Metabolic Dysfunction, Testosterone Levels Tied

BY MARY ELLEN SCHNEIDER
New York Bureau

TORONTO — Higher free testosterone levels appear to be associated with metabolic dysfunction in women from the general population, according to a cross-sectional study of more than 1,600 women in the Framingham Heart Study Offspring Cohort.

Free testosterone was positively associated with body mass index (BMI), waist circumference, diabetes, metabolic syndrome, and systolic and diastolic blood pressure in a community-based sample of women. The findings raise questions about whether higher testosterone levels predispose women to increased cardiovascular risks, lead investigator Dr. Andrea Coviello of Boston University said at the annual meeting of the Endocrine Society.

Studies have shown that women with polycystic ovary syndrome (PCOS) are at a fourfold increased risk for developing diabetes and a twofold increased risk for developing metabolic syndrome. But there are many unanswered questions about the clinical consequences of androgen excess in women who have mild to moderate hyperandrogenism without accompanying PCOS, Dr. Coviello said.

Dr. Coviello and her colleagues measured circulating testosterone levels in 1,678 women from the Framingham Heart Study Offspring Cohort in an effort to find out if healthy women with higher testosterone levels face risks for metabolic problems. They assessed circulating testosterone levels using liquid chromatography tandem mass spectrometry, which has a sensitivity of about 2 ng/dL, and measured sex hormone–binding globulin (SHBG) through immuno- lourometric assay. They also evaluated the relationship between testosterone and metabolic dysfunction, particularly metabolic syndrome and diabetes.

The women in the sample ranged in age from 33 to 87 years, with a mean age of 61. Most of the group was postmenopausal, Dr. Coviello said. They had a mean SHBG of 92 nmol/L, a mean total testosterone of 30 ng/dL, and a mean free testosterone of 3 pg/mL.

The investigators found that free testosterone was positively correlated with BMI, waist circumference, both systolic and diastolic blood pressure, triglycerides, total cholesterol, LDL cholesterol, and fasting glucose. Free testosterone was inversely associated with HDL cholesterol.

In addition, diabetic women had higher free testosterone and lower SHBG levels than women without diabetes. SHBG was inversely correlated with most of the components of metabolic syndrome. For example, higher BMI and waist circumference was associated with lower SHBG. Higher blood pressure, higher total cholesterol, higher triglycerides, and higher LDL cholesterol were all associated with lower SHBG. Higher fasting glucose was associated with a lower SHBG.

For total testosterone, only HDL cholesterol and triglycerides were significantly correlated. HDL cholesterol was positively correlated with total testosterone, and triglycerides were negatively correlated.

There were a number of limitations. The sample included only Caucasian individuals, and there was no information on the timing of the blood draws in relation to menstrual cycle among the premenopausal women. In addition, the reproductive histories were not adequate to determine whether women in the sample had PCOS, Dr. Coviello said.

The study was funded by grants from the National Institutes of Health. ■

Children of Type 1 Mothers Are at Greater Risk of Type 2 as Adults

BY TIMOTHY F. KIRN
Sacramento Bureau

CHICAGO — Children born to mothers with type 1 diabetes have a three times higher risk of developing type 2 diabetes as adults, according to a Danish cohort study that followed a group of adult individuals born to diabetic mothers.

The study also showed that the same individuals, who ranged in age from 18 years to 27 years, had more than twice the risk of being overweight and almost three times the risk of having metabolic syndrome, Dr. Tine D. Clausen said at the annual scientific sessions of the American Diabetes Association.

The study adds to a growing body of literature suggesting diabetes begets more diabetes, though most previous studies have investigated children born to mothers who were overweight or had type 2 diabetes.

"In the offspring born to women with type 1 diabetes, we found an association between median maternal glucose in late pregnancy and offspring risk of type 2 diabetes or prediabetes," said Dr. Clausen, of the department of obstetrics, Rigshospitalet, Copenhagen. Her group studied 160 adults born to mothers with type 1 diabetes between 1978 and 1985, and matched them to a group of 128 similar-aged adults born to mothers without type 1 diabetes.

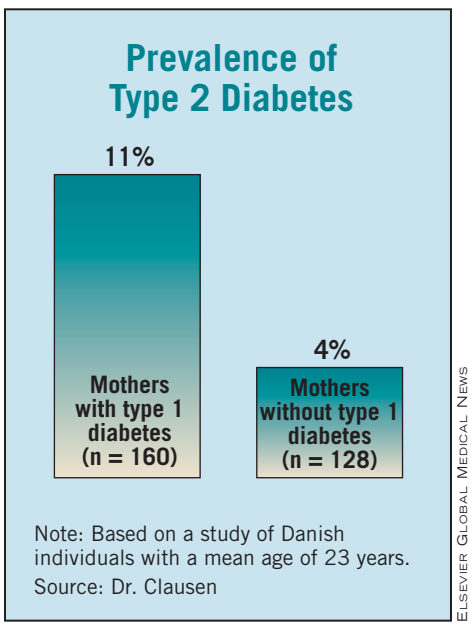
In the two groups, the prevalence of type 2 diabetes was 11% in the subjects born to mothers with diabetes, compared with 4% in the control group. Of the diabetic-mother subjects, 41% were overweight (a body mass index [kg/m^2] of 25), compared with 24% of the control subjects, and 14% had metabolic syndrome, compared with 6% of the controls.

An additional 9% of the subjects born to diabetic mothers had impaired glucose regulation—either a high fasting glucose, or an abnormal oral glucose tolerance test result—compared with 3% of the controls.

Offspring of mothers with type 1 diabetes also were more likely to be born prematurely, to have a lower gestational age, and to be large for gestational age. Moreover, the mean hemoglobin A_{1c} level was higher in the offspring of the mothers with type 1 diabetes (5.0% vs. 4.8%).

The groups were similar in having a family history (other than the mother) of diabetes, in the percentage of mothers who were overweight before pregnancy, and in the mother's age at delivery. They differed in that a greater proportion of the children born to mothers with diabetes were of "lower social class," Dr. Clausen said.

After statistical adjustments for age, maternal overweight status, and social class, the researchers found that the odds ratio of the diabetic offspring having prediabetes or type 2 diabetes was 3.3, of being overweight was 2.1, and of having the metabolic syndrome was 2.8, she said. Adjusting the statistical model for preterm birth made no difference in those odds ratios. ■



ELSEVIER GLOBAL MEDICAL NEWS

Maturity-Onset Diabetes Mimics Type 2 Disease in Children

BY MIRIAM E. TUCKER
Senior Writer

CHICAGO — About 5% of antibody-negative/C-peptide–positive children and adolescents diagnosed with diabetes in the United States may have Maturity-Onset Diabetes of the Young rather than type 2 diabetes, Dr. Lisa Gilliam reported at the annual scientific sessions of the American Diabetes Association.

Maturity-Onset Diabetes of the Young (MODY) is a clinically heterogeneous group of disorders characterized by nonketotic diabetes, an autosomal dominant pattern of inheritance, and typical onset below the age of 25 years. It can arise from mutations in any one of at least six different genes associated with beta-cell function. The most common form, MODY3, arises from a mutation in the HNF [hepatocyte nuclear factor]-1[α] gene (N. Engl. J. Med. 2001;345:971-80).

New findings suggest that MODY is underrecognized and often inappropriately treated. Physicians "need to maintain a high level of suspicion for MODY in antibody-negative children who have residual beta-cell function, and certainly consider screening in individuals who meet the classic criteria for MODY," said Dr. Gilliam, of the division of metabolism, endocrinology and nutrition at the University of Washington, Seattle, in an interview.

The data come from SEARCH, a federally funded study of physician-diagnosed diabetes in individuals under 20 years of age in six U.S. centers located in Southern California, Colorado, Ohio, Washington state, South Carolina, and North Carolina. Of 3,993 participants in whom diabetes-associated autoantibodies and fasting C-peptide were measured, 438 were autoantibody-negative. Direct sequencing for the HNF-1[α] gene was performed in a subset of 266 patients who were autoantibody-negative and who had fasting C-peptide levels greater than 0.8 ng/mL. Of those, 13 patients had 14 gene mutations, including 7 that had not previously been described.

Only 1 of the 13 patients had been clinically diagnosed with MODY, whereas 5 had been misdiagnosed with type 1 diabetes, and 7 with type 2 diabetes. Seven were currently being treated with insulin, and none was taking sulfonylureas, which is the recommended pharmacologic treatment for MODY3. MODY patients are sensitive to sulfonylureas, which are cheaper and easier to take than multiple daily insulin injections, Dr. Gilliam explained.

Several clinical characteristics helped distinguish MODY3 from type 1 diabetes. Compared with those 3,484 individuals with type 1 diabetes in this study, the 13 MODY3 patients were less likely to have had weight loss (46% vs. 74%) or polyuria (54% vs. 93%) at diagnosis. The MODY group also tended to be older, heavier, much more likely to have a parent with diabetes (62% vs. 14%), and much less likely to have medium- to high-risk HLA types (46% vs. 85%). Just 3 of the 13 were non-Hispanic white (23%), compared with 69% of the type 1 group.

In contrast, virtually no clinical or biochemical characteristic was identified that could help in distinguishing MODY3 from type 2 diabetes on an individual basis. Although the MODY group was somewhat younger and less obese than the type 2 patients, there was a great deal of overlap between the two groups. The type 2 patients were as likely as the MODY group to have a positive family history for diabetes—including an autosomal dominant three-generation family history—and fasting C-peptide levels were similar.

"With the prevalence of obesity and type 2 diabetes increasing in the pediatric population, it's becoming more challenging to distinguish MODY from type 2 diabetes," she noted. Genetic screening is very expensive, at this point it's not feasible to recommend it in every antibody-negative child or adolescent with residual fasting C-peptide. ■