age 52±8 years, HbA1c 8.0±1.5%) with serial EBCT (mean follow-up 2.5±0.4 years). At baseline, CAC was present in 211 patients (53%). Progression occurred in 118 (29.6%) and regression in 3 (0.8%). Age, male gender, hypertension, baseline HbA1c, baseline CAC score, IL-6, and OPG were found to be univariate predictors of progression. In a multivariate logistic regression model adjusted for baseline CAC, serum HbA1c (OR 10.5 [95% CI 2.04, 53.9], $p=0.02$), plasma OPG (OR 2.50 [1.19, 5.22], $p=0.02$), and IL-6 (OR 2.06 [1.13, 3.75], $p=0.05$) were independent predictors of progression. The researchers concluded that suboptimal glycemic control and elevated concentrations of both IL-6 and OPG are risk factors for atherosclerosis progression in Type 2 diabetes. Uniquely, OPG predicted both the extent of CAC at baseline and its subsequent progression. OPG may therefore emerge as a useful biomarker of previously unrecognized atherosclerosis in diabetes. One obvious question stemming from this study is how OPG behaves as a marker of cardiovascular events in patients with clinically overt CAD.

Clearly, there is much yet to learn about these interesting associations between diabetes, cardiovascular disease, and bone biology.

Figure 1. A Variety of Factors That May Promote Fracture Risk in Diabetes



PCOS Update

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders, affecting between 5-10% of women. It presents with hirsuitism, acne, oligomenorrhea, or infertility, and encompasses women with a varied spectrum of symptoms (see Figure 2). While PCOS is a description applying to pre-menopausal women, its metabolic implications last a lifetime, in particular the increased risk of Type 2 diabetes and CVD. Approximately one third of all women with PCOS fit criteria for the metabolic syndrome, and about 10% have diabetes.

The diagnosis of PCOS can be difficult because there is a wide spectrum of phenotypic expression, and debate still rages as to its precise definition and which criteria might satisfy the diagnosis. The NIH Consensus Criteria of 1990 is the more stringent of the two more established guidelines. It requires the presence of oligo-ovulation and either clinical features or biochemical evidence of hyperandrogenism. The Rotterdam Criteria of 2003 included more women in the diagnosis by relaxing the criteria to the presence of two out of three features: 1) oligo- and/or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism,

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PCOS Update

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or 3) polycystic ovaries by ultrasound imaging. All agree that initial evaluation must exclude other causes of oligomenorrhea and/or hyperandrogenism (ovarian or adrenal androgen-secreting tumor, congenital adrenal hyperplasia, Cushing's Syndrome, hyperprolactinemia, and exogenous androgenic steroids (Table 3). Although evidence of insulin resistance is not officially part of either set of diagnostic criteria for PCOS, it may be included in the future because it plays a significant part in the underlying pathophysiology.

The hallmark of PCOS is ovarian hypersecretion of testosterone, which is in response to dysfunctional hypothalamic gonadotropin-releasing hormone (GnRH) secretion and increased luteinizing hormone (LH) production. This leads to chronic ovulatory dysfunction and infertility. It is known that high serum insulin levels synergistically act with LH to enhance the production of ovarian androgens. Insulin also inhibits the synthesis of sex hormone binding globulin (SHBG), allowing an increased amount of free or active testosterone to circulate. For this reason, the use of insulin sensitizers that effectively decrease the amount of circulating insulin may help reverse the menstrual irregularity and infertility associated with PCOS.

Conversely, there is also evidence that high androgen levels induce insulin resistance in adipose tissue. In women with PCOS, dyslipidemia, especially increased levels of low density lipoprotein (LDL)-cholesterol are more tightly correlated to serum androgen levels than to BMI. This suggests that insulin and androgens work together, perhaps synergistically, to produce the metabolic abnormalities present in these women.

As in many metabolic diseases, it is thought that both genetic and environmental factors play roles in the pathogenesis of the syndrome. PCOS not only has major ramifications for the woman diagnosed, but it may also have significant implications for her first-degree relatives and offspring. At this week's EASD meeting, this issue was further explored by several investigative groups.

In one study, from India, Yadav *et al.* (abstract 789) looked at the mothers, fathers, sisters, and brothers (n=199) of 99 women with PCOS. Control subjects (171) had no family history of PCOS and were matched for age and BMI. Anthropometric measurements, fasting and two-hour glucose and insulin levels during an oral glucose tolerance test (OGTT), and fasting lipid profiles were checked and compiled to determine the presence of IGT, insulin resistance, and/or a diagnosis of the metabolic syndrome as defined by the NCEP-ATP III guidelines. While high prevalences of IGT and metabolic syndrome was found in both groups, the first-degree relatives of PCOS women were three times as likely to have the metabolic syndrome and twice as likely to have IGT when compared to controls. Therefore, the clinical identification of a woman with PCOS may prompt an inquiry as to diabetes risk factors in family members.

Although insulin sensitizers are not FDA-approved for use in women with PCOS, metformin has been used for years in this group to treat menstrual disorders and infertility. In addition, it is a logical choice to use in those women with PCOS who have developed diabetes. It has been demonstrated to reduce insulin resistance and may also have direct effects on ovarian function. There is less experience with TZDs in this setting, however, primarily because they are a newer drug class, are associated with weight gain, and are not to be used in women who are or may become pregnant. Nonetheless, there continues to be active investigation in this area. A pilot study reported by Lee and Chinese collaborators (abstract 863), compared the effect of combining a TZD with metformin in PCOS women. For a six month treatment period, 58 women with PCOS were randomly assigned to receive either metformin 1500 mg QD only or the combination of metformin 1500 mg plus rosiglitazone 4 mg QD. An OGTT was performed before and after the treatment period, and demonstrated a statistically significant decrease in insulin levels for both groups. However, only the combination group produced a statistically significant decrease in HOMA, a calculated measure of insulin resistance. There were no notable changes in fasting or post-OGTT glucose levels for either group. Women on combination therapy maintained their BMI during treatment. Of particular note in this study, there were six successful pregnancies with combination therapy versus two with metformin alone—an interesting observation since pregnancy may indeed be considered the ultimate demonstration of reversal of the underlying ovarian dysregulation in this syndrome. Although neither metformin nor the TZD family are approved for infertility treatment in PCOS, both have been shown to increase pregnancy rates over placebo in other trials. These data underscore the importance of starting contraception methods in any woman of childbearing years treated with an insulin sensitizing drug who does not wish to become pregnant. Moreover, the safety of TZDs in pregnancy has not been established, and there are particular concerns with this class of drugs which are nuclear receptor activators and alter the manner in which genes are transcribed.

Table 3. Evaluation and Treatment of the Women with PCOS: Overview

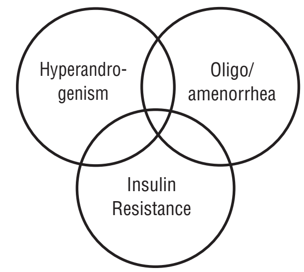
■ History:
- Symptoms of hyperglycemia
- Menstrual pattern
- Hyperandrogenic symptoms
- Conception planning
- Family history of Type 2 diabetes
- Lifestyle habits

■ Exam:
- Blood pressure
- BMI, abdominal girth
- Androgenic signs (hirsutism, acne, etc.)
- Acanthosis nigricans
- Features of Cushing's Syndrome

■ Laboratory studies:
- Fasting plasma glucose (FPG) (?DM or IGT)
- Fasting lipid panel (↑TGs, ↓HDL common)
- Consider insulin level (?insulin resistance)
- Consider OGTT (?DM or IGT)
- HbA1c (if abnormal FPG or OGTT)
- Testosterone profile
- Consider DHEA, prolactin, LH/FSH
- Consider 24-hour urine cortisol

■ Management Options
- *Lifestyle changes:* promote weight loss, improve insulin resistance, reduce DM risk
- *Oral Contraceptives:* regularize menses, lower SHBG, and improve hyperandrogenism
- *Metformin:* reduce insulin resistance and DM risk, promotes weight loss, improves ovulatory capacity and fertility
- *Anti-androgen (i.e., spironolactone):* reduces hyperandrogenemic signs/symptoms (but MUST be used with adequate contraceptive method ([teratogenic])

Figure 2. Variable Features of PCOS



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