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Review

The role of androgens in women's health and wellbeing

Vittorio E. Bianchi [a], Elena Bresciani [b], Ramona Meanti [b,*], Laura Rizzi [b], Robert J. Omeljaniuk [c], Antonio Torsello [b]

[a] Endocrinology and Metabolism, Clinical Center Stella Maris, Strada Rovereta 42, Falciano 47891, San Marino
[b] School of Medicine and Surgery, University of Milano-Bicocca, Via Cadore 48, Monza 20900, Italy
[c] Department of Biology, Lakehead University, 955 Oliver Rd, Thunder Bay, Ontario P7B 5E1, Canada

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ABSTRACT

Androgens in women, as well as in men, are intrinsic to maintenance of (i) reproductive competency, (ii) cardiac health, (iii) appropriate bone remodeling and mass retention, (iii) muscle tone and mass, and (iv) brain function, in part, through their mitigation of neurodegenerative disease effects. In recognition of the pluripotency of endogenous androgens, exogenous androgens, and selected congeners, have been prescribed off-label for several decades to treat low libido and sexual dysfunction in menopausal women, as well as, to improve physical performance. However, long-term safety and efficacy of androgen administration has yet to be fully elucidated. Side effects often observed include (i) hirsutism, (ii) acne, (iii) deepening of the voice, and (iv) weight gain but are associated most frequently with supra-physiological doses. By contrast, short-term clinical trials suggest that the use of low-dose testosterone therapy in women appears to be effective, safe and economical. There are, however, few clinical studies, which have focused on effects of androgen therapy on pre- and post-menopausal women; moreover, androgen mechanisms of action have not yet been thoroughly explained in these subjects. This review considers clinical effects of androgens on women's health in order to prevent chronic diseases and reduce cancer risk in gynecological tissues.

1. Introduction

In men, and in women, endogenous androgens which include testosterone, dihydrotestosterone (DHT), androstenedione (A), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are synthesized in various tissues including the (i) adrenal glands, (ii) ovaries, (iii) testis, (iv) placenta, (v) brain, and (vi) skin [1].

In women, circulating testosterone is derived in part from ovarian and adrenal gland secretion; by comparison, similar amounts are derived from the enzymatic conversion of A and DHEAS [2]. In the ovary,

Abbreviations: 17β-HSD, 17β-hydroxysteroid dehydrogenase; 3α-HSOR, 3α-hydroxysteroid oxidoreductase; 3βHSD, 3β-hydroxysteroid dehydrogenase; A, androstenedione; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; AR, androgen receptor; ASC, adipose stem cell; Aβ, β-amyloid; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; BMD, bone mineral density; C/EBPα, CCAAT-enhancer-binding prontein α; C/EBPβ, CCAAT-enhancer-binding protein β; CNS, central nervous system; CVDs, cardiovascular diseases; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; EPIC, European Prospective Investigation into Cancer and Nutrition; ERα, estrogen receptor α; ERβ, estrogen receptor β; FAI, free androgen index; fALS, familial amyotrophic lateral sclerosis; FSH, follicle-stimulating hormone; GLUT-4, glucose transporter type 4; GSM, genitourinary syndrome of menopause; HA, iperhydrogenism; HC, hormonal contraceptives; HER2, human epidermal growth factor receptor 2; HRT, hormone replacement therapy; RLS, reproductive life span; HSDD, hypoactive sexual desire disorder; IARC, International Agency for Research on Cancer; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; KO, knock out; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LH, lutheinizing hormone; LSD1, lysine-specific demethylase 1 A; ND, nandrolone decanoate; NDs, neurodegenerative diseases; NR3C4, nuclear receptor subfamily 3, group C, member 4; PCOS, polycystic ovary syndrome; PD, Parkinson disease; PKA-RegIIβ, protein kinase A regulatory-IIβ component; PNS, peripheral nervous system; PPARγ, peroxisome proliferator-activated receptor γ; PR, progesterone receptor; sALS, sporadic amyotrophic lateral sclerosis; SARMs, selective androgen receptor modulators; SC, subcutaneous; SERMs, selective estrogen receptor modulators; SHBG, sex hormone-binding globuline; SOD1, superoxide dismutase 1; SSEs, satisfying sexual events; T2DM, type 2 diabetes mellitus; TMN, Tumor Size Nodal Status and Distant Metastasis Staging; TNBCs, Triple-Negative Breast Cancers; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor; VVA, vulvovaginal atrophy

* Corresponding author.
E-mail addresses: dott.vbianchi@gmail.com (V.E. Bianchi), elena.bresciani@unimib.it (E. Bresciani), r.meanti@campus.unimib.it (R. Meanti), laura.rizzi@unimib.it (L. Rizzi), romeljan@lakeheadu.ca (R.J. Omeljaniuk), antonio.torsello@unimib.it (A. Torsello).

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testosterone production increases during follicular phases and achieves maximal levels at ovulation and the luteal phase [3–15]; the adrenal glands, by comparison, produce only small amounts of testosterone [2]. The bulk of circulating testosterone is reversibly bound to plasma proteins including (i) sex hormone-binding globulin (SHBG) (50–60%), and (ii) albumin (40–50%). Only 1–2% of plasma testosterone is free, and bioavailable [16]; moreover, this free fraction may be further reduced by increased levels of SHBG induced by estrogen replacement therapy [4].

Half of the circulating levels of testosterone and DHT are derived from enzymatic conversion of circulating adrenal pre-androgens (DHEAS, DHEA and A) and estradiol [11,17]. Testosterone conversion to DHT is mediated by 5α-reductase (type I and II Isoforms). Of these androgens, DHT has the greatest affinity for the androgen receptor (AR) and is the most biologically potent of the endogenous androgens. DHT cannot be further aromatized to estrogen [2], thereby enhancing its half-life.

Plasma DHEA is derived from (i) secretion from zona reticularis cells of the adrenal cortex (50%), (ii) ovarian secretion (20%), and (iii) peripheral DHEAS metabolism (30%) [2]. DHEA itself is fragile and may be converted to A by 3β-hydroxysteroid dehydrogenase (3βHSD); subsequently, A may be converted to testosterone by 17β-hydroxysteroid dehydrogenase (17βHSD), as well as to DHT by 5α-reductases in endometrial tissue [8,9].

In women, approximately one half of circulating DHEA is derived from pre-androgens [11]; in particular, the zona reticularis accounts for 80% of the DHEAS in females' circulation, [5] with the balance arising from the ovaries [6]. The principal pre-androgen is DHEAS, which is converted into DHEA, DHT and estrogens [7]. Plasma DHEAS, which exists in substantial concentrations, serves as a large substrate reservoir for conversion to DHEA, androgens and/or estrogens in peripheral tissues. Substantial plasma concentrations of DHEAS are, in part, a consequence of its avid binding by albumin which prolongs its half-life [18,19]; consequently, plasma DHEAS concentrations are reflective of adrenal androgen production [2]. DHEAS secretion is mainly under hypothalamic/pituitary control, being stimulated by ACTH [2]; however, its secretion is modulated by other hormones such as estradiol, prolactin, and IGF-1.

To a great extent, testosterone is derived from A metabolism by 17βHSD (Type 5) (Fig. 1) [10].

In women, high plasma levels of testosterone are correlated with the incidence of polycystic ovary syndrome (PCOS) [12], observed approximately in about 20% of young women. PCOS is associated with oligomenorrhea, ovulatory dysfunction and infertility [13]. Hyperandrogenism in PCOS is a critical factor in predisposing women to obesity, insulin resistance, and metabolic syndrome [14].

In adult women, plasma androgens and SHBG levels decline progressively with advancing age, with large and significant decreases correlated with menopause; to illustrate, total testosterone levels in women aged 65–74 years is approximately one-third that observed in 20 years olds. By comparison, free testosterone levels decrease with age by 90% while levels of DHEAS and A both decrease by approximately one-third [17,20]. In premenopausal women, the ovaries are the principal source of estradiol, which functions as a circulating hormone acting on distal target tissues. In postmenopausal women, due to cessation of ovarian function, estrogens are produced in a number of extragonadal sites, including adipose tissue, bone, brain and vascular endothelium and aortic smooth muscle cells, where they act locally in a paracrine or intracrine fashion. Their local tissue concentration depends on an external source of androgenic precursors, because the extragonadal tissues are not able to convert cholesterol into steroids [21].

Whether the postmenopausal ovary has significant endocrine activity in androgen production is somewhat controversial. Some studies reported that circulating levels of androgens (i.e. T, A, DHEA and DHEAS) are extremely relevant in providing substrate for peripheral estrogens biosynthesis, through peripheral aromatization of A and T [22]. As aromatase activity remains unaltered in oophorectomized women, it has been proposed that the postmenopausal ovary is not a source of significant androgen production [23]. Conversely, other studies observed that bilateral oophorectomy resulted in a pronounced and sustained reduction in both total and bioavailable T levels, suggesting that the postmenopausal ovary represents a critical source of androgens throughout the lifespan of older women [24].

From a pharmacologic perspective, anabolic-androgenic steroids (testosterone congeners) which may be derived from testosterone include oxandrolone, stanozolol, nandrolone, trenbolone, and other species [25]. Androgens are classified into two pharmacologic classes: (i) aromatizable androgens, such as testosterone, which is metabolized to estradiol by aromatase which then interacts with both estrogen receptor alpha and beta (ERα, ERβ) [26], and (ii) non-aromatizable an-

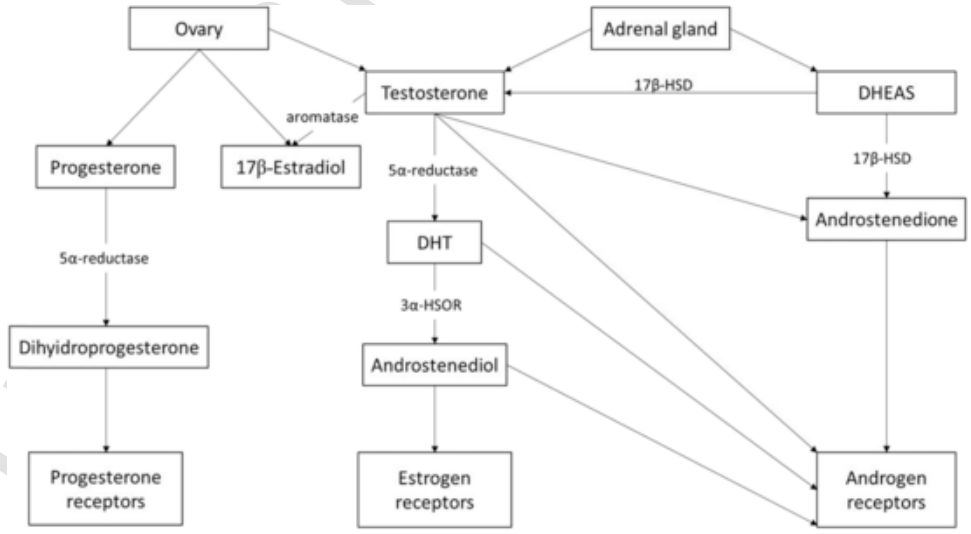

Fig. 1. Androgens production in women. In women, androgen production occurs largely in the ovaries and adrenal glands. Ovaries secrete progesterone, 17β-estradiol, and testosterone. Dihydroprogesterone, which binds to progesterone receptors, is derived from progesterone reduction by 5α-reductase. Adrenal glands predominantly secrete testosterone and DHEAS. Testosterone may be (i) partially aromatized to estradiol or (ii) reduced to DHT by 5α-reductase. Androstenenediol, which may derived from DHT by the action of 3α-hydroxysteroid oxidoreductase (3α-HSOR), binds estrogen receptors. DHEAS is converted to (i) androstenedione or (ii) testosterone by 17β-HSD. Testosterone, DHT, androstenediol and androstenedione activate androgen receptors.

drogens, such as DHT, which binds exclusively to the AR. Synthetic androgens, such as oxandrolone and stanozolol, are only modestly susceptible to aromatization thereby mitigating their estrogenic potential.

A most confounding difficulty with clinical studies involving gonadal hormones is accurate and reliable measurement of plasma hormone levels [27]. Furthermore, as plasma androgen concentrations in women are low, commercially available testosterone immunoassays usually provide conflicting results. As a consequence, accurate measurement of plasma levels of testosterone, DHT, and estradiol in women require an alternative validated method such as liquid chromatography-tandem mass spectrometry (LC-MS/MS) [28] which is far more technically involved and expensive than a commercial immunoassay.

2. Androgen receptors in women

Androgen receptors (AR), also known as nuclear receptor subfamily 3, group C, member 4 (NR3C4), are broadly expressed in several female tissues including the ovary [29], endometrial tissue [30], breast, brain, bone, and heart [31] and which mediate crucial functions. Several AR-dependent diseases include cancer of the prostate, breast, ovary, pancreas, as well as anabolic deficiencies such as muscle atrophy and osteoporosis [17]. Several specific AR-ligands are considered potential therapeutic tools, depending on the specific type and stage of the disease [32].

In reproductive tissues, the absence of AR, as observed in female mice knock-out (KO) for AR, significantly reduces the uterine and endometrial area, compared to wild mice [33], probably causing an alteration in neuroendocrine signaling. The loss of AR is associated with dysfunctions in the follicle development, ovulation, and fertility [34]. AR contribute to endometrial gland function and uterine homeostasis [35]; to illustrate, uterine glandular epithelial cell development is AR-dependent and specifically sensitive to DHT in ovariectomized mice [36]. More recently, there is an increasing recognition of the potential of androgen bioactivity being expressed through novel non-genomic pathways [37].

3. Androgens and ovarian function

Androgens play a direct and important role in regulating female reproductive function; specifically, they are essential to coordination of ovarian function and fertility, stimulation of granulosa cells and oocytes, favoring follicular development [30,38], and regulation of all phases of the follicular maturation [39]. In farm animals, androgen administration stimulated follicular and ovulatory responses [40], increasing AR mRNA levels in the follicle [29], and determining the number of the ovulatory follicles [41]. Testosterone promoted the first follicular activation, while 17β-estradiol had no significant effect [42]. In AR KO mouse model, the reproductive capacity was reduced, thereby indicating that ovulation is an AR-dependent mechanism [43].

Sen et al. [44] demonstrated that physiological levels of androgens are needed to increase follicle-stimulating hormone (FSH) secretion and favor follicle development and ovulation in mice. Another study reported that high FHS/LH ratio and low plasma levels of testosterone could be used to identify women at risk of inadequate ovulatory responsiveness. [45]. This finding has accentuated the critical role of androgens in follicular development and fertility and has significantly influenced the treatment of infertility in women.

Various studies have demonstrated that DHEA supplementation in women with inadequate ovarian responses significantly increases numbers of oocytes, fertilization, and the pregnancy rate [46–48]; these findings have been confirmed by a further meta-analysis [49]. In women with a low live birth rate, pre-treatment with testosterone, compared with placebo, was correlated with higher live birth rates up to four times, from 8% to 32% [50]. By comparison, androgen plasma levels after ovarian stimulation were not correlated with frequency of conception and live birth rates in young women with unexplained infertility [51]. However, these findings should be augmented with data from additional studies performed on large numbers of patients before a meaningful conclusion can be made.

Recently, the relationships between plasma androgen levels and incidence of ovarian cancer development have been a matter of debate. Trabert et al. showed that androgens and their metabolites were not associated with ovarian cancer risk (although their data were not adjusted for estradiol levels). Their findings, demonstrated that tissue levels of AR, rather than testosterone levels, were a more reliable predictor of the risk of ovarian cancer [52]; nonetheless, the role of AR in the etiology of ovarian cancer requires further elucidation.

Other data discount the role of androgens in development of ovarian cancer [53]; to illustrate, treatment with synthetic androgen analogues was not found to be related to the onset and/or development of ovarian cancer [54]. In sharp contrast, Ose et al. [55] demonstrated that high levels of plasma testosterone were correlated with development of invasive epithelial ovarian cancer, the most severe gynecological malignancy, and with other different subtypes of cancer. Recently, the relationship of plasma androgen levels and incidence of ovarian cancer was further clarified [56]; specifically, a large case-controlled study in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort did not find any correlation between androgens and SHBG with invasive ovarian cancer [57].

In women with PCOS, no association between androgen levels and ovarian cancer was observed [58] even if excess of androgens may play a role in the origins of the PCOS. Androgens exert a common inhibitory effect on the ovary and endometrium [59]. The administration of androgens in women may, however, cause macro and microscopic alterations in the ovary, endometrial atrophy, and reduction of the breast gland accompanied by fibrotic tissue formation [60].

4. Effects of androgens on the endometrium

Recent findings suggest that androgens may modulate both physiological [36] and pathophysiological conditions of the endometrium by acting directly through AR-mediated mechanisms, and indirectly, as precursors for local estrogen synthesis. Endometrial androgen effects have been studied using human as well as rodent tissue samples [61]. Results obtained by immuno-histochemistry and Real-time PCR analysis showed that human and mouse AR expression changed significantly during the menstrual/estrous cycle; it increased in epithelial cells during the proliferative phase and significantly decreased in the secretory phase [62]. This temporal pattern of AR expression reflects the up-regulation by estrogens and the down-regulation in response to falling progesterone levels [36,62,63]. Indeed, in ovariectomized mice, the administration of estrogens caused an increase in AR immunoreactivity, whilst that of progesterone downregulated AR expression, as observed in the secretory phase of the menstrual cycle [64] and in response to synthetic progestins in women [65].

A crucial AR-mediated action of androgens [63] is to influence the dynamic changes in cell functions that regulate the restoration of endometrial tissue integrity before the onset of the proliferative phase of the normal cycle, thereby modulating the repair of the tissue without scars after the menstrual cycle and pregnancy, including placental accretion [66–68]. In the menstrual period, plasma concentrations of androstenedione and testosterone are relatively high, whereas estrogen and progesterone levels progressively decline [65]. It has been postulated that elevated blood concentrations of androgens in women with PCOS may be functionally associated with heavy or prolonged bleeding during menstruation [69]. The delayed wound healing caused by DHT in *in vitro* experiments [63] is in agreement with data which shows the impact of androgens on skin repair, a process which shares key features with endometrial repair [65,70].

Long-term testosterone administration in female to male transsexual subjects causes glandular atrophy of the endometrium, and reduced cellular proliferation similar to that observed in the postmenopausal endometrium [71,72]. The same effect is observed during treatment with androstenedione, a weak androgen [73], suggesting that androgens may have direct impacts on both endometrial epithelial and stromal cells, inducing an anti-proliferative effect, possibly by antagonizing the bioactivity of estrogens [36]. By contrast, data obtained in experiments performed in ovariectomized rodents were at variance with findings from humans with respect to DHT effects on uterotrophic responses [36,74]. These discrepancies may be due, in part, to the rats' lack of ovaries, and/or to the supraphysiological dosages of androgens administered. As well, these discrepancies may arise, in part, from differential capacities for steroidogenesis and fundamental differences in adaptive physiology between rodents and humans [36].

A number of studies have highlighted possible roles for androgens in hormone-dependent cancers in women and have proposed AR as potential therapeutic targets in breast, ovarian and endometrial cancers (EC) [75,76]. Indeed, it has been reported that the presence of AR in the endometrial epithelium of postmenopausal women is critical for reducing the incidence and severity of EC [77], the fourth most common cancer in women in the industrialized world. AR is expressed by healthy postmenopausal endometrial epithelium; its subsequent deficit in EC is associated with poor survival, and may be considered a negative clinical prognostic marker. Various studies indicate that AR expression in stromal and epithelial cells in women with EC is preferentially lost in high-grade cancers compared to low-grade cancers [77]. As well, precursor lesions and well-differentiated primary tumors have the highest levels of AR, with a progressive decrease in AR levels associated with de-differentiation. Unfortunately, a large AR:ERα ratio is typically correlated with a severe prognosis, which suggests that AR signaling is context-dependent and that ERα status may influence the effects of AR. [78–80].

The population incidence of EC has been linked to various factors including (i) rates of obesity in premenopausal women [81], (ii) exposure to endogenous hormones, particularly androgens [36] and, (iii) estrogens only hormone replacement therapy [82]. Compelling evidence for androgen influence on EC risk arises from studies which evaluated PCOS women with androgen excess and clinical manifestations, such as hirsutism and irregular periods [83], associated with increased EC risk [84]. Plasma levels of testosterone, androstenedione and DHEAS were determined in a large cohort of pre- and post-menopausal women in EPIC [85]. Concentrations of total and free testosterone, evaluated prior to clinical diagnosis, were thereafter found to be positively correlated with EC risk; by comparison, plasma concentrations, of androstenedione and DHEAS were not similarly correlated with EC risk [85]. These findings were supported more recently by Audet-Walsh and coworkers, who demonstrated that plasma androgen levels were positively correlated with the risk of EC in postmenopausal women [86]. In pre-menopausal women, by comparison, administration of exogenous testosterone did not correlate with the incidence of EC [85]. In light of multiple endocrine treatments currently in clinical practice (some which target AR), these findings collectively recommend a rigorous examination of the relationship of AR activation and the risk, as well as, related cellular mechanisms associated with EC. AR dysregulation is also observed in endometriosis; administration of the synthetic androgen danazol (17α-ethinyl testosterone) is considered as an effective therapy in reducing lesion size [87]. Although effective, danazol in Europe is now less recommended as a consequence of its virilizing effects [88].

In conclusion, AR management has a significant therapeutic potential for endometrial repair, and prevention of diseases; as well, tissue AR density should be considered a prognostic marker of EC. However, the specific mechanism by which androgen interact with estradiol in the regulation of the endometrium requires further investigation.

5. Effects of androgens on vulvovaginal tissue and on sexual activity

From embryogenesis and throughout adult life, the vagina is a hormone-dependent organ; after genetic sex is established, subsequent sex differentiation depends on sex-specific response to androgens [89]. The influence of steroid hormones during vaginal organogenesis is reflected, in part, in the expression of AR in different vaginal tissues, including the mesenchyme of the vaginal plate and vagina, cervix and the uterine tube [90].

In the adult vagina, the ubiquitous expression of AR, both in proximal and distal regions, in epidermal keratinocytes and dermal fibroblasts suggests the importance of androgens in maintaining trophism and functionality [91–93].

Declines in AR expression are related to alterations of vaginal structure, including atrophy, thinning of the vaginal epithelium, as well as reductions in smooth muscle, collagen, and elastin [94,95]. Furthermore, attenuations of AR expression occur in concert with reductions in circulating androgen levels, typical of the menopausal period but common also during the reproductive years.

Classically, *de novo* synthesis of gonadal steroids from cholesterol was regarded to occur principally in gonads and the zona reticularis of the adrenal cortex; however, in 1995 the expression of steroidogenic enzymes was demonstrated in vaginal tissue [96]. This finding stimulated interest in the possible use of testosterone, and synthetic congeners, for the treatment of vulvovaginal atrophy (VVA) and genitourinary syndrome of menopause (GSM).

Multiple *in vivo* studies have demonstrated that testosterone promotes pelvic blood flow, which induces vascular smooth muscle relaxation, mucin secretion and enhanced lubrication. Moreover, T modulates pain and inflammation typical of VVA and GMS, but also modulates vulvar pain syndrome, genitopelvic pain/penetration disorder and chronic pelvic pain syndrome [90], which are associated with activation of cell-mediated immunity and increased secretion of cytokines.

To date, only a local androgen-based therapy is approved by the EMA and FDA and is restricted to treatment of VVA/GMS (Prasterone); paradoxically, there are no approved T preparations, because of the heterogeneity in study populations of the associated clinical trials.

T is the primary sex steroid responsible for libido. As a consequence, research on use of T in treatment of hypoactive sexual desire disorder (HSDD) and improvement of satisfying sexual events (SSEs) and sexual desire [97] began in the 1990s [98,99].

The World Health Organization has recognized female sexuality as an important component of women's health and a basic human right (https://www.who.int/reproductivehealth/publications/sexual_health/defining_sh/en/).

To date, sexual desire is evaluated by the Female Sexual Function Index [100] or the Brief Index of Sexual Functioning for Women [101]: women are questioned for sexual desire, sexual arousal, lubrication, orgasm, satisfaction, and pain to describe their sexual functioning.

Is well known that sexual activity in women is regulated by sex steroids (androgens, estrogens and progestins), whose plasma levels change during childhood, reproductive years, premenopausal and menopausal states, and in clinical conditions [94]. In normal conditions, plasma levels of testosterone [102], estradiol [103,104] and DHEAS [11] correlate with sexual desire and frequency of masturbation [105,106]. In fact, sexual behaviors increase near ovulation when the probability of conception is highest, in follicular and ovulatory phases of menstrual cycle, which correspond to an increase of estradiol and testosterone levels in plasma and saliva [104]. Moreover, in women with loss of libido, ovariectomized or at menopause onset [103,107], estradiol and testosterone levels significantly decrease by approximately 50–80%. These findings suggest that the development of androgen therapies for the treatment of female low libido are necessary and well founded.

Different studies have demonstrated that estradiol is more involved in female sexual functioning than is testosterone [108–110], but the effectiveness of estrogen therapy alone is insufficient to mitigate incidences of hot flashes, alleviate depression, and low-mood, or to increase sexual desire [111].

On the contrary, in menopausal women with HSDD, systemic testosterone treatment improved not only desire but also arousal, orgasmic function, pleasure, and sexual responsiveness [112]. As estrogen administration alone in postmenopausal women did not significantly improve sexual desire, several authors investigated effects of combined estrogen and testosterone treatment.

Lobo et al. [113], in a double-blind randomized study, examined the effects of esterified estrogen administration (0.625 mg/day) alone, or, in combination with methyltestosterone (1.25 mg/day) for sixteen weeks. Patients that received estrogen plus testosterone manifested a significant improvement in sexual desire, correlated with increased plasma levels of testosterone and reduced levels of SHBG.

Shifren et al. [114] evaluated the effects of conjugated equine estrogens (0.625 mg per day) and trans-dermal testosterone (150 μg and 300 μg per day) for 12 weeks in seventy-five young women (31–56 years old), who had undergone oophorectomy and hysterectomy. The higher testosterone dose correlated with an increased frequency of sexual activity and orgasm, but despite these positive results, trans-dermal testosterone treatment was commercially unsuccessful.

Their findings identified that testosterone enhanced the efficacy of estrogen therapy by its direct metabolization to estradiol in breast, bone, adipose, and brain, resulting in an increase in the amount of intracellular estradiol availability, resulting in increased sexual desire [103].

There were, unfortunately, several limitations in those testosterone trials which affected data interpretation including (i) heterogeneity of study populations, (ii) differences in instruments used to assess patient-reported outcomes [115] and (iii) difficulties in assessing testosterone effects due to differing testosterone doses and interactions with other hormones [116].

6. Androgens and breast cancer

According to statistics released by the International Agency for Research on Cancer (IARC), breast cancer is the most common cancer among women in the world and accounts for 15% of all female cancer deaths (https://www.who.int/news/item/03–02–2021-breast-cancer-now-most-common-form-of-cancer-who-taking-action [117]). Evidence indicates that life style (i.e., high-fat diet, alcohol consumption, lack of physical exercise and late motherhood) may influence the development of mammary gland cancer.

Prevention and early diagnosis employing diagnostic tests such as mammography, ultrasonography, magnetic resonance imaging and breast self-examination are necessary for detection of tumors or lesions, which may become tumors. However, imposed movement restrictions, as well as reprioritization of clinical tasks associated with the COVID-19 pandemic has effectively (i) deleted availability of clinical testing, (ii) exacerbated problems of late-stage diagnosis, and more significantly (iii) reduced or eliminated access to treatments (https://www.who.int/news/item/03–02–2021-breast-cancer-now-most-common-form-of-cancer-who-taking-action).

Consequent to diagnosis, cancer classification aims to provide an accurate prediction of cancer behavior in order to facilitate oncologic decision-making. In addition to traditional classification of breast cancer based on histologic type, grading, immunophenotype and TMN (Tumor Size, Nodal Status, and Distant Metastasis Staging), molecular classification includes intrinsic subtypes, integrative clusters, Next-Generation Sequencing and multiomics approach [118]. The refinement of traditional breast cancer classification by molecular screening techniques now allows for resolution of breast cancers based on the presence of (i) estrogen receptor (ER+), (ii) progesterone receptor (PR+), (iii) human epidermal growth factor receptor 2 (HER2 +), or by (iv) their absence in triple-negative breast cancers (TNBCs; i.e., ER–PR–HER2–) [119].

The role of androgens in breast cancer development and progression has long been disputed. Up to 85% of ER positive and 95% of ER negative breast cancers express AR [120]. AR positive tumors are associated with improved overall survival and disease-free survival when compared to AR negative tumors [121]; these findings suggest that the expression of androgen receptors in breast cancer likely confers survival advantage by modulating ER signaling, reducing the risk of metastasis and an aggressive disease [120]. The biological activity of AR is characterized by different pathways, including PI3K/Akt/mTOR and MAPK signaling, and by the interaction with other receptors, like ER, PR, and EGFR-2.

Some studies have proposed that in patients with breast cancers, administration of AR agonists, AR antagonists, and PI3K inhibitors may offer promising results [122].

Measurements of AR expression could have a prognostic value as well as therapeutic implications. Conceivably, modulation of AR activation and/or expression could become a valuable therapeutic strategy in breast cancer [123,124]; to illustrate, AR activation exerted a protective effect reducing tumor mass, metastasis and relapse [125], and prevented occurrence of the invasive form of the tumor [126,127].

In their study, Peters et al. [127] showed that loss of AR expression, due to DNA hyper-methylation, was significantly associated with poor 10-year survival outcomes in Grade III invasive breast ductal adenocarcinomas. The loss of AR expression was associated with a poor prognosis [128,129]. Conversely, a higher expression of AR in breast cancer was associated with better survival outcomes [130], and lower risk of recurrence [131] and longer overall survival [132].

Circulating androgen levels, including DHEAS, DHEA, A, testosterone and DHT, are associated with increased breast cancer risk. Androgens could function directly by enhancing cellular growth and proliferation or, indirectly through their aromatization to estrogens. Notwithstanding the reason for their amplification, androgens play crucial roles in cell proliferation [133].

Clinical studies in postmenopausal women have shown a positive correlation between the incidence of breast cancer and circulating androgen levels [134–137], as well as with elevated levels of estradiol and testosterone [135,138].

Feng et al. [139] showed that DHT induced the transition from epithelial-to-mesenchymal cells in breast cancer depending on AR expression but not on ER expression. This process is dependent on the demethylation activity of lysine-specific demethylase 1A (LSD1) which epigenetically regulates the target genes E-cadherin and vimentin. *In vivo*, DHT promotes metastasis in a nude mouse model, wherein AR and LSD1 are crucial in this process [139].

In some studies, androgens have been shown to enhance tumor growth and possibly synergize with estrogens in breast carcinogenesis [140].

Selective estrogen receptor modulators (SERMs) and selective androgen receptor modulators (SARMs) are drugs endowed with agonist and antagonist actions in a tissue selective manner and for this reason these compounds have been proposed for therapeutic treatments.

The use of hormonal therapies such as hormonal contraceptives (HC) and postmenopausal hormone replacement therapy (HRT) have been shown to influence breast cancer risk. At present, SERMs are recognized as a first-line, relatively nontoxic medical therapy for women affected by steroid hormone receptor-positive breast cancer.

SARMs are also useful in treatment of breast cancer [121]. SARMs are tissue-selective AR agonists and may offer a novel approach to inhibit the growth of AR/ER+ breast cancers. For example, DHT and SARM were shown to reduce proliferation of tumor growth, improve weight and lean body mass of patients affected by triple-negative breast cancer whose cells that expressed a mutated AR. Similarly, in another

study, administration of enobosarm and anastrozole reduced cancer density, suggesting that SARMs can improve poor prognosis and drug resistance [141]. A clinical trial, currently in the recruitment phase, is evaluating a pembrolizumab and enobosarm co-therapy for treatment of AR positive metastatic triple negative breast cancer [142]. However, as testosterone can be aromatized to estrogen in target tissues, the direct use of testosterone in women with a history of estrogen-sensitive breast cancer should not be suggested at this time.

7. Androgens and cardiovascular diseases

Sex hormones, especially testosterone, mediate a crucial role in regulation of myocardial function and efficiency, in men as well as women [14,143].

In women, androgen and testosterone levels rise after menarche, to reach a peak around the age of 20, and gradually decline thereafter. Several studies have shown an association between androgen exposure throughout a women's life and the manifestation of cardiovascular diseases (CVDs) [144].

In several studies, to illustrate, women of fertile age and in the premenopausal phase who presented anomalously low androgen and high estrogen plasma levels, were at risk of detrimental effects on cardiac function [145] and subsequent increased CVD risk [146] in their subsequent menopausal periods. A consequence of enhanced CVD risk is predisposition for development of coronary heart disease, heart failure, myocardial infarction, stroke, and peripheral artery disease [147].

Accordingly, efforts have been made to define more precisely estrogen influence on CVD risk in menopausal women. The "Reproductive Lifespan" (RLS) was defined as the period between the age at menarche and the age at menopause, taking into account pregnancy, breastfeeding, stillbirths and miscarriages [144], as well as hormone use (i.e., oral contraceptive pills and menopausal hormone replacement therapy) [148,149]. Findings indicated that a shorter RLS was related to higher CVD risk, further enhanced by an early menarche and menopause [144]. Curiously, data revealed a bi-phasic (U-shaped) relationship between RLS and CVDs, wherein RLS < 30 years and RLS≥ 40 years [150]. These findings reinforce the need for further investigation of the relationship between RLS and CVDs [151,152]. However, a principal confounding factor in conducting meaningful clinical trials is the difficulty in obtaining adequately sized, homogenous, sample groups. Candidate exclusion criteria are numerous and may include depression, homosexuality, and other factors, which reduce the size of the candidate pool. Indeed, in the preceding studies the lack of blinded placebo groups, or a comparator treatment group, may have contributed to controversial results [115]. For example, Meun and colleagues demonstrated that in a subpopulation of women affected by hyperandrogenism (HA) there was no significant association between high androgen levels and incidence of CVDs, but only with enhanced surrogate markers for CVDs [151].

The most common cause of HA in women in reproductive age is PCOS, which results in (i) hirsutism, (ii) increased serum levels of testosterone and its precursors (DHEA and A), (iii) prevalence of metabolic abnormalities (such as diabetes mellitus 2) and, (iv) early atherosclerotic disease [151]. Presumably, HA continues also in the postmenopausal period, thereby precipitating a decrease of endogenous estrogen levels, due to lack of ovarian production [151], and the increase of androgens, as a direct consequence of the menopausal transition [149]. A validated marker of androgenicity used both at premenopause and menopause, is represented by the free androgen index (FAI), calculated as the ratio of total testosterone to SHBG [148], and which nominally ranges from 7 to 1.

FAI changes caused by increasing testosterone levels, a low estrogen environment, and SHBG reduction represents an elevated risk for higher incidence of CVDs, heart failure [143], and carotid atherosclerosis [144]. Higher FAI values correlate with increased blood pressure and C-reactive protein (CRP), insulin resistance [143,145,146], and are strongly correlated with central adiposity, elevated triglycerides, and decreased HDL cholesterol level [153]. In fact, women from the onset of reproductive competency who are affected by PCOS, as well as atypically elevated levels of testosterone, DHEA and androstenedione, present an elevated FAI [148,154]. There are, as well, multiple reports of PCOS association with early atherosclerotic disease, and in menopausal women associated with increased risk of CVDs, morbidity and mortality [155]. By contrast, Khatibi et al., reported that in their population-based study of Swedish perimenopausal women with CVDs, lower serum androgen levels and SHBG were associated with more favorable lower levels of LDL and triglycerides and elevated levels of HDL [147]. These results suggest that androgens may exert cardioprotective effects in peri-menopausal women by promoting an anti-atherogenic mechanism.

Collectively, these findings suggest that at least a physiological level of testosterone is necessary to maintain cardiovascular health in women. Favorable bioactivities of testosterone appear to be interdependent with estrogen levels; to illustrate, elevated risk of ischemic heart disease was associated with depressed plasma levels of estradiol as well as excessive plasma levels of testosterone [156]. A further complicating factor is that in young women, plasma levels of SHBG are inversely correlated with CVDs and thus constitute an independent CVD risk factor [154].

Although these findings provide significant insights into the relationships between these steroids, their receptors and cardiac health, a more comprehensive analysis is needed in order to provide any measure of certainty. An obvious requirement includes a long-term follow-up study constituted of a large group of women, with sufficient numbers to provide statistically meaningful group sizes representing women who are (i) clinically depressed, (ii) homosexual, and not formally partnered and (iii) sexually inactive. Study design and sample sizes must also be able to account for variation in fertility phase (fertile, pre- and postmenopausal women).

8. Androgens and metabolic regulation

Sexual dymorphism of body fat distribution indicates that sex steroids influence the differentiation of adipose stem cells (ASC) into mature adipocytes, and adipose cell functions [157].

Androgens have been proposed to play a primary role, and convincing data shows that the administration of physiological amounts of testosterone to women reduced the activity of adipose hormone-sensitive lipase in subcutaneous (SC) abdominal adipocytes, and inhibited *in vivo* lipolysis [158]. The development of adipose tissue dysfunctions also rely on the interplay of several factors, including metabolic stress, insulin resistance, hyperglycemia, and hyperandrogenism, the latter often associated with polycystic ovaries [159,160].

After menopause testosterone, which is no longer counter-balanced by ovarian estrogen, can stimulate the accumulation of abdominal adipose tissue, possibly resulting in visceral and/or central obesity [161].

Visceral obesity has been proposed to play a very important role in the progression of insulin resistance and the development of metabolic syndrome [162]. Insulin resistance also promotes hyperinsulinemia, which in turn is associated with an increase of IGF-I circulating levels which stimulate ovarian production of androgens, and inhibits production of SHBG [163]. Testosterone further stimulates the accumulation of visceral fat and the synthesis and release of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which along with insulin resistance, promote a picture of metabolic syndrome [164].

In vitro studies show that testosterone inhibits ASC differentiation into preadipocyte and also reduce early-stage preadipocyte differentiation to adipocytes. At the intracellular level testosterone inhibits peroxisome proliferator-activated receptor γ (PPARγ), CCAAT-enhancer-

binding prontein α (C/EBPα) and CCAAT-enhancer-binding prontein β (C/EBPβ) mRNA expression, an effect at least in part mediated by the AR, since it can be antagonized by flutamide, an antiandrogen [159].

Other *in vitro* studies on SC abdominal adipocytes obtained from normal-weight women have shown that testosterone can reduce insulin-stimulated glucose uptake, a mechanism involved in the generation of insulin resistance [165,166].

The bulk of evidence regarding androgen induced metabolic dysfunction is derived from studies of women with polycystic ovary syndrome (PCOS). PCOS is most common metabolic disorder of reproductive-aged women, and is characterized by glucose intolerance, dyslipidemia and abdominal fat accumulation [13]. Globally, approximately 50% of women affected by PCOS are overweight or clinically obese; by contrast, in the USA 80% of women affected by PCOS are overweight or clinically obese globally [167]. In about half of obese woman with PCOS, hyperinsulinemia and hyperandrogenism contribute to metabolic syndrome, which strongly indicates important androgen-insulin interactions. Hyperandrogenism plays a key role in women with PCOS, impairing insulin-mediated glucose uptake, reducing the expression of glucose transporter type 4 (GLUT-4), β2-adrenergic receptor, hormone-sensitive lipase and protein kinase A regulatory-IIβ component (PKA-RegIIβ) [168,169]. Impaired glucose tolerance may evolve into type 2 diabetes mellitus (T2DM) in about 40% of women with PCOS, who frequently have increased triglycerides and total and low-density lipoprotein-cholesterol; however, there are only limited data regarding increased risk of cardiovascular events in women affected by PCOS [170].

9. Androgens and neurodegenerative diseases

Neurodegenerative diseases (NDs) are ultimately fatal conditions characterized by the progressive loss of neurons that leads to cognitive and motor function deterioration. The causes are multi-factorial and still require full elucidation; moreover, their precise definition is complicated by sex differences in terms of onset and progression, which suggests that sex steroid hormones may be involved in NDs pathogenesis.

In this context, it should not be surprising that androgens and estrogens are also involved in the regulation of neuronal growth, differentiation and survival, in addition to maintaining brain efficiency [171].

Accordingly, numerous studies have demonstrated the expression of ARs, ERs and PRs in various brain areas [172,173], although their levels of expression are highly variable among animal species, developmental stage, sex, and endocrine state [174].

In mammalian brains, for example, both ERs isoforms (ERα and ERβ) are mainly expressed in limbic-related areas, the hypothalamus, amygdala, hippocampus, and thalamus, which suggests a supporting a role for estrogens in modulation of mood, anxiety, fear, and cognitive function (learning and memory) [175]. Moreover, ERs are expressed also in microglia, astrocytes, and in dorsal horn neurons of the spinal cord. These localizations correlate with estrogens' neuroprotective role (s) against neurotoxic insults, with bioactivities including pain modulation, and their neuroinflammatory responsiveness and neuroprotective activity in spinal cord injuries [174].

Androgens are endowed with various activities in neurons, such as increasing neuronal survival [176], stimulating neuronal differentiation and plasticity [177], and promoting synaptic density [178,179] and connectivity [180]. ARs are generally expressed at higher levels in males than in females and are present in both central and peripheral nervous systems (CNS and PNS). In the CNS, ARs are concentrated in hypothalamic nuclei, in the horizontal diagonal band of Broca, in neurons of the mamillary nucleus, in the preoptic area and in the infundibular neurons [174]. AR activation increases the release of trophic factors, such as vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1), which support neurogenesis in the brain [181,182], cognitive function in aging, and the induction of different neuroprotective pathways [183]. ARs are also expressed in axons and dendrites of neurons localized in brainstem and spinal cord areas associated with sensory functions [184]. AR inhibition is associated with motor neuron degeneration and vulnerability, as well as loss of their morphology and survival [185]. By contrast, AR activation is associated with trophic effects on motor neurons including, enlargement of cell bodies and dendrites, extended life span, and enhanced recovery from damage.

Brain sex hormone receptors recognize, bind and are activated by circulating sex steroids, which arise from gonads and adrenal cortical cells, and which freely diffuse through the blood-brain barrier (BBB) [185]. In addition, neurosteroids (indistinguishable from circulating steroids) are synthesized *de novo* from cholesterol in both the CNS and PNS. CNS/PNS steroids include testosterone, deoxycorticosterone, progesterone, DHEAS, and their metabolites; these species interact with non-sex hormone receptors to influence neuronal excitability and function [174]. Their in situ synthesis might be an adaptive mechanism following brain damage and neurodegenerative conditions, resulting in neuroprotective and reparative roles and in the regulation of survival and regeneration [186,187].

Alzheimer's disease (AD) is the most common cause of dementia, characterized by the extracellular deposition of β-Amyloid (Aβ) plaques and the accumulation of abnormally hyperphosphorylated bundles of tau protein inside neuronal cells [188]. The etiology of AD is complex but is allegedly the consequence of an interaction between genetic and environmental factors [183]. The potential role of androgens as therapeutic agents is supported by evidence that low testosterone levels are correlated with increased plasma Aβ levels in elderly men with memory loss and dementia [172,189–192]. In women, higher free testosterone and gonadotropin levels were associated with lower cerebral Aβ positivity [193]. Several studies have shown that testosterone could regulate the levels of Aβ both *in vitro* and *in vivo*; in female mice, testosterone supplementation decreased amyloid precursor protein (APP) mRNA [194] and reduced Aβ formation and deposition, acting directly on neurons [195]. Both APP cleavage and Aβ protection are dependent on AR activation [195,196]. In addition, testosterone can prevent hyperphosphorylation of tau [197] by modulation of glycogen synthase kinase-3 β activity [198]. Systematic reviews of the risk of cognitive impairment in men who received androgen deprivation therapy for prostate cancer have reported either an increased risk of dementia and/or AD [199] or non significant correlations [200].

Parkinson's disease (PD) is the second most common neurodegenerative disease after AD, and is considered a multifactorial neuropathology characterized by the reduction of dopaminergic, cholinergic, and non-dopaminergic neurotransmitters, that induce neuron atrophy in the hippocampus and brain cortex [201]. The higher susceptibility of men compared to women for PD suggests a modulatory effect of sex steroids in the brain. The associated degeneration of dopamine neurons is caused by progressive deposition of intracellular α-synuclein protein and Lewy bodies [183]. In PD testosterone deficiency has been proposed to be involved in disease pathogenesis; testosterone therapy may have beneficial effects through inhibiting of oxidative stress, increasing antioxidant responses and potentiating respiratory chain activity, as well as by inducing the expression of mitochondrial proteins and enzymes [174]. The therapeutic potential of testosterone and DHT has been shown in a preclinical triple transgenic mouse model of Alzheimer's disease, in which androgens improved cognitive performance [189]. In men affected by prostate cancer and subjected to androgen deprivation therapy, the incidence and/or severity of non-motor and extrapyramidal symptoms was increased, but the androgen protective role in PD remains a matter of debate [183].

Amyotrophic Lateral Sclerosis (ALS) is an adult-onset and progressive neurodegenerative disease characterized by degeneration of both upper and lower motor neurons within the motor cortex, brain stem, and spinal cord. ALS appears as a sporadic (sALS) or a familial form

(fALS), which are clinically indistinguishable; in both cases, symptoms include progressive muscle weakness and wasting, body weight loss, fasciculation, emotional lability and cognitive dysfunction. Despite the knowledge of ALS etiology, the pathogenetic mechanisms of this disease are still unknown, and no effective therapies exist.

The higher incidence of ALS in men suggests a possible role of sex hormones also in ALS pathogenesis. Sex steroids might modulate mechanisms involved in the disease or in the sex predominance; a recent study demonstrated that prolonged exposure to female hormones had neuroprotective effects on motoneurons in ALS [202]. Moreover, McLeod [187] demonstrated that anti-androgen treatment in pre-symptomatic SOD1^{G93A} mice accelerated disease onset and motor dysfunction, suggesting a potential protective role of androgens in modulating the disease severity. Finally, the evidence that androgens mediate the release of trophic factors suggests a possible use for the treatment of ALS by stimulating motor neuron recovery, extending survival time, and decreasing disease progression [198].

10. Effect of androgens on bone metabolism

Kasperk et al. described the ability of androgens to stimulate proliferation of human osteoblastic cells *in vitro*. They also showed that testosterone and two synthetic anabolic steroids, methenolone and fluoxymesterone, stimulated mouse bone cell DNA synthesis, indicating the presence of AR on bone tissue [203]. Testosterone, DHT, and synthetic androgens are essential regulators of bone mass [204–206]. The androgen anabolic action on bone is either direct, mediated by AR interaction, and partly indirect, depending on aromatization of androgens into estrogens, such as the effects on cancellous compartments [207].

No significant differences in osteoblasts' AR expression were observed between males and females [208]. Androgens' effects on bone, both in men and women, was integrated with estrogen activity [209]. Both hormone classes played a prominent role in development and maintenance of bone integrity in female as well as in male subjects [210,211], by exerting an anti-apoptotic effect on osteoblasts [207, 212] and inhibiting osteoclast activity [213]. Androgen administration alone stimulated osteoblast proliferation (Fig. 2) [214].

AR, ERα, and ERβ are expressed in bone chondrocytes, bone marrow stromal cells, osteoblasts, osteoclasts and their progenitors [207,215]. For this reason, it is difficult to separate the effect of androgens and estrogens on bone metabolism. AR activation increases trabecular bone mass, while the activation of both AR and ERα promotes the growth of the bone cortical compartment [216]. Testosterone, which is an aromatizable androgen, is very useful in sparing bone mass in ovariectomized rats, even if administered at minimal doses. However, the administration an anti-estrogen with testosterone did not inhibit its action on biochemical markers of bone metabolism, suggesting that the effects of testosterone are not associated with its aromatization to estradiol [217].

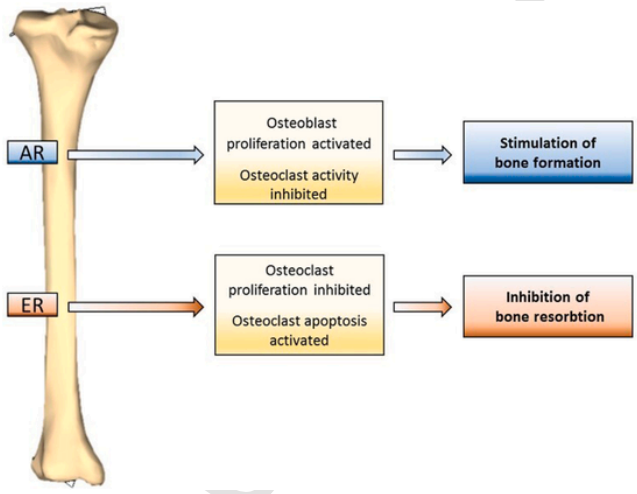

Fig. 2. Androgens and bone. Bone metabolism is strongly regulated by the activation of AR and ER. Androgens, such as testosterone, after being aromatized in 17β-estradiol, directly bind and activate AR and ER. AR activation stimulates osteoblast proliferation and the blockade of osteoclast activity, inducing bone formation. Conversely, ER activation inhibits osteoclast proliferation and stimulates their apoptosis, resulting in the inhibition of bone resorbtion.

In premenopausal women, bone loss was significantly linked to lower plasma androgen levels, while in postmenopausal women bone loss correlated with both low estrogen and androgen concentrations [218]. Hyperandrogenism is a typical feature of PCOS, the most frequent endocrinopathy in premenopausal women [208]. The outcome of different studies performed in premenopausal women regarding fracture risk and bone mineral density (BMD) of a PCOS population compared to controls are controversial and still inconclusive, thereby undermining understanding of whether PCOS might improve or worsen the bone health. This dichotomy is well represented by results obtained in two wide longitudinal studies performed on national registries, grounded respectively on a Danish population-based cohort study [219] and a national cohort in Taiwan [220]. Although a recent work attempted to make a statement on the risk of the fractures in PCOS women, no definite conclusions could be drawn on the basis of the available evidence [221]. A reduction in SHBG, a transport carrier that binds estrogen and androgens and regulates their biological activities, is often used as an indicator of hyper-androgenism in women with PCOS.

In postmenopausal women, plasma levels of SHBG, have been recognized as markers of BMD and are inversely correlated with those of testosterone; specifically, high SHBG and low testosterone levels are associated with an increased risk of bone loss and hip fracture, independent from other risk factors [222].

A cross-sectional study of 232 U.S. community-dwelling older women aged 67–94 years, indicated that plasma free testosterone levels positively correlated with BMD and lean body mass, suggesting that circulating androgens may play a role in maintenance of bone density in the setting of low estradiol levels [209]. Since testosterone, also at minimal doses, possesses protective actions on bone mass in ovariectomized rats [217,223], hormone replacement therapy based on androgens and estrogens interaction has been proposed in the elderly and in conditions characterized by androgen deficiency. The treatment of osteoporosis in elderly women appeared to offer excellent clinical outcomes and was also well-tolerated [224–226]. The administration of a combined therapy of estradiol plus testosterone (estrogens or esterified estrogen 1.25 mg, plus methyltestosterone 2.5 mg daily) in surgically menopausal women for two years was associated with increased BMD at the hip and lumbar spine [225], compared to the administration of estradiol alone [224]. In these patients, a more significant improvement of libido and sexuality was observed due to the androgen effects. Similar results were found in menopausal women after therapy with estrogens plus testosterone at different dosages (conjugated equine estrogen 0.625 mg/day + methyltestosterone 1.25 mg/day, and with a double dosage 1.25 and 2.50 respectively). Both treatments improved BMD, in particular with the higher doses [226]. A double-blind placebo-controlled trial showed that testosterone therapy in hypopituitary women caused an improvement of BMD [227].

Nandrolone decanoate (ND), a weak anabolic-androgenic steroid, has been studied since the end of the 1960 s as an option for the treatment of idiopathic osteoporosis in women [228–237]. The therapeutic effect of ND on bone consists of inhibition of bone resorption complemented with a temporary increase in bone formation and increase in BMD in the whole skeleton; after one-year administration of 50 mg every 3 weeks, BMD of the lumbar spine increased about 3.4% and that of the femoral neck 4.1% [236]. Furthermore, ND treatment improved

calcium balance and muscle mass, diminished vertebral pain, increased spine mobility and reduced the incidence of new vertebral fractures. At the end of the two-year treatment, hemoglobin levels were significantly higher compared to baseline (14.3%), thus contributing to an increased perception of well-being [236]. No side effects, particularly in short term treatment, were reported [238], although virilization (mainly vocal hoarseness and hirsutism) occurred in around 50% of the patients, causing a dropout rate of about 9% of these groups [236]. As the available data points to the potential for more promising outcomes in the treatment of osteoporosis in postmenopausal women, especially when they have low muscle mass associated with debilitating disease, further randomized trials are warranted. The virilization effects may represent a deterrent for clinicians in prescribing steroids, as well as for the patient acceptability of the treatment.

11. Effect of androgens on muscle mass and performance

Androgen levels are associated with increased muscle mass in men and women [239]. In women, the use of androgens is a critical issue in modern society related to the desire to improve muscle mass and physical performance. Anabolic steroids are the most widely used drugs for performance enhancement among competitive athletes [240], and by elite female athletes [241], but also in recreational athletes, in particular bodybuilders who aim to improve body image and muscle definition. It was estimated that about 3.5–4 million fitness subjects in the USA had used anabolic steroids [242]. Some documents revealed that in the German Democratic Republic, female athletes regularly assumed anabolic steroids to increase athletic performance [243].

Women with PCOS have a greater muscle mass correlated with higher plasma androgen levels [244] and increased competitive performance [241], showing a significantly decisive advantage compared to other competitors. As a consequence, regulations pertaining to serum androgen concentration have been incorporated into the Athlete Biological Passport [245]. Factors associated with these regulations include the influence of ethnicity, menstrual status, and oral contraceptive use. In female athletes, anabolic steroid abuse has resulted in enhanced ergogenic performance, stress resistance, and muscle mass maintenance [246]. The most frequently observed side effects in women taking high doses of androgens are hirsutism, alopecia, deepening of the voice, clitoridean enlargement, oligomenorrhea/amenorrhea, and aggressiveness [247].

In postmenopausal women, the intramuscular administration of testosterone enanthate at the doses of 3, 6.25, 12.5, or 25 mg weekly for 24 weeks, contributed to a significant and dose-dependent improvement of sexual function, lean body mass, chest-press power, and full stair-climb power [248]. Oxandrolone, a synthetic androgen [249], induced muscle protein synthesis [250], muscle strength [251], and was well tolerated. In older women (age 74.9 ± 6.8 y), oxandrolone at a physiological dose (10 mg/day) for 12 weeks improved muscle mass and performance after resistance training [251]. Oxandrolone was effective in the treatment of neuromuscular diseases such as body myositis [252], in Duchenne dystrophy [253], in neurodegenerative diseases such as Charcot-Marie Tooth [254], and in wasting and catabolic disorders [255]. In postmenopausal women, the association of estrogen plus androgen therapy showed a more significant effect, compared to estrogen-alone, on muscle mass and strength, body composition and quality of life without specific side effects [256].

12. Future perspective

Although androgen therapy in women is relevant from a clinical point of view, there are many limiting factors. First, gynecologists and internists do not know precisely the benefit of androgen therapy in women. The Endocrine Society "Guidelines" are extremely limitative in the prescription of androgens in women. Furthermore, clinical studies on the therapeutic effects of androgens in women are few. Studies conducted on large populations are necessary to evaluate specific correlations between androgen deficiencies and clinical signs.

13. Conclusions

Diagnosis of androgen deficiency in women is of clinical relevance because restoring physiological levels of androgens is essential in the prevention and treatment of many chronic diseases. However, based on experimental and clinical studies, androgen administration in women under specific clinical conditions, such as loss of sexual desire, loss of muscle mass and sarcopenia, osteoporosis, mental disorders, cardiovascular disease and memory loss is therapeutically relevant. Androgens are useful in young women for the prevention of diseases and for fertility improvement, by regulating uterine and ovarian function. Androgen therapy in women at physiological doses and with cyclic treatment appears to be safe and well-tolerated. Adverse side effects are typically associated with supraphysiological doses and excessive treatment duration. Testosterone therapy in women can give clinically relevant benefits at low doses [257]. The rational prescription of androgen in women must take into account plasma hormonal levels achieved with the therapy and the clinical benefits. The premature decline in plasma androgen levels in women should be considered a risk factor for health.

The global consensus of the Endocrine Society about the use of androgen therapy in women [258] recommends against the routine prescription of testosterone; the only indication, based on clinical evidence, is for the treatment of HSDD. The long-term safety for treatments with testosterone remains to be evaluated, and the panel highlighted the need for more research in this area.

Conflict of interest

The authors have no conflict of interest to declare.

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