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MINI REVIEW

Androgens for postmenopausal women's health?

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Abstract Obesity, metabolic syndrome, and diabetes are becoming a leading health concern in the developed Countries, due to their link to cardiovascular disease. These conditions are common in women in the post-menopausal period. Unfortunately, actual lifestyle change strategy fail to prevent cardiovascular events for several reasons, thus specific medications are needed. In addition, it was showed an increased cardiovascular diseases and breast cancer risk in postmenopausal women taking estrogens alone or with progestin, thus the optimal therapy for the preventions of chronic disease in women is still lacking. Androgens exert different actions on organs like adipose tissue, brain, bone, and on cardiovascular system. However, a debate still exists on the positive role of androgens on human health, especially in women. Furthermore, the vascular effects of androgens remain poorly understood and have been controversial for a long time. Sex hormones are important determinants of body composition. Aging is, often, accompanied by a decrease in free testosterone levels, a concomitant reduction in muscle mass and an increase in fat mass. Furthermore, numerous studies showed that total serum testosterone levels were inversely related to the atherosclerosis disease incidence in postmenopausal women. New therapeutic targets may, therefore, arise understanding how androgen could influence the fat distribution, the metabolic disease onset, the vascular reactivity and cardiovascular risk, in both sex.

Keywords Menopause · Women · Androgens · Atherosclerosis · Adipose tissue

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Introduction

Obesity, metabolic syndrome (MS), and diabetes (T2DM), are becoming a leading health concern in the developed countries, due to their link to cardiovascular disease. These conditions are common in women in the post-menopausal period, as well as, in women who have a premature natural menopause, or in young women who have had both ovaries removed [1–4]. Overall, death rates for heart disease and stroke have decreased worldwide in men but not in women. In fact, about 55,000 more women, than men, have a stroke each year in Europe [5]. Unfortunately, strategies targeted to adopt a correct lifestyle are not well accepted by individuals and consequently the prevention of cardiovascular events, fail. Thus, specific medications are needed, causing an increase of economic costs in the countries, therefore the postmenopausal women's health actually represents a major item of expenditure.

Recently, the unexpected results of two large clinical trials [6, 7] have led to the need of further scientific investigations of the causal factors involved in cardiovascular disease onset in menopause, as well as, of other chronic diseases. In fact, it was showed an increased cardiovascular diseases and breast cancer risk in postmenopausal women taking estrogens alone or with progestin [6, 7], thus the optimal therapy for the preventions of chronic disease in

women is still lacking. In particular, it was demonstrated that oral estrogen increases the risk of venous thromboembolism, especially during the first year of treatment [8]. Actually, more data are required to investigate differences in risk across the wide variety of hormone regimens, including the different types of progestogens [8] and androgens. For these last, a debate still exist on the positive role of androgens on human health, especially in women. Furthermore, the vascular effects of androgens remain poorly understood and have been controversial for a long time. Consequently, it is important to clarify whether androgens could have a protective role on women's health, and whether they could represent a future promise as therapy.

In addition, hyperandrogenism occurred in women with polycystic ovary syndrome (PCOS), which is a condition associated to an increased risk of cardiovascular disease and metabolic complications, contributed to the negative opinions on the effects of androgens on women's health. Hyperandrogenemia is one of the essential biochemical features of this syndrome. In fact, despite insulin resistance is implicated as the major player in the metabolic abnormalities and contributes to the increased cardiovascular risk associated with PCOS, some authors suggested that androgen excess appears to participate as an independent parameter, which further aggravates the cardiovascular and metabolic aberrations in affected women [9–11].

Aim of this work is to re-examine several clinical and experimental evidences on the possible beneficial effects of these hormones, in particular on adiposity and on cardiovascular system, to suggest a future research area and the development of new therapies for postmenopausal women.

Androgens and the adipose organ

Many authors developed the concept that adipose tissue is organized as a true organ, with all the anatomical and physiological characteristics [12]. Mammal adipose organ includes two types of adipose tissue, the white adipose tissue (WAT) and the brown adipose tissue (BAT).In BAT, the multilocular adipocytes can dissipates energy through an uncoupling protein-1 (UCP-1), a specific protein properly expressed in this tissue, uncoupling fatty acid oxidation from ATP production [13]. In mammals BAT is involved in the control of body weight [14] and it is now considered as a potential pharmacological target to treat human obesity [13]. WAT has unilocular adipocytes highly adapted to store excess energy as triglycerides, as well as, for thermic insulation or mechanical forces. However, recently studies in WAT showed the presence of cells with a multilocular morphology, expressing the UCP-1 [15–17].

The distribution pattern of body fat has important implications in the development of the chronic disease. There are two main form of accumulation of the adiposity in the body: abdominal or central accumulation (called android distribution) and peripheral (called gynoid distribution). The fat distribution as well as fat cell size is gender-specific, since influenced by sex hormones [18]. Abdominal or visceral fat, that is prevalent in male and in female after menopause, is associated with higher risk of cardiovascular and metabolic diseases onset, than subcutaneous adipose tissue or gynoid distribution type, that instead may exert a protective action [18, 19]. Visceral adipose tissue plays an important role in cardiovascular complications appearance because it is associated to an altered production pattern of modulator substances or specific factors, such as leptin, TNFα, IL-6, PAI-1, involved in the systemic inflammation and in the atherosclerotic process [20]. On the contrary, subcutaneous adipose tissue is metabolically less active than visceral one and it can produces anti-inflammatory mediators, such as adiponectin and IL-10 [21]. Furthermore, central obesity is associated to the insulin-resistant state, i.e., caused partially by the adipokines release [22] as well as, by the high-lipolytic activity in the visceral fat, leading to elevated FFAs in the portal and systemic circulation. Thus, accumulation visceral adipose tissue contributes to dyslipidemia, enhanced gluconeogenesis, and insulin resistance.

While there is now general agreement that testosterone administration increases muscle mass, the effects of androgen administration on fat mass are not as well characterized.

Androgens may have a depot- and gender-specific effect on adipose tissue and insulin resistance.

Dehydroepiandrosterone-sulfate (DHEA-S) is the major circulating steroid hormone in humans [23]. DHEA-S represents the sulfated form of androgen hormone DHEA, i.e., produced and released from the adrenal glands. DHEA-S can be interconverted with DHEA by DHEA sulfotransferases and hydroxysteroidsulfatases enzymes which are present in a wide variety of tissues, including adipose tissue [24]. It could exert a variety of actions in several tissues, including brain, liver, kidney, and gonads, where it is metabolized in other biologically active steroids, such as testosterone, androstenedione, and estradiol [25].

DHEA-S is no only the hydrophilic storage form that circulates in the blood, but also the main form used in steroid synthesis. In humans, plasma DHEA-S concentrations are found in a range that is 250–500 times higher than DHEA levels [26, 27]. This concentration shows the peak during the second decade of life, with levels higher in males than in females [28, 29]. Testosterone is a central intermediate in both women and men, being converted to estrogen by the action of an aromatase enzyme, and to dihydrotestosterone by the 5α-reductase enzyme [26]. Conversion of testosterone to dihydrotestosterone, by either type 1 or type 25α-reductase, amplifies testosterone action.

Despite its abundant presence, the specific role of DHEA hormone is not yet clear [30]. A receptor for DHEA and DHEA-S has not been identified. However, it is known that DHEA-S exerts several effects independently of its conversion into other sex hormones [31, 32]. Studies showed that DHEA and its metabolites could bind important receptors like the peroxisome proliferators activated receptor (PPAR), or the estrogen receptor β [33–37]. A crucial finding from several epidemiological studies in humans was that obesity, diabetes, and other chronic disease are associated to low circulating concentration of DHEAS [38–41]. Furthermore, in adult men affected by diabetes or MS a lower DHEA-S concentration than in normal controls men was showed [42, 43].

A study showed that 24 h of DHEA-S treatment of cultured visceral adipose tissue samples causes the upregulation of adiponectin gene expression [44] and other authors showed the positive effects of DHEA and testosterone on leptin secretion in female adipose tissue [45], probably related to estrogen conversion.

It was also demonstrated that women's subcutaneous tissue is more receptive to DHEA-S and its addition into adipocytes cultures may lead to a significant increase of lipolysis [46, 47]. However, the mechanism underlying these effects remains unclear.

A possible mechanism of action of DHEA-S, contributing to its anti-obesity effects, could be the inhibition of 11β-hydroxysteroid dehydrogenase type 1(11 β-HSD1) enzymes [48], catalysing the conversion of cortisone to cortisol. Consequently, this reaction may reduce the glucocorticoid levels, which play an important role in development of visceral obesity [49].

In addition, some evidences showed that treatment with DHEA-S could modify the fatty acids profile in the adipose tissue, in particular it may influence the ratio between saturated and unsaturated fatty acids in the adipose tissues [50] and it can affect the fatty acid β-oxidation [51]. It was showed that DHEA inhibits adipocytes development and differentiation in adipose tissue cultures [52].

Sex hormones are important determinants of body composition. Aging is accompanied by a decrease in free testosterone levels, a concomitant reduction in muscle mass and an increase in fat mass. In particular, in women it was showed that plasma concentration of DHEA [53] and DHEAS [54] are inversely associated to total body fat.

Contradictory results have been found when the effect of testosterone was investigated on adipose tissue.

In a study performed in women, testosterone and androstenedione levels correlated positively with waist diameter [18] and with an increased abdominal fat [55]. A study showed, in obese postmenopausal women treated with testosterone for 9 months, an increased visceral fat mass in comparison to a control group-receiving placebo [56]. It was demonstrated that testosterone could increase insulin gene expression [57]. However, a study showed insulin resistance in hyperandrogenic condition [58]. In addition, testosterone administration in hypogonadal men resulted to improve the insulin sensitivity [59].

The reconsideration of several studies on T2DM may help us to understand the link between testosterone and adiposity. Testosterone replacement therapy seems to improve glycometabolic control as well as fat mass in T2DM subjects [60]. Prospective studies [61] showed that the incidence of T2DM was greater in those persons with lower levels of total testosterone [62, 63] or free testosterone even after adjusting for body mass index [64]. A study, however, found that the risk ofT2DM associated with testosterone, as well as, to estradiol and SHBG levels, was not independent of the body mass index or the waist circumference [65]. Contradictory results have also been found when the dependent variable was the metabolic syndrome. Although testosterone levels usually predict the risk of this syndrome [63, 66, 67], this association disappeared after adjusting for indexes of adiposity [63, 67]. We believe that to clarify whether testosterone could have a role on adiposity or in the development of the metabolic disease in women, further investigations are needed, but it could be a mistake to conclude that endogenous or exogenous testosterone is even deleterious in women.

Androgens and the cardiovascular system

Androgens are fundamental hormones not only for men, but also for women in whom represent the precursors for estrogen biosynthesis in ovaries and extragonadal tissues [67], and exert important actions in all body directly through androgen receptors [68, 69].

Before menopause, testosterone is produced primarily in the ovary and adrenal cortex. Its conversion to dihydrotestosterone amplifies testosterone action because dihydrotestosterone strongly bind a specific receptor, the androgen receptor (AR) [69, 70]. Furthermore, there is a decline of serum androgen levels with age, after menopause [71].

Also, after the menopause transition, the classical pathway of androgen action involves binding to its receptor, although testosterone continues to be produced by ovarian stromal tissue and by peripheral conversion of delta 4 Androstenedione (A4) and DHEA [72]. AR is a ligand-activated transcription factor, a member of the nuclear receptor superfamily acting on the genome [73]. Furthermore, there is evidence for rapid, nongenomic effects of androgens leading to smooth muscle relaxation or neuromuscular signal transmission [74]. DHEA and DHEAS are the most abundant circulating adrenal steroid hormones in humans [30] consequently it could be

important to investigate on their actions on vasculature. It was showed that DHEA increases endothelial NO release, with a consequent effect on vasodilation [31]. Recent evidence on DHEA showed that it inhibits human vascular smooth muscle cell proliferation independently of AR and estrogen receptors (ER) [75]. Recently, a membrane-bound, G protein-coupled receptor for DHEA has been identified in bovine vascular endothelial cells (ECs), suggesting again a direct effects of this hormone on vascular system [75]. If these sites could represent, in a future, a possible therapeutical targets remain to clarify, however, an androgen therapy developed to prevent, for example, the coronary restenosis could be an interesting option.

However, data are insufficient on this issue and their effects remain to be clarified.

Differently, conversion of testosterone to estradiol, by the aromatase enzyme, may explain some of its effects by ER activation. Aromatase activity has been detected in many vascular tissue, especially in endothelium and smooth muscle layers [68, 76, 77].

Moreover, it is well known that testosterone binds its transporter protein, SHBG, having a cell surface receptor, which may have a variety of biological actions [78, 79], needing further demonstration.

However, AR is expressed in all cells type in the vascular system, including endothelial cells and smooth muscle cells, with differences between sex [80]. AR expression is related to androgens exposure, as demonstrated by a study performed in rabbit arteries where AR mRNA increased after a short-term exposure to testosterone [81]. This study is also relevant since showed, after endothelium damage, that testosterone administration can inhibit the atherosclerotic plaque formation [81]. Furthermore testosterone may induce a vasodilatation response via a rapid, nongenomic mechanism [82] and vasodilatation occurs in many arterial beds, including coronary arteries [83].

The relation between endogenous androgens and cardiovascular disease in women has been explored [69] contributing to elucidate the beneficial role of these hormones.

In a case–control study in postmenopausal women it was found that higher total testosterone and SHBG were inversely related to carotid atherosclerosis [84]. Other authors showed a low prevalence of carotid atherosclerotic plaques in postmenopausal women having high levels of total endogenous testosterone [85]. Furthermore, endogenous levels of androgens also affect vascular reactivity, in fact it was found that high levels of endogenous Testosterone in menopause were associated with high flow-mediated dilation measured at brachial artery [86] suggesting, that the development of cardiovascular disease after menopause may be due not only to the estrogen decline.

Flow-mediated dilation, expressing the endothelium-dependent artery vasodilation, was increased by administration of parenteral testosterone, in postmenopausal women taking estrogen [87]. These investigations support the concept that testosterone could have important physiological actions in postmenopausal women.

It has been found that also oral DHEA therapy (100 mg/day for 12 weeks) improves flow-mediated dilation of the brachial artery and increases acetylcholine induced vasorelaxation in postmenopausal women, via an AR- or ER-independent pathway [74].

Moreover, in healthy menopausal women, DHEA administration over 12 weeks significantly increases endothelium-mediated vascular reactivity in both large and small blood vessels, with no change in blood pressure or plasma lipid profiles [74]. The studies on the effects on vascular reactivity are relevant since it is well recognized that cardiovascular disease presence, also in coronary arteries, is associated with endothelial dysfunction [88–90].

Studies in animals and humans indicate that parenteral testosterone does not adversely affect the coronary artery district [91–93].

Although a study shows that about a third of women taking 1.25 mg methyltestosterone report at least one symptom of virilisation after 2 years [94], in a study it was showed that a low dose of methyl testosterone (1.25 mg) is lipid neutral when given with standard doses of estrogen [95]. Actually, testosterone results safely used as hormone replacement therapy for libido disturbances in postmenopausal women [96–98].

In a study it was seen that long-term testosterone implant therapy does not adversely affect lipoprotein lipids associated with estrogen use [96].

Conclusions

Substantially, new therapeutic targets may arise understanding how androgen could influence the fat distribution, the metabolic disease onset, the vascular reactivity, and cardiovascular risk, in both sex.

Many studies confirm that DHEA-S has anti-obesity properties thank to its influence on body fat distribution, metabolic profile, and on expression of specific adipokines [44, 45]. Obesity causes a chronic inflammatory state that plays an important role in cardiovascular complications. DHEA-S may represent a possible therapeutic agent and was yet proposed as medications. New evidences are now emerging on the positive actions of endogenous testosterone on cardiovascular system in postmenopausal women, as well as of exogenous testosterone, without hyperandrogenemia. Further investigations are needing on this area, in particular interventional trials including populations of

postmenopausal women. We believe that the dream of a single medication, probably an hormonal therapy, for postmenopausal women, is not come to an end [3, 4, 99, 100].

Conflict of interest All authors state that they have no conflicts of interest, no exist financial arrangement between authors and companies, or work being concurrently published or reviewed that is relevant to the review of the manuscript being submitted.

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