Low Androgen Levels Linked to Diabetes in Men

More studies are needed to examine the mechanism by which sex hormones contribute to diseases.

BY DIANA MAHONEY
New England Bureau

Low levels of androgen may be a risk factor for diabetes in men, according to the findings of a population-based study.

In a sample of 1,413 adult men, concentrations of free and bioavailable testosterone in the low normal range were associated with diabetes independent of adiposity, reported Elizabeth Selvin, Ph.D., of Johns Hopkins Bloomberg School of Public Health, Baltimore, and her colleagues.

"To our knowledge, this is the first study to examine the association between sex steroid hormones and diabetes in a large, nationally representative male population," the authors wrote (Diabetes Care 2007;30:234-8).

The study sample included multiethnic men aged 20 years or older who participated in the morning session of phase I of the Third National Health and Nutrition Examination Survey (NHANES III), which was conducted between 1988 and 1991.

"Morning session participants were chosen for this hormone study to reduce extraneous variation due to diurnal production of sex hormones," the authors wrote.

As part of the survey, all of the study participants underwent an interview, an extensive physical examination, and collection of a blood sample.

Height, weight, and waist and hip circumferences were measured as part of the physical examination, and body mass index was calculated.

The information on age, race and ethnicity, and diabetes status was collected by patient self-report. With respect to diabetes specifically, the interviewers asked the participants if they had ever been told by a health professional that they had diabetes or sugar diabetes, the authors noted.

The main hormone measurements of interest in the investigation included serum total testosterone as well as estimated bioavailable and free testosterone levels, which were calculated from serum total testosterone, sex hormone–binding globulin, and albumin concentrations. "Measurements of free and bioavailable testosterone levels more accurately represent concentrations readily available to tissues and metabolic processes," the authors stated.

In a multivariate model adjusted for age, race/ethnicity, and adiposity, there was no clear association of total testosterone concentration with diabetes; however, men in the lowest tertile (0.09 ng/mL or below) of free testosterone level were more than four times as likely to have prevalent diabetes, compared with men in the highest tertile (higher than 0.14 ng/mL).

Similarly, men in the lowest tertile of bioavailable testosterone (2.11 ng/mL or below) were nearly four times as likely to have prevalent diabetes as were men in the highest tertile (higher than 3.02 ng/mL), the authors reported. They also noted that "these associations persisted even after further adjustment for total cholesterol, triglycerides, and systolic blood pressure."

Men with free testosterone levels in the lowest tertile were more than four times as likely to have prevalent diabetes, compared with men who had levels in the highest tertile.

In addition, the association with low free testosterone persisted even after the exclusion of men with clinically low levels of total testosterone (less than 3.25 ng/mL) and/or clinically low levels of free testosterone (less than 0.07 ng/mL), suggesting the observed associations were "not entirely driven by hypogonadal men," the authors wrote.

A sensitivity analysis that included 58 cases of undiagnosed diabetes showed no appreciable alterations in the adjusted models, the authors reported.

"The independent association of low free and bioavailable testosterone levels in our adjusted models suggest[s] that testosterone insufficiency may be a risk factor for diabetes," the authors wrote.

Despite the fact that the directionality of the associations between low androgen levels and adiposity are unclear based on the analysis, "our data are consistent with the hypothesis that androgens may directly influence glucose metabolism and the development of insulin resistance independently of the effects of adiposity," they stated.

The study is limited by its cross-sectional design, which precludes evaluation of the temporality of the observed associations between androgen levels and diabetes, the authors wrote.

"However, several previous prospective analyses suggest that decreases in testosterone level may precede the development of diabetes, lending support to a temporal if not causal relation," they said. "Additionally, including individuals with undiagnosed diabetes, a population at an earlier point in the progression of diabetes, did not change our results."

Additional studies are needed to investigate the mechanisms by which sex steroid hormones contribute to diabetes as well as other chronic diseases, the authors concluded.

The study is the third from the Hormone Demonstration Program, which is supported by the Maryland Cigarette Restitution Fund Research Grant Program that is based at Johns Hopkins University. ■

Risk for Diabetes Is Lower in Women on Hormone Therapy

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Women who are considering the risks and benefits of hormone therapy should be informed of the link between hormones and a decreased risk of diabetes, especially if they are at risk for the disorder, according to Dr. Wulf Utian, executive director of the North American Menopause Society, in Cleveland.

"While hormone therapy [HT] is not indicated for the prevention of diabetes, women with diabetes risk factors who are considering it for a valid indication should understand the evidence in this area," Dr. Utian said in an interview. "For these women, the link between HT and diabetes might fall on the benefit side of the equation."

For diabetes-prone women who were compliant with therapy throughout the 5 years, the risk of diabetes was 33% less than that of the placebo group.

NAMS' newly revised position statement on hypertension is the group's first to review this evidence, Dr. Utian said. "In 2004 [when NAMS issued its last position paper], there were not enough data to address this issue.

Since then, a number of published studies have shown the same link between HT and a decreased incidence of diabetes."

The paper reviewed three studies on the subject, granting Class I status to the evidence presented in each one: two subanalyses of the Women's Health Initiative (WHI) and one subanalysis of the Heart and Estrogen/Progestin Replacement Study (HERS).

The first of the WHI studies, published in 2004, examined the effect of HT on diabetes development in the 16,600 women included in the estrogen/progestin arm (Diabetologia 2004;47:1175-87).

After 5 years of follow-up, women in the active group were 21% less likely to develop diabetes than those in the placebo group (277 cases vs. 324 cases—a significant difference).

The numbers achieved greater significance when the analysis was restricted to the small subgroup of women who remained compliant with therapy throughout the follow-up period. In this group, the decreased risk was 33%.

The difference seemed to be driven by steady improvements in fasting glucose and insulin resistance in the active group, the authors wrote. The risk ratios remained unchanged after adjusting for body mass index (BMI) and waist circumference.

Insulin resistance and glucose level were also the driving forces behind the smaller risk reductions seen among women in WHI's estrogen-only arm (Diabetologia 2006;49:459-68).

This study included 9,712 women (about 1,000 were excluded from the analysis because of a baseline diagnosis of diabetes).

At year 6, women in the active group were 12% less likely to have developed diabetes than those in the placebo group (a rate of 8.3% vs. a rate of 9.3%). This difference was not significant in the overall group, but became highly so in the smaller group of women who were compliant with therapy through the study's end. These women were 27% less likely to develop diabetes than the placebo group.

Again, adjusting for BMI and waist circumference did not account for the difference, the authors said. Instead, the risk reduction seemed to be related to improvements in fasting glucose and insulin resistance. These were significant within the first year of therapy and then waned in the overall group, but remained significant in the compliant group.

The final study, a subanalysis of the HERS data, confirmed HT's beneficial effect on diabetes development in women with preexisting coronary heart disease. The subanalysis followed 2,029 patients who did not have diabetes at baseline (Ann. Intern. Med. 2003;138:1-9).

At 4 years' follow-up, the incidence of diabetes in patients in the active group was 6.2%, compared with 9.5% in patients in the placebo group—a significant risk reduction of 35%. The authors concluded that in this group, 30 was the number needed to treat to prevent 1 case of diabetes.

The risk differential was related to significantly higher fasting glucose levels in the placebo group; these levels remained stable in the active group.

There was no association of decreased diabetes with the active group's modest decreases in BMI or waist circumference.

More research is necessary to further define HT's impact on diabetes, Dr. Utian said.

In the meantime, patients who are at risk of diabetes should receive lifestyle counseling in addition to information about the hormone/diabetes link. "We need to focus on healthy living, diet, exercise, and moderation in alcohol.

"If patients would comply with those recommendations, they would be much more beneficial than any hormone therapy," he noted. ■