Karolinska Institutet

Department of Woman and Child Health
Karolinska Institutet, Stockholm, Sweden

Effects of testosterone treatment on metabolism and endometrium in postmenopausal women

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av

Hong Zang

Leg. Läkare

Huvudhandledare
Docent Angelica Lindén Hirschberg
Institutionen för Kvinnor och Barns hälsa,
Karolinska Institutet

Fakultetsopponent
Docent Tord Naessén
Institutionen för Kvinnor och Barns hälsa,
Uppsala Universitet

Betygsnämnd
Professor Outi Hovatta
Institutionen för klinisk vetenskap,
Karolinska Institutet

Docent Stefan Arver
Institutionen för medicin,
Karolinska Institutet

Professor Inger Sundström Poromaa
Institutionen för Kvinnor och Barns hälsa,
Uppsala Universitet

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Effects of testosterone treatment on metabolism and endometrium in postmenopausal women

Hong Zang, MD

From the Department of Woman and Child Health, Division of Obstetrics and Gynecology, Karolinska Institutet, Stockholm, Sweden

Abstract

There is an increasing interest in androgen treatment of postmenopausal women. Testosterone administered to surgically or naturally postmenopausal women improves sexual function, well-being and quality of life. Androgens have also an additional positive effect on bone mineral density as compared to estrogen alone and may be protective in the breast. However, there is little knowledge about metabolic side effects and endometrial safety of testosterone treatment.

Our aims were to evaluate the effects of three months treatment with oral testosterone (testosterone undecanoate, 40 mg every second day) in naturally postmenopausal women as compared to estrogen alone (estradiol valerate, 2 mg daily) or the combination of both on: 1) insulin sensitivity, body composition and serum lipids; 2) expression of proteins and genes involved in lipolytic signaling in abdominal subcutaneous adipose tissue; 3) endometrial proliferation and 4) sex hormone receptor expression in the endometrium.

Testosterone treatment resulted in a two-fold increase of total testosterone in serum with median levels within the normal range of premenopausal women. 1) Insulin sensitivity as assessed by a euglycemic hyperinsulinemic clamp was impaired, high density lipoprotein-cholesterol decreased and lean body mass tended to be increased by testosterone treatment. 2) Testosterone, but not estrogen, down-regulated the expression of hormone sensitive lipase (HSL), the final rate limiting step in lipolysis, in abdominal subcutaneous adipose tissue. Testosterone also up-regulated phosphodiesterase 3B, an antilipolytic step of the insulin signaling pathway. Plasma glycerol, an indirect measure of lipolytic activity, correlated positively with HSL expression. 3) Short-term treatment with testosterone did not stimulate endometrial proliferation as evaluated by endometrial histopathology and the proliferation marker Ki-67. Rather, testosterone tended to counteract estrogen-induced endometrial proliferation. 4) Testosterone added to estrogen induced less endometrial expression of estrogen receptor (ER)α and progesterone receptors, while the expression of ERβ and the androgen receptor was higher, than with estrogen only therapy.

In conclusion, short-term treatment with testosterone in postmenopausal women induces insulin resistance, an adverse lipid profile and a change in the expression of lipolytic signaling proteins in relation to lipolytic activity, which may promote the accumulation of fat. Testosterone treatment does not stimulate endometrial proliferation but may counteract estrogen-induced proliferation. Furthermore, testosterone may influence endometrial proliferation and differentiation by a modulation of sex hormone receptors in the endometrium. The clinical significance of our findings has to be determined in long-term studies as well as with other testosterone preparations.

Key words: testosterone, insulin sensitivity, body composition, lipids, lipolysis, endometrial proliferation, sex hormone receptors, menopause.

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