

## REVIEW

# The effects of androgens on metabolic functions in females

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**Abstract:** The metabolic effects of androgens and their underlying mechanisms in females have been revealed by recent studies. An excess of androgens can have adverse effects on feeding behavior and metabolic functions and induce metabolic disorders/diseases, such as obesity, insulin resistance, and diabetes, in women and experimental animals of reproductive age. Interestingly, these effects of androgens are not observed in ovariectomized animals, indicating that their effects might be dependent on the estrogen milieu. Central and peripheral mechanisms, such as alterations in the activity of hypothalamic factors, reductions in energy expenditure, skeletal muscle insulin resistance, and  $\beta$ -cell dysfunction, might be related to these androgens' effects. *J. Med. Invest.* 68 : 228-231, August, 2021

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## INTRODUCTION

Energy balance and reproductive function are closely linked in most species (1, 2). Sex hormones, i.e. estrogens and androgens, are involved in the regulation of energy metabolism, food intake, and body weight in mammals and humans (2). Generally, estrogens prevent excess body weight gain and obesity in females of reproductive and postmenopausal ages by suppressing food intake and increasing metabolic expenditure (2-4). On the contrary, it is assumed that androgens increase the risk of metabolic dysfunctions and excess body weight in women of reproductive age, however, a cause-effect relationship remains to be established. In addition, the roles of androgens on metabolic functions in postmenopausal women are highly controversial. Some studies have reported that high testosterone level is associated with increased risk of insulin resistance and cardiovascular disease, whereas other studies have shown that circulating DHEA-S level dose not affect the risk of cardiovascular disease and mortality (5). Similarly, recent study has proposed that it is unknown whether hyperandrogenic women truly have increased risk of mortality and cardiovascular disease later in life (6). Interestingly, contrary to case in females, it has been demonstrated that androgens have favorable effects on metabolic functions in males ; i.e., androgens prevent some metabolic disorders, such as insulin resistance (IR) and obesity, in males (7).

Here, we review the available literature on the roles of androgens in metabolic functions in females of reproductive age, with special emphasis on the mechanisms that have recently been proposed to underlie these roles.

## EFFECTS OF ANDROGENS ON METABOLIC FUNCTION IN FEMALES OF REPRODUCTIVE AGE

### *Effects of endogenous androgens*

It has been suggested that endogenous androgens affect metabolic functions in women of reproductive age and that an excess of androgens might increase the risk of some metabolic disorders/diseases, such as visceral obesity, IR, and metabolic syndrome. Women with polycystic ovary syndrome (PCOS), frequently accompanied by a hyperandrogenic status, exhibit increased prevalence rates of type 2 diabetes and metabolic syndrome compared with women without PCOS (8, 9). Similarly, hyperandrogenic women with PCOS display higher prevalence rates of abdominal obesity, IR, and adverse metabolic profiles than women without PCOS and those with non-hyperandrogenic PCOS. These effects of a hyperandrogenic status on metabolic functions are also observed in women without PCOS. Specifically, hyperandrogenic premenopausal women with high free androgen indices (FAI) demonstrated higher waist circumference values, fasting glucose and insulin levels, systolic and diastolic blood pressure levels, and serum triglyceride levels and lower serum high-density lipoprotein-cholesterol levels (10). In addition, women with idiopathic hirsutism or PCOS displayed greater waist-hip ratios (WHR) than age- and weight-matched non-hirsute women, and the plasma testosterone level was found to be positively correlated with the WHR (11). Based on the findings of these studies regarding the relationships between hyperandrogenic status and metabolic disorders, further studies evaluated whether antiandrogenic treatment improves the metabolic status of women with PCOS. It was demonstrated that treatment with flutamide, an antiandrogenic medicine, during 12 months caused reductions in visceral and subcutaneous fat mass, lipid profile improvements, and increases in insulin sensitivity in overweight-obese women with PCOS (12).

Interestingly, some studies have suggested that androgens might affect food cravings and food preferences in young women. For example, young women with high FAI exhibited increased craving for certain foods, such as high-fat foods and fast foods (13), and women with PCOS displayed higher prevalence rates of abnormal eating behaviors, such as bulimic behavior (14). In

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addition, women with bulimia nervosa tended to have higher androgen levels than normal women (15), and antiandrogenic oral contraceptive use reduced meal-related hunger and eating behavior in bulimic women (16).

Thus, endogenous androgens play roles in the regulation of metabolic functions and feeding behavior in women of reproductive age, and an excess of androgens might increase the risk of metabolic disorders/diseases.

#### *Effects of exogenous androgens*

The hypothesis that an excess of androgens is related to various metabolic disorders/diseases, has been supported by studies that evaluated the effects of exogenous androgens on metabolic functions. Androgen-treated female-to-male transsexual patients exhibited higher HOMA-IR (homeostatic model assessment of insulin resistance) values than those who did not receive hormonal treatment (17), indicating that exogenous androgens might increase IR. In addition, the administration of methyltestosterone reduced glucose uptake during insulin infusions in non-obese premenopausal women, suggesting that hyperandrogenemia induces IR (18). These phenomena can be reproduced in experimental animals via the chronic administration of androgens. The chronic (4 weeks) administration of dihydrotestosterone (DHT) increased visceral adiposity in female mice of reproductive age (19), and the administration of testosterone (around 2 weeks) increased visceral and subcutaneous fat weight and body weight in female rats of reproductive age (20, 21) (Table 1). Interestingly, such effects of androgen on fat and body weight are observed in gonadally intact or estradiol-supplemented ovariectomized rats, but not in non-supplemented ovariectomized rats (20, 21) (Table 1). Animals that were subjected to longer-term (5 to 19 weeks) androgen treatment display increased food intake and body weight gain, IR, and hyperlipidemia, as well as irregular estrous cycles and morphological ovarian changes (22-24). In addition, the chronic administration of testosterone also increased the preference of female rats of reproductive age for a high-fat diet (25), indicating that the effects of androgens on feeding behavior can also be reproduced in animal models.

**Table 1.** Effects of androgen administration on body weight, food intake, fat amount, and hypothalamic factors in ovariectomized with E2 administered and ovariectomized female rats.

	ovariectomy+E2	ovariectomy
Body weight	↑	↓
Food intake	→	↓
Fat amount	↑	↓
Adipocyte size	↑	↓
Hypothalamic Aromatase	→	↑
Hypothalamic androgen receptor	↓	→
Hypothalamic IL-1, TNF $\alpha$	↑	↓

E2; estradiol, IL-1; interleukin-1, TNF- $\alpha$ ; tumor necrosis factor- $\alpha$ , ↑; increase, ↓; decrease

## HYPOTHESES OF THE MECHANISMS OF ANDROGENS' EFFECTS

### *Changes in hypothalamic functions*

It has been shown that an excess of androgens alters the activity and mRNA expression of some hypothalamic factors, and these alterations might be involved in the adverse effects of androgens on metabolic functions. The chronic administration

of DHT reduced the hypothalamic mRNA expression of proopiomelanocortin (POMC), which is an anorectic factor, and POMC neuronal innervation into other hypothalamic regions in female mice of reproductive age (19). In addition, we observed that chronic testosterone administration reduced the hypothalamic mRNA expression of estrogen receptor- $\alpha$  (ER- $\alpha$ ) and/or increased the mRNA expression of pro-inflammatory cytokines (20, 21). It has been established that the favorable effects of estrogens on metabolic functions are partly mediated by hypothalamic ER- $\alpha$  (2-4) and that low-grade hypothalamic inflammation undermines homeostatic responses that protect against obesity (26). Therefore, the downregulation of ER- $\alpha$  expression and the upregulation of pro-inflammatory cytokine expression in the hypothalamus, which were observed in our studies, might underlie androgen-induced metabolic disorders. We also found that such alterations in hypothalamic ER- $\alpha$  and pro-inflammatory cytokine expression, as well as increases in fat mass, occurred in gonadally intact or estradiol-supplemented ovariectomized rats, but not in ovariectomized rats (20, 21). This indicates that the effects of androgens on metabolic functions might depend on the estrogen milieu; i.e., androgens have adverse effects on females of reproductive age, whereas their effects might be decreased or reversed in post-menopausal females and males.

### *Reductions in energy expenditure*

It has been reported that an excess of androgens reduces energy expenditure, which is associated with visceral obesity. In female mice of reproductive age, chronic DHT administration prevented the leptin-induced activation of brown adipose tissue (BAT) thermogenesis, resulting in a reduction in energy expenditure and an increase in visceral fat mass (19). Similarly, chronic dehydroepiandrosterone (DHEA) administration reduced BAT activity, body temperature, and O<sub>2</sub> consumption in female rats of reproductive age, whereas the transplantation of BAT from rats that had not been administered DHEA negated these DHEA-induced changes and normalized systemic insulin sensitivity (27). These results indicate that reductions in endogenous BAT activity are closely related to the adverse effects of androgens on metabolic functions.

### *Skeletal muscle insulin resistance*

It has been shown that an excess of androgens can induce IR in women and female experimental animals. High testosterone levels produced IR, which was detected using the hyperglycemic and euglycemic hyperinsulinemic clamp tests, in premenopausal women (18, 28), and such testosterone-induced IR might mainly occur in skeletal muscle (18). The administration of testosterone also induced IR in muscles, together with reductions and increases in the relative numbers of type 1 and type 2 muscle fibers, respectively, in female rodents (29, 30). Although the detailed mechanisms by which androgens promote muscular IR remain unclear, it has been suggested that androgens might act as aggravating factors rather than as initiators of IR.

### *$\beta$ -cell dysfunction*

It has been suggested that an excess of androgens causes a predisposition towards pancreatic  $\beta$ -cell dysfunction by activating some  $\beta$ -cell stressors. Hyperandrogenic women exhibit  $\beta$ -cell hyperfunction, which might induce secondary  $\beta$ -cell dysfunction (31). In addition, excess testosterone induced  $\beta$ -cell dysfunction via an androgen receptor-dependent mechanism (32) in female mice, and direct androgen exposure to isolated pancreatic islets induced an impaired response to glucose stimulation (32, 33). These effects of androgens on  $\beta$ -cells might be caused by systemic oxidative stress, low-grade inflammation, and/or IR (32, 34).

## EFFECTS OF ANDROGENS ON METABOLIC FUNCTIONS IN POSTMENOPAUSAL WOMEN

As noted above, the effects of androgens on metabolic functions in postmenopausal women are disputed. It has been reported that androgen activity is higher in postmenopausal women with impaired glucose tolerance than in normal women (35) and that high testosterone levels in postmenopausal women predict insulin resistance and the future incidence of type 2 diabetes (36). On the other hand, higher serum estradiol levels are strongly related to the pathogenesis of type 2 diabetes in postmenopausal women (37). These findings indicate that excesses of estrogen and androgens might act as risk factors for metabolic disorders in postmenopausal women. Interestingly, some data have shown that testosterone therapy has favorable effects on body composition and cardiovascular function, as well as on libido, bone, and cognitive performance (38). Thus, contrary to endogenous androgens, exogenous androgens might help to protect against metabolic disorders.

## CONCLUSION

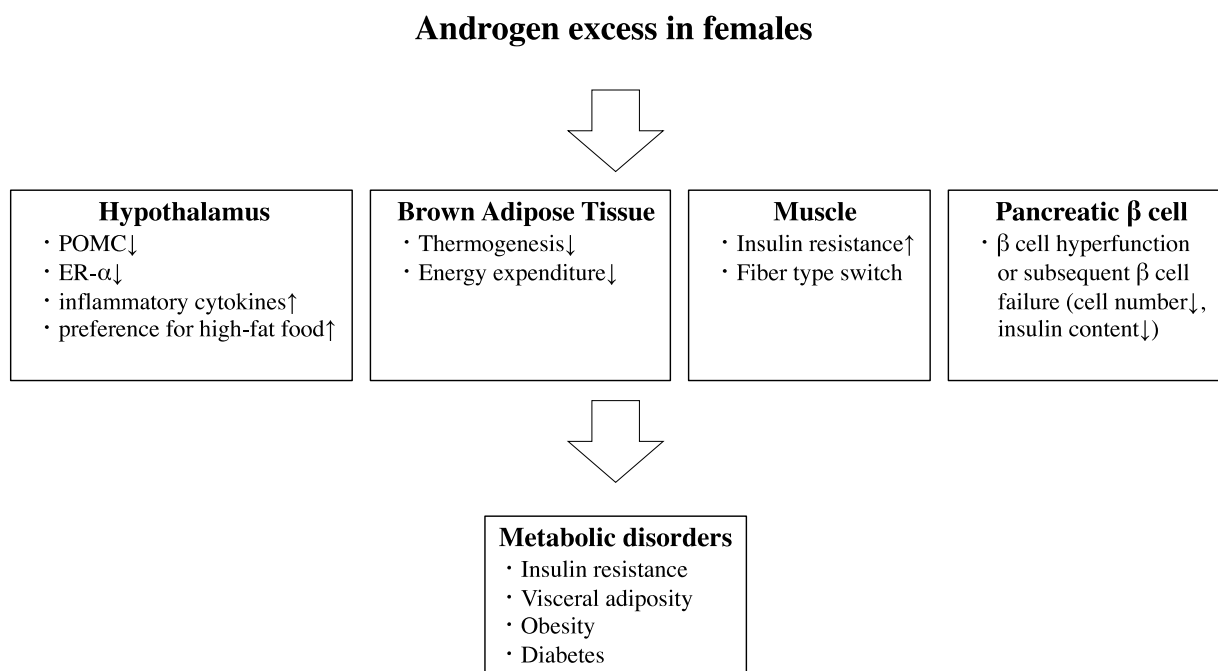
Androgens affect metabolic functions and feeding behaviors in females of reproductive age, and an excess of androgens might increase the risk of metabolic-related disorders/diseases. It can be assumed that increased consumption of high-fat diet might enhance the adverse effects of androgens on metabolic functions. Central and peripheral mechanisms are considered to contribute to these effects of androgens (Figure 1).

## CONFLICT OF INTEREST

The author declares no conflicts of interest.

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**Figure 1.** Effects of androgen excess on function of central and peripheral tissues in females. These androgen's effects increase the risks of some metabolic-related disorders.

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