Review Article

FEMALE ANDROGEN DEFICIENCY

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ABSTRACT
The evidence suggest that androgen deficiency in women induces sexual dysfunction as its main clinical manifestation, in particular reduced libido. However, other factors may be involved in the genesis of this disease, such as interpersonal relationships, social stressors, physical inactivity and the partner. The prevalence of sexual problems among women ranges from 9 to 43% and, recently, many studies have reported that androgens are beneficial not only for women's sexual function, but also for mood disorders and vasomotor symptoms. This is why physicians should include androgen deficiency syndrome in their differential diagnosis, even in women with adequate estrogen levels. Our objective was to present the practical aspects of this disease, emphasizing diagnosis and focusing on treatment. This review searched PUBMED for publications from the last 51 years, up to May 2010, including consensus statements and expert opinions and identified 105 articles. We concluded that the androgen deficiency syndrome in women is overlooked in clinical practice. There is no consensus in the literature regarding diagnosis or treatment, including choice of drug, route of administration and time of application.

Key words: Testosterone. Androgens. Menopause.

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Introduction

Androgen deficiency (AD) is a syndrome in which either androgen production or activity is reduced and can occur at any age.

Reductions in androgen production may be physiological in aging, both in the ovaries and in the adrenal glands, especially reductions in dehydroepiandrosterone (DHEA) production[1]. However, in young women any type of reduction in androgens may be a sign of AD, as is observed in women who undergo oophorectomy , those who have hypogonadotropic hypogonadism, gonadal dysgenesis or adrenal dysfunction (Addison's syndrome). Furthermore, other conditions can also result in ethanol and also hyperthyroidism, pregnancy and liver cirrhosis[2]. This is because, by increasing levels of sex hormone binding globulin (SHBG), they can reduce free androgen levels[3].

Female androgen deficiency began to be considered an important clinical entity in 2002, when a meeting held at the University of Princeton culminated in a consensus defining it as a syndrome consisting of reduced libido, reduced feeling of wellbeing or mood changes, persistent tiredness and inexplicable loss of bone mass, reduction in muscle strength, thinning of hair and altered cognitive function and memory[4].

Although there is no data on the prevalence of this condition, it is estimated that 16 million North American women over the age of 50 have reduced libido (the syndrome's principal symptom) and a significant proportion of them have reduced androgen concentrations in serum[5]. For this reason, many authors support increasing testosterone prescriptions, despite a lack of consensus regarding their efficacy for sexual dysfunction[6]. Furthermore, it should also be taken into account that prescribing testosterone without estrogens, does not provide benefits in terms of libido or coital frequency, irrespective of the route of administration[7].

In response to the lack of consensus, this review began by searching for articles published between 1959 and May of 2010 and indexed on PUBMED. This search identified a total of 105 articles, 17 of which were chosen for analysis (four double blind placebo-controlled randomized studies of up to 4 months' duration, eight bibliographic reviews and two specialists' consensus statements). The primary objective of the review is to describe the practical features of diagnosing androgen deficiency syndrome

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and the options for treating this condition that significantly compromises women's quality of life.

The review

Androgens are C19 steroids that originate from cholesterol and the main sources of production in women are the adrenal glands, ovaries and peripheral tissues such as adipose, muscle and cutaneous tissues. Figure 1 illustrates steroidogenesis with rates of production and the organs involved. It will be observed that testosterone (T) is the end of the androgen pathway and that it is created by conversion of androstenedione (A) in the blood (50% from the ovaries, 25% from the adrenal glands and 25% peripheral conversion). In turn, dehydroepiandrosterone (DHEA) is the principal precursor of A and T androgens and is produced in the ovaries (20%) and adrenal glands (50%) and also derived from dehydroepiandrosterone sulphate (DHEAS) in the blood (30%). During the post-menopause, DHEA, which is the primary source of androgens, suffers a 60% reduction, leading to hypoandrogenism, which can compromise the bones, muscles, brain, mammary glands and vagina and affect metabolism of lipids, insulin and glucose[8].

In contrast with estradiol, which is an active steroid produced by the ovaries and which reaches all tissues, DHEA is an inactive precursor that is only transformed into active androgens in peripheral tissues containing the enzymes necessary for continuation of the process of steroidogenesis and, as a result, each tissue type builds its own hormonal identity (intracrinology), avoiding unnecessary exposure to active circulating steroids[9]. In contrast with DHEA, the sulphate form, DHEAS, is lipophilic and, because it is unable to penetrate cells, it functions as a reserve pool.

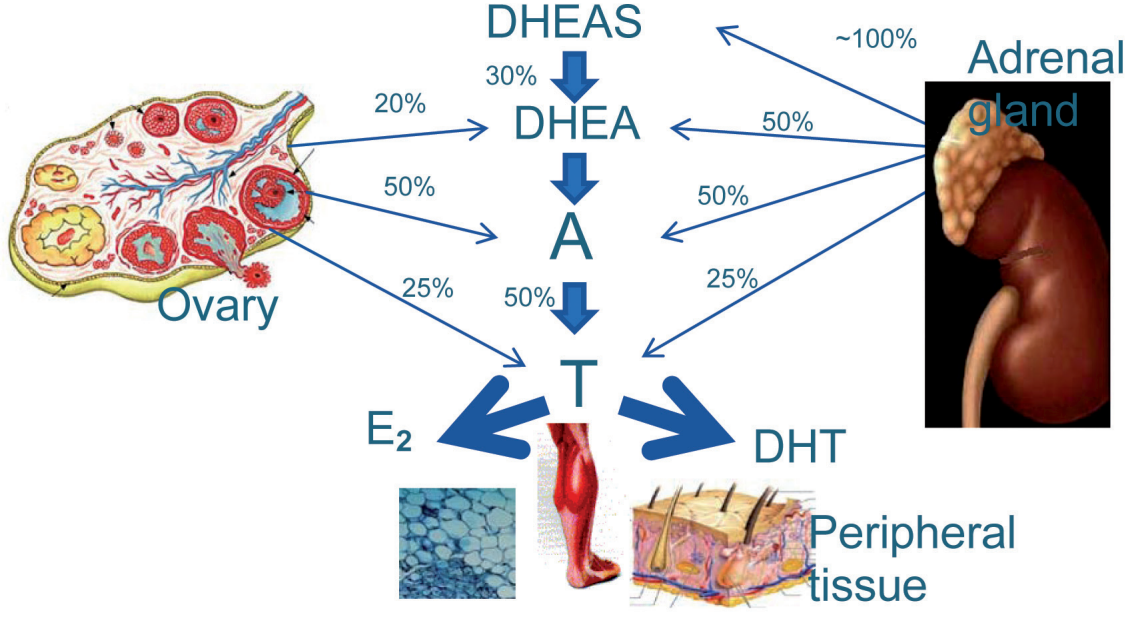
In turn, testosterone and its principal active metabolite (dihydrotestosterone -DHT) are more powerful androgens. Their biological effects are expressed by their free fraction, they are preferentially inactivated in the liver and excretion is fecal or renal.

Diagnosis of female androgen deficiency is based on patient history, physical examination and laboratory results. Serum testosterone assay is an accessible test from an economic point of view, but its use is questionable because of the low specificity and sensitivity of the radioimmunoassay. Furthermore, it is incapable of detecting extremely low testosterone levels and there is not yet a reference for normal levels in the female population[10]. Currently, the principal indication for serum testosterone assay is to monitor supraphysiological concentrations during treatment. The gold standard for serum testosterone assay is to measure free testosterone by equilibrium dialysis, but its high cost and restricted availability means the test has limited applications.

Despite all of these limitations and even in the knowledge that serum testosterone levels may not correspond with their biological activity (intracrinology), many authors still recommend their use in clinical practice and consider that levels of free testosterone ≤ ¼ of the normal level for the patient's reproductive age are suggestive of androgen deficiency syndrome[11].

The Princeton consensus suggests the diagnosis of AD and recommends that it should be treated when women with premature ovary failure or physiological menopause exhibit signs and symptoms including reduced libido, reduced feeling of wellbeing

Figure 1 - steroidogenesis in the ovaries, adrenal glands and peripheral tissues of the principal hormones related to female sexual function



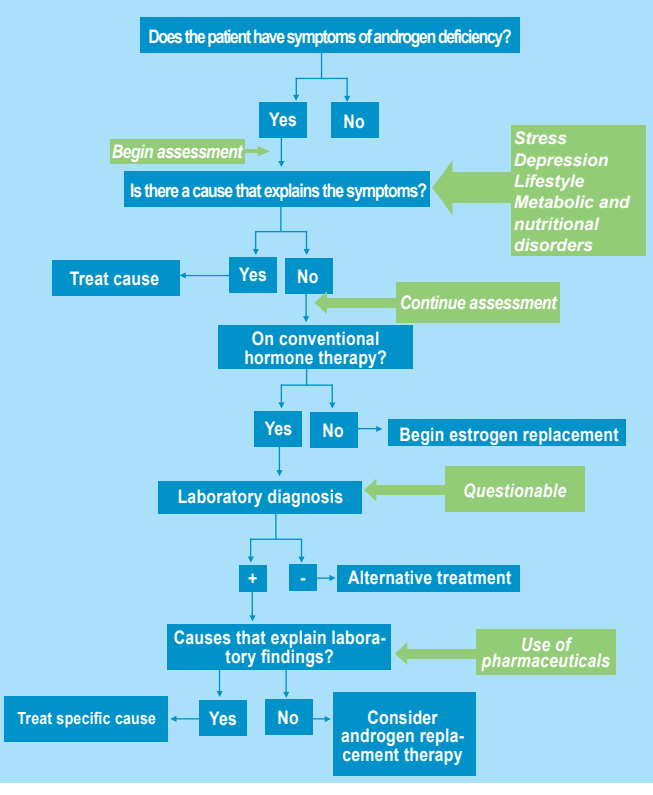
E2= estradiol and DHT= dihydrotestosterone DHEA= dehydroepiandrosterone
DHEAS= dehydroepiandrosterone sulphate A= androstenedione and T= testosterone

or mood changes, persistent and unexplained tiredness, loss of bone mass, reduced muscle strength, thinning of hair and altered cognitive function and memory[3] (Algorithm 1).

The explanation for symptoms persisting among patients given appropriate conventional hormone therapy is based on reduced DHEA production in the adrenal glands and reduced enzyme activity to convert it into active steroids; and this is the reason that many authors believe that it is DHEA and not estrogen that is the physiological hormone that should be replaced after menopause[11].

Although no androgens have been approved by the FDA (Food and Drugs Administration) for the treatment of female sexual dysfunction, an abusive number of prescriptions are issued on the basis of this complaint. Therefore, at the time of writing, sexual dysfunction treatment using androgen replacement is being carried out empirically, including in Brazil.

Algorithm 1 - Diagnosis of androgen deficiency



Authors who recommend treating with testosterone combine it with estrogen. Many of them have demonstrated efficacy for treating the symptoms of androgen deficiency, especially sexual dysfunction, vasomotor symptoms, bone mineral density and muscle strength[12], and there are also studies that of observed that this combination reduces cardiovascular risk and the incidence of liver damage.[10]

Adverse effects that should be taken into account include acne, weight gain, increased facial hair, worsening of the lipid profile, altered liver function and, more rarely, changes in the pitch of voice, clitoromegaly and virilization of female fetuses if pregnancy occurs during treatment[13]. However, with appropriate doses of 300 mcg of testosterone per day, such effects are reported rarely.

There is also concern about the impact of testosterone and its metabolites on the breasts and endometrium of women who express aromatases in an abnormal manner. In this subset it is possible that a greater proportion of androgens are converted into estrogens, which would explain the increased oncogenic risk. Nevertheless, there is as yet no consensus in the literature with relation to these findings, since some epidemiological studies have demonstrated an increased risk whereas others did not detect this association[13]. Notwithstanding, it is recommended that women taking androgens should be monitored for cancer of the endometrium or breasts, following the same recommendations as for conventional hormone treatment.

Another question that remains to be answered relates to the possibility of cardiovascular risk when testosterone is administered orally[14], since studies have detected increases in LDL and reductions in HDL cholesterol and greater abdominal fat accumulation (androgenic pattern) promoting an increase in inflammatory cytokines and a reduction in adiponectin.

More recently, studies have been published on the use of testosterone patches[15] with menopausal women that have demonstrated improvement in sexual function. Nevertheless, these results must be supplemented by assessments of the longer-term effects, indicating a need for further studies in this area. Additionally, this method is not yet available in Brazil and has not been approved by Anvisa.

Commercially available androgens

The most common routes of androgen administration are listed below. Neither, sublingual, buccal nor subcutaneous products are recommended by pharmaceutical surveillance authorities.

A) Injectable (industrial):

These may be oil-based, in which case release is slow, or they maybe ester-based, which makes free T rapidly available in circulation. These are marketed as different esters of testosterone, combined or not with estrogens. They involve an increased risk of exposure to supraphysiological doses, increasing the risk of adverse effects.

Testosterone decanoate is an anabolic steroid which has an indirect androgenic activity because it reduces SHBG levels and increases free testosterone. Administered (at a dosage of 50mg) every 40 days up to a maximum of six times per year, it is the safest option and is well tolerated by patients[16].

B) Oral (industrial or compounded):

When androgens are administered orally, they are rapidly metabolized by the liver, which may lead to hepatotoxicity and gastrointestinal disorders, in addition to reducing HDL and raising LDL cholesterol. Methyltestosterone is of greatest interest of the formulations available because it causes fewer gastrointestinal reactions and is better tolerated[16]. This product should be made up by a compounding pharmacist and the dosage varies from 1.25mg to 2.5mg per day.

Other options include micronized testosterone and DHEA[17].

C) Transdermal testosterone patches (industrial)[17]:

Each 28cm^2 patch contains 8.4mg of testosterone and releases 300μg/day. Patches are the most physiological treatment option and should be changed every 3 or 4 days. Not yet available in Brazil or approved by Anvisa.

D) Topical testosterone (compounded)[17]:

Testosterone propionate cream, 1% to 2% in white petroleum jelly, is a good option and should be applied to the clitoris and labia minora daily.

Conclusions

Despite the reports of beneficial effects on sexual dysfunction and other symptoms of AD syndrome and despite its short-term safety being well-established (6 months), the long-term effects of androgen therapy are not well-documented[17].

Menopausal women with androgen deficiency syndrome are one of the most important applications for androgen therapy because the treatment improves quality of life. Physicians who judge the treatment to be necessary should inform their patients about possible risks and adverse effects and the efficacy of treatment. When prescribing, care must be taken with the dosage, route of administration and length of treatment and lipids should be controlled rigorously and breasts and liver must be monitored.

Conflicts of interest: none

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