

# Metformin May Improve Metabolic Parameters

BY DIANA MAHONEY  
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BOSTON — Treatment with metformin significantly improves body mass index and other metabolic parameters in women with polycystic ovary syndrome and significantly decreases the prevalence of metabolic syndrome in this population, a retrospective study has shown.

The findings confirm the utility of metformin, coupled with diet and exercise, as a primary therapy for minimizing the long-term risks of developing metabolic syndrome-associated cardiovascular disease and diabetes in women with the hormonal disorder, Kai I. Cheang, Pharm.D., said at the Fifth Annual World Congress on the Insulin Resistance Syndrome.

To date, short-term studies have demonstrated beneficial metabolic effects associated with metformin in women with polycystic ovary syndrome (PCOS), but long-term data have been lacking, according to Dr. Cheang, of Virginia Commonwealth University, Richmond.

To assess the impact of long-term metformin use, Dr. Cheang and colleagues reviewed the charts of consecutive PCOS patients treated at the university-affiliated clinic from 2000 to 2005. Patients with more than 6 months of treatment with metformin were included in the final analysis if baseline and follow-up assessments of metabolic syndrome parameters were available. Those patients with diabetes at baseline and those taking other medications that would affect metabolic parameters, such as thiazolidinediones, weight-loss agents, antihypertensives, lipid-lowering agents, or antidiabetic agents, were excluded.

Of the nearly 250 PCOS patients treated with metformin during the study period, 71 met the inclusion criteria; their mean age was 31.2 years. For the purposes of the investigation, metabolic syndrome was defined by National Cholesterol Education Program Adult Treatment Panel III (ATP-III) criteria, with the exception of waist circumference; body mass index (BMI) was substituted for that criterion.

"This is because waist circumference was not available for most of the patients," Dr. Cheang noted. "Based on correlation

between BMI and waist circumference of local PCOS women with PCOS women who entered into our clinical studies, we determined the BMI cut-off value corresponding to a waist circumference of 88 cm was 32 kg/m<sup>2</sup>," she reported.

The average period from initiation of metformin therapy to the most recent assessment for the study population was 31 months. The data for those who began lipid-lowering or antihypertensive therapy during follow-up were analyzed up until the beginning of such therapy, said Dr. Cheang.

The investigators assessed baseline and follow-up metabolic syndrome parameters using a two-sided student's paired t test and observed that, compared with baseline, follow-up values for BMI, diastolic blood pressure, and high-density lipoprotein were significantly improved with metformin therapy, Dr. Cheang reported. Additionally, metformin therapy significantly decreased the overall prevalence of metabolic syndrome from 31% at baseline to 14% following 31 months of treatment. Observed improvements in systolic blood pressure, triglycerides, and fasting glucose measures did not reach statistical significance.

The findings were limited by the study's retrospective design, Dr. Cheang said. "As information was not being collected specifically for the study, certain data [were] not available for all patients." The time between patient visits was inconsistent, and there is a possibility of selection bias because the clinic from which the patient pool was collected specializes in PCOS care, she said.

According to study coauthor Dr. John E. Nestler, chair of the university's division of endocrinology and metabolism, previous studies have shown that treatment with metformin, coupled with diet and exercise, improves ovulation and lowers androgens in PCOS women and possibly prevents or retards progression to glucose intolerance. With these new data, "[metformin treatment] also appears to ameliorate several components of the metabolic syndrome," he said in an interview.

The clinical significance of these findings is substantial, given the extremely high risk for the metabolic disorder in PCOS, he said.

No conflicts of interest were reported relative to this study. ■

# Hyperinsulinemia and Obesity Are Linked to PCOS in Teens

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BOSTON — Adolescent girls with polycystic ovary morphology have severe hyperinsulinemia after glucose stimulation, and the degree of insulin elevation is correlated with obesity, a study has shown. The findings emphasize the role of obesity and hyperinsulinemia in the pathophysiology of polycystic ovary syndrome, Dr. Marianna I. Bak said at the Fifth Annual World Congress on the Insulin Resistance Syndrome.

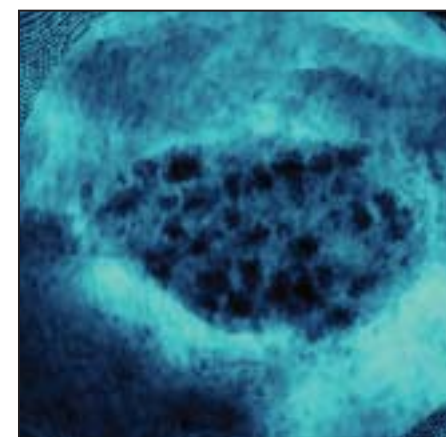
"Hyperinsulinemia directly influences the ovary function by potentialization of [luteinizing hormone] secretion and, as a consequence, may lead to increased ovarian androgen production," said Dr. Bak of the Medical University of Warsaw. It has been suggested that hyperinsulinemia and luteinizing hormone together could induce the changes that lead to polycystic ovary morphology, such as ovarian stroma and theca interna hyperplasia, and could contribute to menstrual dysfunction in adolescent girls, she said.

For this reason, Dr. Bak and colleagues hypothesized that identifying the subset of adolescent girls with polycystic ovary morphology could provide important information for the role of obesity and hyperinsulinemia in polycystic ovary syndrome (PCOS). They evaluated the insulin resistance, glucose, and insulinogenic response to glucose stimulation in a sample of 13- to 18-year-old girls with clinical manifestations of irregular menstrual cycles and various degrees of polycysticlike ovary morphology on ultrasound, and they correlated circulating insulinemia with ovarian morphology and clinical features.

Of the 114 girls who met the study criteria, 36 with a body mass index (BMI) in the normal range (less than 25 kg/m<sup>2</sup>) and 42 with a BMI in the obese range (greater than 27) were included in the final analysis. Each girl underwent a complete physical examination and evaluation for degree of hirsutism. A thorough medical history, anthropometric measurements, and detailed biochemical and endocrine profiles were obtained, as were the glycemic and insulin responses to 75-g oral glucose tolerance testing (OGTT).

"In all of the studied ovaries, we observed small subcapsular follicles and increased stromal score," Dr. Bak reported. She noted, however, that the degree of advanced morphological changes was differentiated based on BMI status. "In 50% of the obese girls, the stromal score was moderately increased [compared with the normal BMI group] and in 30% it was markedly increased," she said.

All of the girls had biochemical features of various degrees of hyperandrogenemia,



An ovary with the cysts (in black) that form in polycystic ovary syndrome.

and all had normal fasting glucose regardless of their BMI. In addition, although fasting and stimulated insulinemia were increased in both groups, "insulin levels during [OGTT] were markedly higher in obese girls relative to normal BMI subjects," said Dr. Bak. In fact, "the obese girls had a threefold higher frequency of prediabetes based on oral glucose tolerance testing relative to normal-weight girls with similar ovarian changes."

The latter finding suggests that the measure of insulin with the OGTT should be considered in all obese girls with irregular menstrual cycles, even in the presence of normal fasting plasma glucose "in order to implement the proper early therapy against hyperinsulinemia," said Dr. Bak. Early intervention is important, she said, because the correlation between hyperinsulinemia and PCOS-like ovarian changes in this population suggests that hyperinsulinemia in adolescent girls could have a significant effect on their fertility. ■

# Insulin Resistance More Severe in PCOS With Metabolic Syndrome

In women with polycystic ovary syndrome, insulin resistance may be more severe in those with metabolic syndrome than in those without it, according to data from a cross-sectional study of women with PCOS.

Even young women with PCOS should be screened for metabolic disturbances to more effectively prevent cardiovascular events later in life, wrote Dr. Hwi Ra Park of the Ewha Womans University College of Medicine, Seoul, South Korea, and colleagues.

The 113 women in the study had a mean age of 26 years and a 15% prevalence of metabolic syndrome (MS), which is lower than what has been reported in studies of PCOS patients in the United States (43%-46%) and Germany (31%). The prevalence of MS is about 4% in the general urban population of age-matched Korean women and about 6% in American women aged 20-29 years (Diabetes Res. Clin. Pract. 2007;77[suppl. 1]:S243-6).

Of the five components of the

diagnosis of metabolic syndrome as per the National Cholesterol Education Program Adult Treatment Panel III, 45% of the women had a high-density lipoprotein cholesterol level of less than 50 mg/dL; 24% had a waist circumference greater than 80 cm; 20% had high systolic blood pressure (130 mm Hg or more) or high diastolic blood pressure (85 mm Hg or more); 13% had fasting triglyceride levels of at least 150 mg/dL; and 1% had fasting blood glucose levels of at least 110 mg/dL.

Compared with women who didn't have MS, those with MS had a higher body mass index, waist girth, systolic and diastolic blood pressures, fasting glucose, fasting and post-glucose load insulin levels, triglycerides, and free testosterone. Levels of HDL cholesterol, sex hormone-binding globulin, and luteinizing hormone were significantly lower in women with MS.

The results of a 75-g oral glucose tolerance test performed after an overnight fast showed plas-

ma glucose and insulin levels were significantly higher in women with MS than in those without it.

"Insulin resistance is most likely the pathogenic link between PCOS and MS," they said. Some data suggest women with PCOS and MS have higher rates of hyperandrogenemia, low serum sex hormone-binding globulin, and acanthosis nigricans, than do those without MS. That "may reflect more severe insulin resistance" in PCOS women with MS.

—Jeff Evans