

Diabetes 2006

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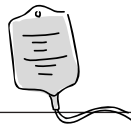
Important data on diabetes presented at the 66th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2006**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc. 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:

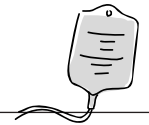
- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the interrelationship 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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Inpatient Glucose Control: A New Clinical Mandate



Once considered nothing more than a paraphenomenon of acute illness, hyperglycemia in hospitalized patients has recently garnered increased attention at a national level. This trend follows the publication of several high-profile clinical trials in major medical journals suggesting a benefit of intensive glucose control on morbidity, length of stay, hospital costs, and even mortality in selected groups of patients—mainly the critically ill. The explanation for this effect is not entirely clear, although it is known that, in addition to deleterious effects on electrolytes and hemodynamic status, hyperglycemia, particularly when severe, promotes a pro-inflammatory state, retards wound healing, alters immune function, and impedes normal endothelial function.

To date, the most convincing data comes to us from studies conducted in the surgical intensive care unit (ICU) (Furnary, *Ann Thorac Surg* 1999; van den Berghe, *N Engl J Med* 2001). Results from the medical ICU (van den Berghe, *N Engl J Med* 2006) and from the coronary care unit (Malmberg, *BMJ* 1997; Malmberg, *Europ Heart J* 2005) have been less consistent. These data have focused the attention of a wide variety of clinicians—endocrinologists, hospitalists, intensivists, cardiac surgeons, pharmacists, nurses—and administrators on the quality of glucose control in our hospitals. While the data in support of tight glucose control in non-critically ill patients are observational only, several professional organizations, including the ADA, have endorsed aggressive regimens in *all* hospitalized patients. In view of the published data, these recommendations are not entirely evidence-based and therefore remain controversial. This week, many abstracts and presentations further explored this emerging issue.

Diabetes Hospitalization Rates

The trend in hospitalization rates was the topic of an abstract by Levetan and colleagues from Pennsylvania, using data from the National Center for Health Statistics Hospital Care Branch

(1156-P). In 2003, 5.2 million hospitalized Americans had a discharge diagnosis of diabetes. (Of note, the number would be significantly greater if patients with undiagnosed diabetes were also considered). This figure has increased by 53%, from 3.4 million one decade earlier. Diabetes was coded as the primary diagnosis 11.5% of the time, down slightly from 13.6%. Of note, only 10% of patients with diabetes had their diabetes coded as “uncontrolled” (which in some circumstances yields a higher reimbursement from certain payors) despite widespread reports of poor glucose control in the inpatient setting and increasingly rigid quality guidelines. The authors suggested that the reported coding levels probably do not adequately reflect the seriousness of diabetes as a comorbid condition in the hospital setting.

A Benchmarking Project

Inpatient data from the University HealthSystem Consortium (UHC) were reported by Baldwin and colleagues from the US (437-P). This retrospective cross-sectional study was conducted to determine the current status of glucose control and its management in patients admitted to academic hospitals. In all, the care of 1718 inpatients >18 years of age was assessed from 37 UHC member hospitals. Patients had to be hospitalized for at least 72 hours because of chest pain, heart failure, CABG, coronary angioplasty or vascular procedures, shock, pneumonia, or renal failure. In addition, patients had to have at least two blood glucose (BG) levels in excess of 180 mg/dl or have been on treatment with insulin. Beginning with the first day of documented hyperglycemia, three consecutive days of BG levels and antihyperglycemic therapy were recorded. Twenty-one percent of patients had no prior history of diabetes. In ICU patients (26% of the entire cohort) only one out of five had a fasting BG on day 2 of <110 mg/dl. Approximately one in ten had a median BG >200 mg/dl; about one in five had a BG either >300 mg/dl or <70 mg/dl on at least two occasions on the same day.

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IV insulin infusion or long-acting insulin was used in only 45% of patients (12%-76% across institutions). In addition, more than one in three patients with a median BG ≥ 180 mg/dl was treated only with short-acting subcutaneous (SQ) insulin. In 75% of all patients, admission diabetic regimens were unchanged at hospital discharge. These limited, observational, retrospective data suggest that there are significant areas for improvement in the quality of inpatient glucose management in US hospitals.

Trials and Tribulations in Hospital Glucose Management

Many groups this week reported their experience in improving glucose control at their home institutions, each taking a slightly different, though usually quite effective approach. DeSantis *et al.* from Chicago and Portland (412-P) developed and validated cost-effective intravenous (IV) and SQ inpatient insulin protocols on surgical wards. The initial IV insulin dose was determined by the initial glucose reading, with adjustments every one to four hours based on trends. Once stabilized, patients were transferred to the SQ protocol involving both long- and short-acting (prandial and supplemental) insulins. The protocols resulted in improved glycemic control (Table 1) in surgical patients, but comparisons to prior strategies, especially for hypoglycemia rates, were not provided. Also, patient outcomes, such as post-operative infectious complications, were not presented.

Donihi *et al.* from Pittsburgh (460-P) reported on their own ICU IV insulin protocol. Prior to its implementation, the medical center had employed a formula that included a "sensitivity factor" to determine the infusion rate, and this led to suboptimal control. A more rigorous program was then instituted and this retrospective review was conducted to assess its efficacy. Thirty patients on the new protocol were compared to 19 treated by the original method. The groups did not differ by age, race, gender, or APACHE score (a measure of the severity of illness). Protocol patients had significantly better mean BG as compared to formula patients (136 ± 26 mg/dl vs. 178 ± 29 mg/dl, $p=0.0001$), and significantly better overall glycemic control (Figure 1). Of note, there was no statistical difference in the time spent with BG < 60 mg/dl and no difference between approaches in hospital or ICU length of stay—not surprising, given the small numbers of patients in this abstract.

Henske *et al.* from Chicago reported on their experience managing glucose after cardiac surgery

Table 1. Glycemic Control by IV/SQ Insulin Protocol

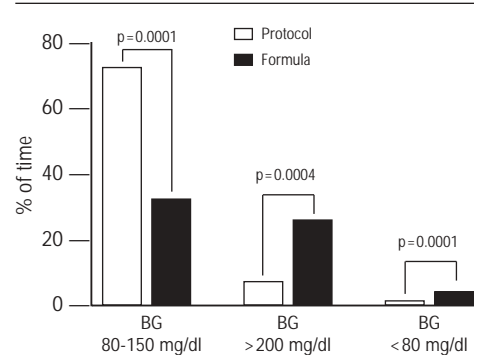
	IV	SQ
No. of patients	276	932
No. of fingersticks	4,058	18,067
Mean BG (mg/dl)	135 ± 50	146 ± 56
Hypoglycemia (BG < 60 mg/dl)	1.5%	1.3%
Hyperglycemia (BG ≥ 400 mg/dl)	0.06%	0.4%

BG=blood glucose.

(694-P). All patients were given IV insulin followed by an intensive SQ protocol to achieve BG levels of 80-110 mg/dl in the ICU and subsequently to 80-150 mg/dl during the remainder of the hospitalization. Morbidity and mortality were assessed for 30 days after surgery in patients with and without a prior diagnosis of diabetes. In all, 443 patients were treated on protocol, 102 with diabetes and 341 without. While the overall complication rate was not affected, mortality was reduced from 6% to 0.4% in the non-diabetic group and from 10% to 2.1% in the diabetic group, as compared to historical controls. (We note that the mortality figures in the control group are much higher than typically reported at most centers, suggesting that other factors may have influenced the outcomes in this abstract). The investigators argued that the previous increased morbidity and mortality were essentially eliminated by their program, which notably did not involve the use of IV insulin for three days, a strategy that has been proposed by some. Accordingly, this more efficient and cost-effective approach was advised.

Another approach championed by some is to employ a diabetes nurse specialist to manage hyperglycemia in the hospital. Iqbal *et al.* from the UK reported their initial experience with this method (1153-P). A diabetes specialist nurse was appointed to direct the initial care of diabetes patients in the emergency room. The 64 patients evaluated by the nurse and 50 historical control patients were similar with regard to age and admitting diagnosis. Notably, in those patients evaluated by the nurse, 19% of admissions were avoided. In those who were admitted, median length of stay was still reduced from 5.5 to 5.0 days, but the results did not achieve statistical significance ($p=0.16$). The investigators estimated that the \$50,000 to employ the nurse would be more than offset by \$1.28 million in savings to the 635-bed hospital. Of course, these figures

Figure 1. ICU Glycemic Control: Standardized IV Protocol vs. Original Formula



would be different in the US, especially in a fee-for-service setting, but they underscore the potential cost benefit of the prompt evaluation and management of hyperglycemic inpatients.

SUGAR Decreases Sugar in the ICU

Juneja and colleagues from Indianapolis and Milwaukee took an entirely different approach with their Systematic Utilization of Glucose Assessment and Response (SUGAR) program (1154-P). This involved the central monitoring of glucose levels throughout the hospital, with the subsequent dispatching of inpatient diabetes nurses for urgent consultations in any patient with a BG > 180 mg/dl on the general wards or > 110 mg/dl in the ICU. In the ICU, the target was then achieved by use of a computerized IV insulin infusion and on the wards by verbal recommendations concerning optimal insulin management. The program also has a staff education component to increase the awareness of inpatient hyperglycemia and its implications. In the ICU, the investigators demonstrated that the program led to a doubling in frequency of BGs between 70-110 mg/dl (24% to 48%) and a 50% reduction in those > 180 mg/dl, with only a modestly increased risk (1.9% to 3.5%) of hypoglycemia, as compared to the baseline period. On the wards, however, the improvements were minimal, likely reflecting the nature of the intervention between the two sites—ward recommendations necessitated subsequent action by the treating physician, whereas the ICU protocol was fully automated.

Cardiac Surgery & Tight Glycemic Control: How Soon To Start?

While few would argue that intensive glucose management improves outcomes after cardiac surgery, how soon aggressive management should start remains unknown. One very

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important issue is whether such management should actually begin in the operating theater. This question was addressed by Gandhi *et al.* from the Mayo Clinic (659-P). The investigators performed a randomized clinical trial in 371 patients undergoing open-heart surgery: 185 were administered IV insulin in the operating room to bring BG into the 80-110 mg/dl range, whereas 186 patients had conventional intra-operative management. The primary outcome was the composite of mortality, sternal wound infections, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure occurring within 30 days of surgery. At induction of anesthesia, the BG levels were identical between groups (111 mg/dl). The intensive treatment group had a significantly lower (each $p < 0.01$) BG after cardiopulmonary bypass (123 ± 24 mg/dl vs. 148 ± 35 mg/dl) and upon arrival to the cardio-thoracic ICU (114 ± 29 mg/dl vs. 157 ± 42 mg/dl). After surgery, both groups were treated intensively with IV insulin, so that by 24 hours there were no appreciable differences between them (103 ± 17 mg/dl vs. 104 ± 22 mg/dl.) Therefore, the study nicely tested the hypothesis that an outcomes advantage would emerge from *intraoperative* euglycemia, superimposed upon euglycemia in the early *post-operative* period. In fact, no benefit was demonstrated, with 44% of the intensively treated group experiencing at least one adverse outcome vs. 46% in the conventional group (Odds Ratio [OR] 0.93; 95% Confidence Interval [CI] 0.62-1.39, $p = 0.36$). There was also no difference between groups in length of stay either in the ICU (2 days each) or in the hospital (8 days each). Of some concern was the finding of *increased* mortality (4 vs. 0 patients, $p = 0.04$) and stroke events (8 vs. 1 patient, $p = 0.02$) in the intensive group. The lack of benefit should actually not be surprising, given the relatively brief intraoperative exposure. Any potential benefit of glucose control may simply be overwhelmed by other more important variables—such as extent of coronary artery disease and the quality of revascularization, the integrity of ventricular function, and the pre-morbid status of the patient, including the presence of diabetes.

The Low-Down on Inpatient Hypoglycemia

Hypoglycemia is a feared complication of intensive insulin therapy in both inpatient and outpatient arenas. In the hospitalized patient,

particularly those admitted with cardiovascular events, the development of hypoglycemia may increase catecholamine levels and further exacerbate myocardial ischemia. With this in mind, Korytkowski *et al.* from Pittsburgh (629-P) queried their hospital's archival database for any BG < 70 mg/dl in non-ICU patients during a single month in 2004. The investigators defined hypoglycemia severity as mild (BG 50-69 mg/dl), moderate (40-49 mg/dl), or severe (< 40 mg/dl). Repeated hypoglycemic readings within a four-hour window were censored, with the nadir BG during this time interval determining the severity of the event. Of 2,562 admissions during the month, 182 patients were affected by hypoglycemia: 239 mild hypoglycemic events occurred during 151 admissions, 45 moderate episodes during 37 admissions, and 40 severe episodes during 29 hospitalizations. Overall, the frequencies of hypoglycemia, graded by increasing severity, were 15.6, 2.9, and 2.6 events per 1,000 patient days. Hypoglycemic patients had a higher Charlson Severity of Illness score (2.2 vs. 1.4, $p < 0.001$) and had longer hospital stays (11.5 vs. 5.6 days, $p < 0.001$). Notably, half of all events occurred during the first two hospital days, with three out of four transpiring within the first five days. The most frequent diagnostic codes in patients with hypoglycemia included diabetes (27%), renal failure (24%), heart failure (14%), and myocardial infarction (9%). The investigators suggested that their method of tracking and analyzing hypoglycemic events might be used by others to assess the quality of glucose management at their institution. We note that such observational data sets tend to be influenced by detection bias—e.g., longer BG surveillance and, therefore, greater likelihood of detecting hypoglycemia in patients with longer lengths of stay.

Don't Forget about Diabetes after AMI!

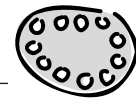
Diabetic patients admitted to the hospital with acute myocardial infarction (AMI) frequently have their antihyperglycemic regimen altered during their hospitalization. The most common scenario is the discontinuation of all outpatient drugs and the institution of an insulin "sliding scale." Not uncommonly, the patient may be discharged off anti-diabetic therapy entirely, with plans for follow-up as an outpatient. While this might be occasionally indicated, the quality of glucose control during the time interval off therapy and its influence on cardiovascular outcomes is not known. Using data from the National Heart Care project, Inzucchi and colleagues from

New Haven and Denver conducted a retrospective analysis of this very point. The study cohort consisted of 8,751 Medicare recipients with diabetes who were hospitalized for AMI and who were treated with an antihyperglycemic agent (oral agent and/or insulin) prior to admission (663-P). Of these, 13% or 1,170 were discharged off of any antidiabetic regimen, of whom 37% died within one year, as compared to 28% of the 7,581 patients whose discharge instructions included at least one antihyperglycemic drug ($p < 0.0001$). After multivariate analysis, controlling for 78 variables, including diabetic complications, admission BG and creatinine, cardiac history, revascularization status, left ventricular function, and other discharge medications (e.g., β -blockers, ACE inhibitor/ARBs, statins and aspirin), there was a survival disadvantage in the group of patients discharged on no antihyperglycemic drug (Hazard Ratio [HR] for mortality of 1.42, 95% CI 1.27-1.59). Slightly lower readmissions in this group of patients (HR 0.92, 95% CI 0.85-1.00) suggested that the increased mortality might have been sudden. As a proportion of its overall mortality at one year, the no-drug group experienced 57% greater mortality during the first 30 days (36% vs. 23% of overall mortality). Because of the concern that the failure to restart antihyperglycemic drugs was more common in those discharged from the acute setting to chronic care facilities, the data were then stratified based on discharge disposition. The association with greater mortality appeared attenuated but remained statistically significant in patients discharged to home (HR 1.24 [1.06-1.44]). These data show that the failure to continue (or resume) antihyperglycemic therapy in diabetic post-AMI patients is associated with excess and early mortality. The reason for this is not clear but the data suggest that the quality of glucose control soon after AMI discharge may influence cardiovascular outcomes.

The take-home message from most of these presentations is that hyperglycemia is very common in patients during—and probably soon after—their hospitalizations and that this is associated with adverse outcomes. Improving glucose management in this setting is achievable but requires significant infrastructural support. The precise form of practice change may not be of paramount importance, since a variety of approaches seems to improve at least *metabolic* outcomes. The question of whether these interventions will improve actual *patient* outcomes remains unknown—outside of the critical care setting.



PCOS: “Diabète des Femmes à Barbe”

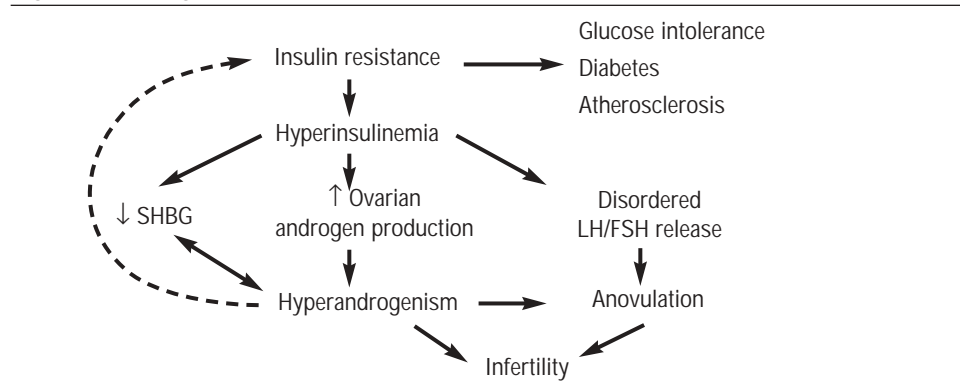


The first mention of polycystic ovary syndrome (PCOS) dates back to 1921, when Achard and Thiers first described “*diabète des femmes à barbe*.” Shortly thereafter, Stein and Leventhal identified a unique disease entity comprised of amenorrhea, hirsutism, obesity, and a characteristic polycystic ovarian appearance. PCOS remains one of the most common hormonal disorders in young women, with a prevalence estimated between 5% and 10%—and probably increasing. In an opening-day symposium on the topic, the speakers reviewed the underlying pathophysiology, treatment, and complications of this often under-diagnosed problem.

Dr. David Ehrmann from Chicago opened the program with an overview. Anovulation and signs of hyperandrogenism are the main concerns that typically prompt affected women to seek the assistance of a physician (Table 2), although metabolic and cardiovascular derangements also may accompany this disorder.

Based on 2000 US census data, with 114 million women in the reproductive age group (20 to 44 years old) and a conservative estimate of the PCOS prevalence of 5% to 8%, it is likely that 5.7-9.1 million women have PCOS. Studies by Dunaif and collaborators have shown that women with PCOS, whether obese or lean, are very insulin resistant. The degree of insulin resistance in lean PCOS women is actually comparable to that seen in obese non-PCOS women. Glucose levels following an oral glucose load may not be markedly elevated, although insulin levels usually are, sometimes dramatically so. Approximately one-third, however, have impaired

Figure 2. Pathogenesis of PCOS



glucose tolerance (IGT), while another 5%-10% have Type 2 diabetes.

No single etiologic factor fully accounts for the wide spectrum of metabolic abnormalities seen in PCOS. Most authorities believe that hyperinsulinemia induces hyperandrogenism, but this relationship is complex (Figure 2). For example, the complete suppression of hyperandrogenism with gonadotropin releasing hormone (GnRH) agonists does not improve either the peripheral or hepatic insulin resistance in these women. Hyperinsulinemia may actually lead to abnormal luteinizing hormone (LH) secretion, which contributes to anovulation. In addition, the ovarian theca cells in women with PCOS are particularly sensitive to insulin, which stimulate androgen secretion. Decreased sex hormone binding globulin (SHBG) (from hyperandrogenism) leads to a further increase in free testosterone levels and, ultimately, to hirsutism and acne. Treatment with insulin sensitizing drugs, such as metformin or thiazolidinediones (TZDs), lowers insulin levels and also reduces testosterone concentrations. Ehrmann also showed that the prevalence of obstructive sleep apnea (OSA) is 30- to 40-fold higher in PCOS females, something

that cannot be accounted for by obesity alone. Moreover, in a vicious cycle, sleep loss can lead to worsening insulin resistance. It is well known that testosterone influences both neural control of breathing as well as upper airway mechanics.

Dr. John Nestler from Virginia reiterated the important role of insulin resistance in fueling ovarian androgen production, causing anovulation and infertility. There is a 16% conversion rate per year from normal glucose tolerance to prediabetes in these individuals. The development of Type 2 diabetes is two-fold higher in patients with oligomenorrhea, independent of body weight. The prevalence of metabolic syndrome is also two- to three-fold higher in PCOS women, with low HDL-cholesterol being the most prevalent feature. In a review of PCOS therapies (Table 3), Dr. Nestler pointed out a 3.9-fold increase in ovulation rate with use of metformin, with 80% of patients responding after six months of treatment. The combination of metformin and clomiphene increases ovulation rate by 4.4-fold. Clomiphene should be used when time is of the essence to improve fertility; otherwise metformin with diet and exercise is the preferred approach.

Table 2. Features of PCOS

<i>Anovulation</i>	<ul style="list-style-type: none"> ■ Oligomenorrhea ■ Amenorrhea ■ Infertility ■ Increased risk of endometrial cancer
<i>Hyperandrogenism</i>	<ul style="list-style-type: none"> ■ Hirsutism ■ Acne ■ Alopecia
<i>Metabolic and Cardiovascular Derangements</i>	<ul style="list-style-type: none"> ■ Obesity ■ Insulin resistance ■ Impaired Glucose Tolerance, Diabetes ■ Dyslipidemia ■ Hypertension ■ Endothelial dysfunction ■ Pro-coagulant state ■ Obstructive sleep apnea

Table 3. PCOS Therapy

<i>Goals</i>	<i>Possible Interventions</i>
Reduce hyperandrogenism (hirsutism, acne)	Weight loss, oral contraceptives, glucocorticoids, metformin,* thiazolidinediones*
Improve ovulation	Weight loss, clomiphene, gonadotropins, metformin,* glucocorticoids
Reduce risk of diabetes	Weight loss, metformin,* thiazolidinediones*
Reduce cardiovascular risk	Weight loss, blood pressure and lipid management, metformin,* thiazolidinediones*

*Note: These drugs do not currently carry an indication other than for therapy of Type 2 diabetes.

PCOS: "Diabète des Femmes à Barbe"

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The differences between oral contraceptives (OCPs) and insulin sensitizing drugs were also highlighted. OCPs may be more effective in reducing risk of endometrial cancer and in decreasing androgens and thus the development of hirsutism and acne. However, OCPs may worsen insulin resistance in some women, and cause glucose intolerance and hypertriglyceridemia. The impact of long-term OCP use by PCOS patients on their risk of cardiovascular disease is not clear at this moment. Nestler recommended that patients have a glucose tolerance test three to four months after starting OCPs and should have other cardiovascular risk factors aggressively

tracked and treated. Dr. Nestler concluded his talk by mentioning the possible additional benefits of using insulin sensitizers, such as the TZDs, which have been shown to improve insulin sensitivity, decrease C-reactive protein levels, and possibly decrease the risk of diabetes in women with PCOS.

The final speaker, Dr. Burton Sobel from Vermont, discussed studies linking insulin resistance and atherosclerosis. The consequences of PCOS clearly extend beyond the reproductive axis, with metabolic and cardiovascular abnormalities putting them at high risk for atherosclerosis and premature heart disease. Levels of plasminogen activator inhibitor-1 (PAI-1), an anti-fibrinolytic factor, in PCOS may exceed those

typically seen in patients with Type 2 diabetes. Increased PAI-1 levels in PCOS may create a prothrombotic state, which makes patients more prone to cardiovascular events, particularly as they age. One recent study showed a higher prevalence of coronary artery calcifications as detected by electron beam CT (EBCT) in premenopausal women with PCOS.

In summary, although we better understand the pathogenesis of PCOS its underlying causes remain largely unknown. Certainly, both genetic and environmental factors play important roles. Further investigation into this increasingly common condition in our young female patients will hopefully further elucidate its biological basis and shed light on more effective therapeutic options.



Micro-Management



Screening for and preventing microvascular complications of diabetes is one of the important tasks for anyone taking care of diabetic patients. Several oral and poster presentations at this week's ADA meeting addressed these issues.

Molitch and colleagues (23-OR) evaluated the association between renal insufficiency and albuminuria. Based on recent data demonstrating normal albumin excretion rates (AER) in over one-third of Type 2 diabetic patients with renal impairment, the researchers performed a similar analysis in Type 1 patients participating in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC). The percentage of EDIC patients with renal insufficiency (defined as an estimated glomerular filtration rate [GFR] <60 ml/min/1.73 m²) increased from 1.6% in EDIC years 1-2 to 4.2% at EDIC years 9-10. Similar to findings in Type 2 diabetes, a substantial proportion of those with renal insufficiency had a normal albumin excretion rate (Figure 3). Based on these findings, the investigators recommend that all patients with diabetes have an annual GFR assessment, irrespective of the presence/absence of microalbuminuria.

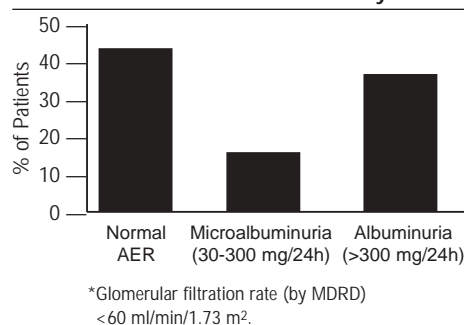
In a related investigation, Niewczas *et al.* from Boston (24-OR) identified the frequency of renal function decline (defined by GFR <60 ml/min) in the absence of proteinuria using data from 5,627 patients with Type 2 diabetes visiting the Joslin Clinic over a two-year period. It was determined that renal function decline was present in

11% of 3,623 normoalbuminuric patients, 21% of 1,542 patients with microalbuminuria, and 58% of 462 patients with frank proteinuria.

Elliott and colleagues from the UK (P-794) evaluated the incidence of painful neuropathy and its potential risk factors in patients with Type 1 diabetes. Data from the EURODIAB Prospective Complications Study (n=3,250; mean duration of diabetes 14.7±9.3 years) indicated that the incidence of neuropathy was 24% over a mean follow-up period of 7.3±0.6 years. The rate of painful neuropathy, defined as deep or burning pain, was much greater in females (74% vs. 48% with no pain, p=0.002) even after adjustment for duration of diabetes and HbA1c (p = 0.003). As compared to those with no pain, patients with painful neuropathy had less macro/microalbuminuria (35% vs. 16%, respectively; p=0.02). Thus, the researchers concluded that female gender is an independent risk factor for painful peripheral neuropathy. The authors hypothesized that the association between painful neuropathy and less albuminuria may indicate early neuropathy with less endoneural microangiopathy.

Lastly, diabetic retinopathy was characterized in patients living with Type 1 diabetes for 50 years or more. Sun *et al.* from the Joslin Clinic (P-825) differentiated the ocular findings in 98 such patients. Parameters evaluated included: visual acuity testing via the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, fundus photography, ocular coherence testing, along with other routine clinical measurements (e.g.,

Figure 3. Albumin Excretion in EDIC Type 1 Diabetes Patients with Renal Insufficiency*



HbA1c, lipid profiles, etc.). The investigators found a larger than anticipated proportion of patients had no (7.2%) or mild nonproliferative (39%) diabetic retinopathy. Among those with more advanced retinopathy, the disease was classified as moderate nonproliferative, severe nonproliferative, or proliferative in 8%, 1%, and 42% of patients, respectively. Interestingly, there was no correlation between diabetic retinopathy or visual acuity with any previously established risk factors such as disease duration and current HbA1c. The investigators suggested that there is a subset of patients with long-term diabetes who may be somehow protected from the microvascular complications of chronic hyperglycemia. This observation is consistent with those of seasoned clinicians in the field. What "protects" these individuals remains a mystery.