Effects of treatment with testosterone alone or in combination with estrogen on insulin sensitivity in postmenopausal women

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Objective: Little is known about metabolic effects of testosterone treatment in postmenopausal women. The aim of the study was to compare the treatment effects of testosterone, estrogen, and testosterone plus estrogen on insulin sensitivities, body compositions, and lipid profiles in healthy postmenopausal women.
Design: An open, randomized clinical study with parallel group comparison.
Setting: Women's health clinical research unit at a university hospital.
Patient(s): Sixty-three naturally postmenopausal women participated in the study.
Intervention(s): The participants were randomly assigned to 3 months of treatment with testosterone undecanoate (40 mg every second day), estradiol valerate (2 mg daily), or the combination of both.
Main Outcome Measure(s): Insulin sensitivity assessed by euglycemic hyperinsulinemic clamp, body composition, and serum lipids.
Result(s): Insulin-induced glucose disposal was reduced by approximately 20% after treatment with testosterone alone, and after the combined treatment, but not by estrogen alone. Body weight, but not total body fat, increased significantly by about 1 kg in all groups. Lean body mass was significantly increased in the group of combined treatment and tended to be increased by testosterone alone. High-density lipoprotein (HDL)-cholesterol decreased significantly by testosterone treatment. In contrast, HDL-cholesterol increased, whereas low-density lipoprotein (LDL)-cholesterol and lipoprotein-(a) [Lp(a)] decreased with estradiol treatment.
Conclusion(s): We conclude that 3 months of treatment with testosterone undecanoate in postmenopausal women induces insulin resistance and an adverse serum lipid profile but may increase lean body mass. (Fertil Steril® 2006;86:136–44. ©2006 by American Society for Reproductive Medicine.)

Key Words: Testosterone, insulin sensitivity, body composition, serum lipids

There is an increasing interest in androgen treatment of postmenopausal women as monotherapy, as well as together with conventional hormone therapy (HT) (1). During the years of menopausal transition, circulating androgen levels decline because of an age-related reduction of both adrenal and ovarian secretion (2). Although estrogen treatment during menopause is effective in ameliorating vasomotor symptoms, sleep disturbances, and vaginal dryness, some postmenopausal women continue to experience sexual dysfunction and loss of energy despite HT (3).

Androgen treatment reportedly has several beneficial effects in postmenopausal women. Testosterone administered to surgically or naturally postmenopausal women improves sexual function, energy, and quality of life (4–9). It also has an additional positive effect on bone mineral density (BMD) compared with HT alone (7, 10) and possibly protective effects in the breast (11). Although androgen treatment appears to be advantageous, little knowledge exists about the side effects and safety of androgens. There are particular concerns about adverse effects on carbohydrate and lipid metabolism leading to an increased risk of type 2 diabetes and cardiovascular disease.

Endogenous androgen excess (e.g., polycystic ovary syndrome [PCOS]) is associated with android obesity, insulin resistance, hyperlipidemia, and hypertension (i.e., the metabolic syndrome) (12). Administration of oral androgens in young, regularly menstruating women causes a reduction in peripheral glucose uptake (13, 14), whereas insulin resistance is partially reversed by antiandrogen treatment in women with hyperandrogenism (15). These findings suggest

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that androgen excess leads to the development of insulin resistance. However, it is not known if testosterone as substitution therapy in postmenopausal women influences insulin sensitivity. In obese postmenopausal women, treatment with an anabolic steroid with weak androgenic activity had no effect on fasting glucose or insulin sensitivity (16).

Testosterone may also have indirect effects on insulin sensitivity, which are mediated by changes in body composition and serum lipids. The central distribution of body fat is recognized as an independent predictor of cardiovascular disease in women (17). Androgen treatment in women has been associated with both increased and decreased abdominal body fat (16, 18–21). Furthermore, oral estrogen-androgen treatment may have adverse effects on serum lipids, raising concerns about cardiovascular safety (10, 22, 23).

Because it is unclear if testosterone treatment in postmenopausal women has effects on insulin sensitivity, we made a head-to-head comparison of treatment with testosterone, estrogen, and the two together. We used testosterone undecanoate (TU), which is an oral testosterone preparation with minor liver-related side effects due to its mainly lymphatic absorption (24). Insulin sensitivity, body composition, and serum lipids were investigated in naturally postmenopausal women before and after a 3-month treatment period.

MATERIALS AND METHODS

Subjects

Sixty-three healthy postmenopausal women who were 44 to 64 years old with a body mass index (BMI) between 20–32 kg/m^2 participated in the study. Two women were obese (BMI >30 kg/m^2). All had last menstrual bleeding >12 months before the study or follicle-stimulating hormone (FSH) levels >30 IU/L. Women using HT had to experience the following washout periods: 8 weeks for oral HT, 4 weeks for transdermal HT or local estrogen applications, and 6 months for progestin implants or injections. Exclusion criteria were: liver, biliary, or renal disease; uncontrolled high blood pressure; endocrine disorder; history or presence of thromboembolic disorder and malignancy. Only nonsmokers were included in the study. All patients gave their informed consent before participating in the study. The Ethics Committee of Karolinska University Hospital approved the study.

Study Design

The women were randomly assigned into three groups of equal size. One group was treated with a 40-mg dose of TU every second day (Undestor®; Organon, Oss, The Netherlands) (T group); another group received a 2-mg daily dose of estradiol valerate (Trivina®; Orion Pharma, Esbo, Finland) (E group); and the third group was treated with a 40-mg dose of TU every second day in combination with estradiol valerate (2 mg daily) (T+E group) for 3 months. The women were instructed to take TU with their evening meal. They were also informed to keep their dietary and physical activity stable during the study. Investigations were performed before and at the end of the treatment period. After an overnight fast, the patients attended the Women's Health Research Unit at the Karolinska University Hospital and underwent a general health examination including registration of body weight, height, waist-to-hip ratio (WHR), and blood pressure. A fasting blood sample was drawn from a peripheral vein at baseline and at 1, 2, and 3 months after the start of treatment for the analysis of hormones and blood lipids. The samples collected during treatment were drawn 12 or 36 hours after intake of TU. After centrifugation, serum was separated and stored at −70°C pending analysis.

Euglycemic Hyperinsulinemic Clamp. Insulin sensitivity was investigated by the euglycemic hyperinsulinemic clamp technique (25). The clamp was performed before and after 3 months of treatment at 12 or 36 hours after capsule intake. Two 12-gauge catheters were inserted into antecubital veins in different arms—one for infusion of insulin and glucose, the other for collection of blood samples. Insulin (Actrapid® Human; Novo, Copenhagen, Denmark) was infused in 250 mL of saline containing 5 mL of blood from the subject (to protect from loss of insulin). A priming insulin infusion for 10 minutes was followed by a constant infusion for 110 minutes to maintain a steady-state hyperinsulinemia. The insulin infusion rate was 1.0 mU/kg/min in all subjects. Euglycemia was maintained by measuring the blood glucose in duplicate with a glucose analyzer (Yellow Springs Instrument Co. Inc., Yellow Springs, Ohio) every 5 minutes and adjusting the rate of infusion of a 20% glucose solution accordingly. Whole body glucose uptake (i.e., glucose disposal) during the clamp was calculated on the basis of the amount of glucose infused during the last 100 minutes of the clamp and was expressed as (mg × kg body weight^{-1} × minutes^{-1}). Before and during the 120-minute insulin infusion, blood samples were drawn twice at 15-minute intervals for measurement of insulin. Serum was separated after centrifugation and stored at −70°C pending analysis. The mean of two samples before and during the clamp respectively was used in the calculations.

Body Composition. Total and regional body composition (i.e., fat mass, lean body mass, and bone mineral density [BMD]) were measured by dual energy X-ray absorptiometry (DXA) using Lunar Model DPX-L equipment (Lunar Radiation, Madison, WI). The software automatically calculates the amount of fat in the trunk and legs. The limit between the leg and trunk regions was defined as the line that could be drawn from the upper margin of the iliac crest through the femoral neck. Values for trunk and leg fat mass were used to calculate upper/lower fat mass ratio. From the whole body DXA measurement, the spinal BMD was also obtained. The spinal region comprised the lower part of the cervical spine, the thoracic, and the most of the lumbar spine. The BMD reproducibility of the whole body was calculated as less than 0.01 g/cm^2 or 0.1 × SD.

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