

REVIEW

Androgen in postmenopausal women

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Abstract : Menopausal symptoms, bone loss, changes in lipid profiles and reduction of insulin sensitivity due to an abrupt decrease in circulating estrogen level are well known in women during the menopausal transition. On the other hand, the effect of androgen on women's health has not been fully elucidated. Circulating levels of testosterone and dehydroepiandrosterone sulfate (DHEA-S) gradually decrease with age in postmenopausal women, although transient increases have been observed during the menopausal transition. High testosterone level has been suggested to be associated with increased risk of cardiovascular disease, increased triglyceride, insulin resistance and increase in the risk of developing breast cancer in postmenopausal women. Circulating DHEA-S level does not affect the risk of cardiovascular disease, mortality or lipid profiles in women. Female androgen insufficiency, which is characterized by the presence of reduced androgen level in circulation, leads to an impairment in sexual drive, reduced libido, depressed mood, and signs and symptoms of limited androgen exposure such as decreased muscle mass, reduced bone density and decreased sense of well-being. An appropriate level of androgen may play important roles in metabolic, psychological and sexual functions in women. In addition, the roles of testosterone and DHEA-S in women's health may be different. *J. Med. Invest.* 59 : 12-27, February, 2012

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ESTROGEN IN WOMEN

Dynamic changes in circulating estradiol level, including increase at menarche and decrease at menopause, occur in a woman's lifetime. Circulating estradiol levels decrease drastically during the menopausal transition, though the levels differ among races. It has been reported that estradiol levels in both Japanese and Chinese women were lower

than those in Caucasians, Hispanic and African-Americans (1).

Based on data obtained in a previous study (2), we re-analyzed data for 169 healthy men and 252 healthy women aged from 40 to 85 years in the population-based study with addition of data for premenopausal women. Change in circulating estradiol in women from the menopausal transition to postmenopause is characterized as follows : high estradiol level in premenopausal women is drastically decreased and estradiol level in postmenopausal women is significantly lower than that in age-matched men. Mean estradiol levels were shown to be 20.1 pg/ml in men and 6.1 pg/ml in postmenopausal women (Figure 1). This dynamic decrease in

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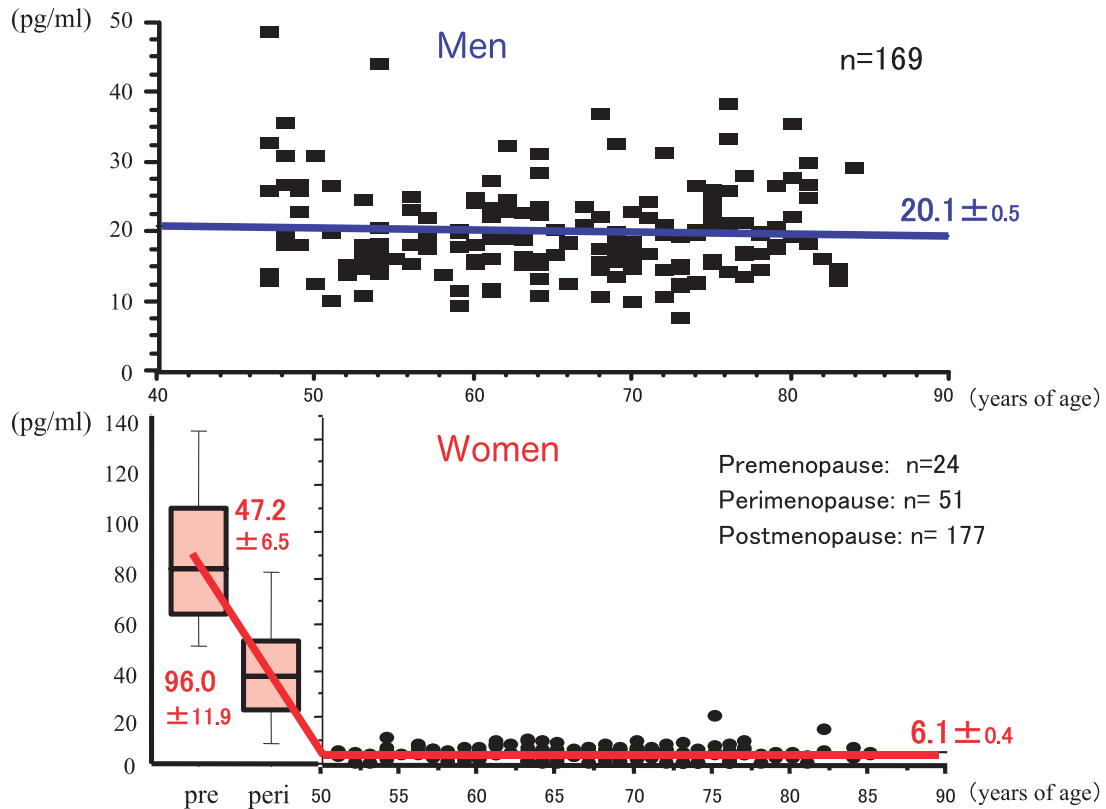


Figure 1. Changes in serum estradiol levels in men and women. upper panel : men, lower panel : women

estradiol level induces menopausal symptoms, such as hot flashes and night sweat, urogenital symptoms, osteoporosis, coronary heart disease, stroke and possibly early onset of Alzheimer’s disease in postmenopausal women as shown in Figure 2.

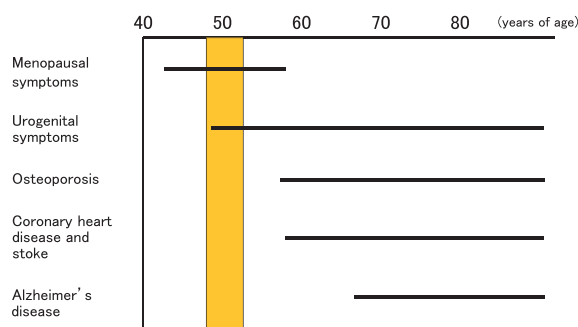


Figure 2. Increased risks of diseases in postmenopausal women.

However, not only estrogen but also other endocrinological hormones may be involved in the occurrence of these diseases. Little attention has been paid to roles of endogenous androgens in women despite the results of studies suggesting that androgens may play important roles. Androgens are

known to be important for normal physiology in women and to play key roles in the physical, sexual and emotional well-being of women (3). Therefore, it is necessary to take account of androgens as well as estrogen when considering women’s health.

CHANGE IN LEVELS OF ANDROGEN IN WOMEN

1. Changes in testosterone level in women

In women of reproductive age, daily production of testosterone is shared equally between the ovaries and adrenal glands and accounts for approximately one-third of the testosterone in circulation. Peripheral conversion of androgen precursor steroids to testosterone in non-steroid producing tissues accounts for the remaining two-thirds of testosterone in circulation. These ratios change after menopause when the ovaries are in senescence. In women, there is controversy about the direction of circulating testosterone levels across the life span. It has been reported that total and free testosterone decreased with age between 15 and 60 years (4) and that bioavailable testosterone decreased by approximately 28% between 25 and 85 years of age

(5). However, it has been shown that testosterone level did not vary during the menopausal transition from 45 to 55 years of age (6). Recent data indicate that total testosterone level increased from 43 to 50 years but not thereafter (7). In a previous study, we found that total testosterone level gradually decreased with age in women but that the change was not significant. However, levels of free and bioavailable testosterone showed significant decreases with age in women (2).

Menopausal transition is characterized by variations in cycle length and elevation in follicle-stimulating hormone (FSH) level. Based on these characteristics, the American Society for Reproductive Medicine proposed the “Stages of Reproductive Aging Workshop (STRAW) staging system” (8). We also divided 231 healthy women into 7 stages by regularity of menstruation and FSH level: 1) women with regular menstruation cycle and normal FSH level (group A), 2) women with regular menstruation cycle and elevated FSH level (≥ 10 mIU/ml) (late reproductive stage, group B), 3) women with irregular menstruation cycle and elevated FSH level (early menopausal transition, group C), 4) women who had irregular menstruation cycle in which the interval of amenorrhea was more than

2 months and elevated FSH level (late menopausal transition, group D), 5) women for whom less than 1 year had passed since menopause (group E), 6) women for whom less than 5 years had passed since menopause (group F) and 7) women for whom more than 5 years had passed since menopause (group G). As can be seen in Figure 3, total testosterone level did not change significantly, though there was a slight increase during the menopausal transition. Changes in free and bioavailable testosterone showed patterns similar to the pattern of changes in total testosterone. On the other hand, estradiol level was drastically decreased but showed a transient increase in the early menopausal transition, possibly due to an increase in FSH stimulation (Figure 3). The ratio of testosterone to estradiol (T/E), as an assessment of the balance of testosterone and estradiol, gradually increased during the menopausal transition and increased significantly in postmenopausal stages (Figure 4). A relative testosterone excess was found in postmenopausal women. Torrens *et al.* reported that a relative androgen excess was found during the menopausal transition and both baseline total T/E ratio and its rate of change were associated with increased incident metabolic syndrome independent of ethnicity (9).

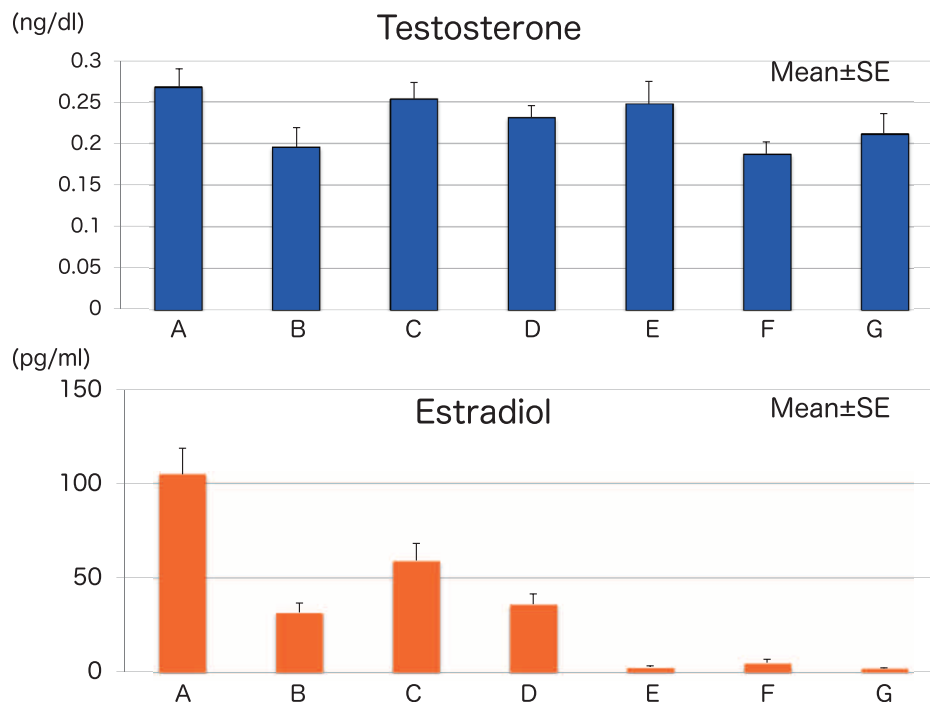


Figure 3. Changes in levels of total testosterone and estradiol during the menopausal transition.

upper panel : total testosterone, lower panel : estradiol

Group A : early reproductive stage, Group B : late reproductive stage, Group C : early menopausal transition, Group D : late menopausal transition, Group E : women for whom less than 1 year has passed since menopause, Group F : women for whom less than 5 years have passed since menopause, Group G : women for whom more than 5 years have passed since menopause

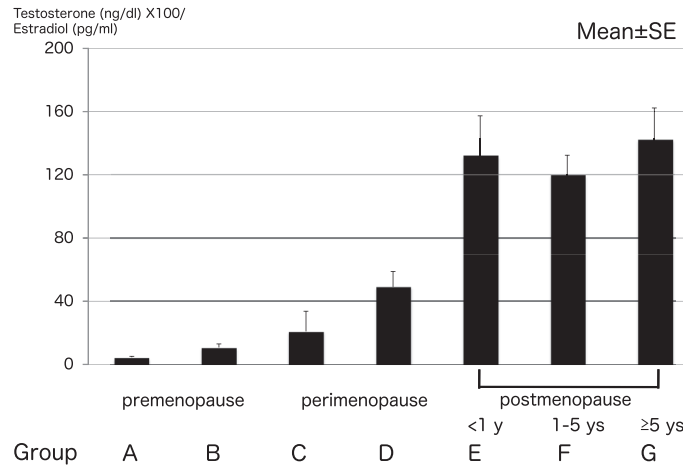


Figure 4. Changes in testosterone/estradiol ratio during the menopausal transition. Group A : early reproductive stage, Group B : late reproductive stage, Group C : early menopausal transition, Group D : late menopausal transition, Group E : women for whom less than 1 year has passed since menopause, Group F : women for whom less than 5 years have passed since menopause, Group G : women for whom more than 5 years have passed since menopause

2. Changes in DHEA-S level in women

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are steroid hormones mainly produced by the adrenal zona reticularis. The daily production rate of DHEA is 6 to 8 mg, 50% being secreted by the zona reticularis. In women, 20% is secreted by the ovarian theca, while the remaining amount is derived from circulating DHEA-S catalyzed by steroid sulfatase. Changes in DHEA-S levels with age differ among races. Circulating DHEA-S level showed the lowest rate of decline with advancing age in Japanese women and the greatest decline with advancing age in Caucasians (10). In addition, a transient increase in DHEA-S level during late

perimenopause and early postmenopause has been shown. As can be seen in Figure 5, we also showed a transient increase in DHEA-S level in the menopausal transition. The rise of DHEA-S during the menopausal transition might be associated with increase in luteinizing hormone. Lasley *et al.* reported that a rise in DHEA-S during the menopausal transition was found in the absence of both ovaries, suggesting that the rise in DHEA-S is most that from the adrenal glands (11). Although its circulating level is the highest of all steroid hormones, little is known about its physiological role. DHEA and DHEA-S were considered to be pro-hormones exerting indirect androgenic and estrogenic effects following peripheral conversion into small amounts

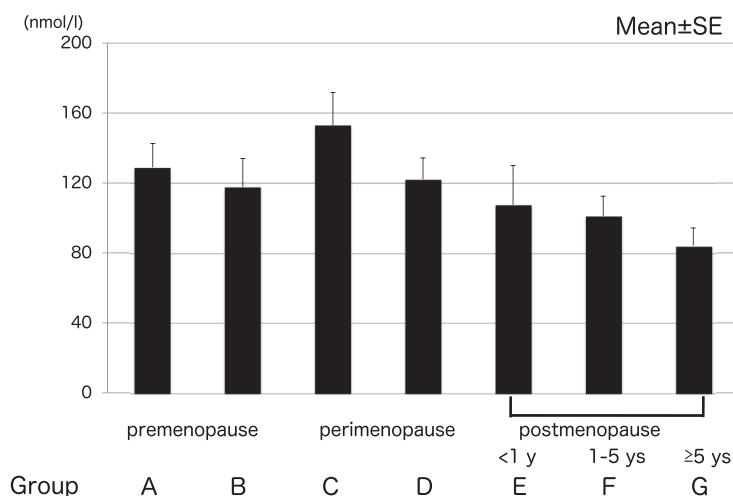


Figure 5. Changes in DHEA-S levels during the menopausal transition. Group A : early reproductive stage, Group B : late reproductive stage, Group C : early menopausal transition, Group D : late menopausal transition, Group E : women for whom less than 1 year has passed since menopause, Group F : women for whom less than 5 years have passed since menopause, Group G : women for whom more than 5 years have passed since menopause

of testosterone and estradiol. However, this concept may change due to the identification of a putative specific DHEA receptor on the plasma membrane of bovine aortic endothelial cells (12).

ACTIONS OF ENDOGENOUS ANDROGENS

1. Female androgen insufficiency

The medical field for testosterone has long accepted the importance of male sexuality, but sexual dysfunction in women and treatment options to address these concerns have met with great controversy. Aging and menopause have been linked to low libido, with 52.4% of naturally menopausal women aged 40-70 years and 36.4% of surgically menopausal women (current age \geq 45 years) who have undergone oophorectomy at less than 45 years of age reporting low sexual desire (13). The decline of androgen levels with ovarian failure and that following oophorectomy have sparked the hypothesis that decreased testosterone is related to diminished desire. In 2002, a consensus conference recommended that female androgen insufficiency syndrome be defined by a pattern of clinical symptoms and signs in the presence of decreased free testosterone and normal estrogen status. Clinical symptoms of the proposed deficiency state include decreased libido, sexual receptivity and pleasure ; a diminished sense of well-being ; dysphoric mood and/or blunted motivation ; and persistent unexplained fatigue. Clinical signs include bone loss, decreased muscle mass and strength, adipose tissue redistribution, decreased sexual hair and changes in cognition or memory (14). There are many causes of low testosterone level in women including dysfunction of the hypothalamic pituitary axis, surgical or medical oophorectomy, surgical or medical adrenalectomy, premature ovarian failure, Cushing syndrome, radiation and /or chemotherapy and thyroid disease. Determination of the root cause of low androgen production in women is important because appropriate treatment can improve the quality of life in many women.

2. Endogenous androgen and symptoms in women

1) Physical functioning

It has been reported that circulating total testosterone level was associated with physical function in women aged 49-65 years (15), though a significant association in women aged 42-52 years was not found in another study (16). On the other hand,

DHEA-S showed a modest association with physical functioning (16) and an inverse association with degree of physical disability in women (15). Bell *et al.* reported that DHEA-S level was associated with greater vitality in premenopausal women, while both testosterone and DHEA-S did not make a contribution to well-being in postmenopausal women (17).

2) Depression

Associations of circulating testosterone and DHEA-S with depressive mood are controversial. Several studies showed no significant association of testosterone with depressive mood (15, 18, 19), although an inverse association of free testosterone with depressive symptoms in elderly women has been found (20). A recent longitudinal study has indicated that higher testosterone levels may contribute more severe depressive symptoms in women during the menopausal transition (21). On the other hand, lower DHEA-S level has been shown to be associated with degree of depressive symptoms in women aged 49-65 years (15). Several studies have shown a significant association of low DHEA-S level with the presence of depressive symptoms in older women (20, 22, 23), while discordant results were obtained in other studies (24, 25).

3) Cognitive function

Testosterone may protect the brain from Alzheimer's disease by regulating accumulation of β -amyloid protein as well as neuroprotective action (26). However, the association of endogenous testosterone level with cognitive function is still controversial, and sex-differential association of testosterone level with cognitive performance has been found (27, 28). Ryan *et al.* reported that higher testosterone/estradiol predicted greater semantic memory improvement in postmenopausal women (29). Several studies failed to find a relationship between DHEA-S level and cognitive performance (24, 30), though Hillen *et al.* reported that lower DHEA-S level was observed in women who subsequently developed Alzheimer's disease (31).

4) Sexual activity

The most common clinical symptom in women due to androgen deficiency is a pronounced reduction in libido (32). It has been reported that endogenous testosterone level was associated minimally with higher sexual desire in women aged 42-52 years (16). Several studies showed a correlation between low testosterone level and decrease in libido in premenopausal women who complained of decreased libido (33, 34). Alarslan *et al.* suggested that low testosterone level is a predictor of sexual

dysfunction (35). DHEA-S level in postmenopausal women with decreased sexual desire was also lower than that in an age-matched control group (36). It has been reported that levels of total testosterone, free testosterone and DHEA-S in both pre- and postmenopausal women with low libido were lower than those in age-matched healthy volunteers with comparable BMI and menopause status (37).

3. Endogenous androgen for bone and lipid profiles in women

1) Bone health

Androgens also play an important role in bone physiology. Androgen receptors are found in osteoblasts, osteoclasts and osteocytes and they are most abundant in the osteoblast (38). Postmenopausal women with hip fracture were found to have significantly lower free testosterone level and higher SHBG level than those in age-matched women (39). A cohort study showed that the relative risk of hip fracture was increased by low free testosterone level and high SHBG level in women aged 65 years or older (40).

2) Lipid metabolism, cardiovascular disease and mortality

Accumulating evidence suggests that a high level of endogenous testosterone is associated with unfavorable lipid profiles, events of cardiovascular disease and insulin resistance in women. Total testosterone and free testosterone showed positive correlations with total cholesterol, low-density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) and

negative correlations with high-density lipoprotein (HDL)-C (41, 42). A high level of free testosterone is associated with increases in events of cardiovascular disease (43, 44) and insulin resistance (45, 46). Recently, a high testosterone level has been shown to be associated with subclinical atherosclerosis in healthy menopausal women (47). In our population-based study, free testosterone level was positively associated with BMI in women but not in men (Figure 6).

On the other hand, associations of DHEA-S with lipid metabolism, occurrence of cardiovascular disease and mortality are controversial. Previous studies suggested that DHEA-S level did not affect the risk of fatal cardiovascular disease (48), mortality (49) and lipid profiles (50) in women. However, Trivedi *et al.* reported that the highest mortality rate was observed in the highest DHEA-S quartile in elderly women aged 65-76 years, while the highest mortality rate was found in the lowest DHEA-S quartile in elderly men (51). We showed that DHEA-S level was positively correlated with LDL-C in Japanese women (52). Recent accumulating evidence suggests that DHEA-S has a vasculoprotective role. Yoshida *et al.* reported that DHEA-S was associated with increased carotid blood flow in elderly women (53). Lower DHEA-S levels may be related to higher cardiovascular mortality in postmenopausal women with CVD risk factors (54). Lower DHEA-S level has been shown to be associated with increased arterial stiffness in menopausal women (47). Casson *et al.* reported that higher

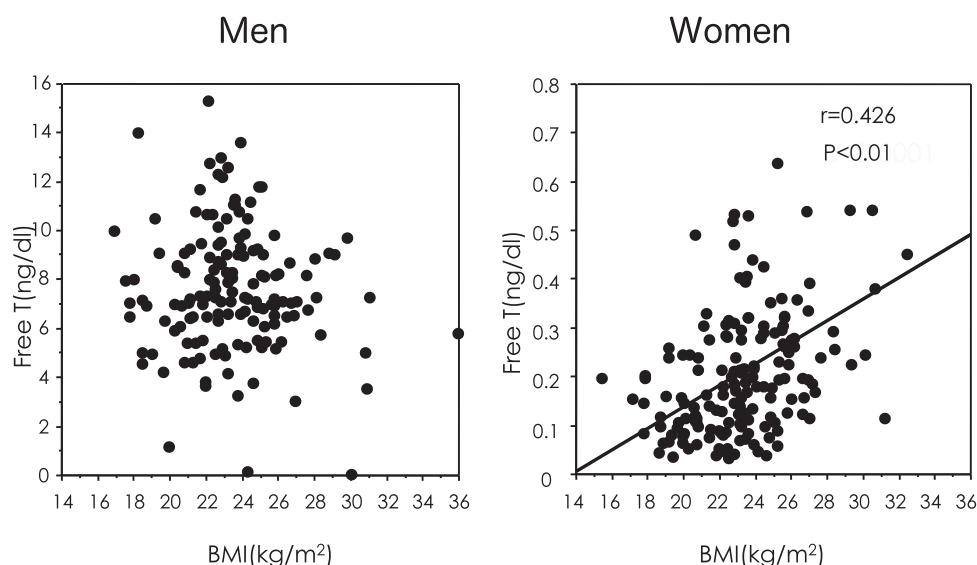


Figure 6. Associations of free testosterone with BMI in men and women. left panel : men, right panel : women

testosterone level was related to greater maximal aerobic capacity and reduced adiposity and that higher DHEA-S level was correlated with greater insulin sensitivity, suggesting that endogenous androgens may play a role in the maintenance of beneficial patterns of metabolic, morphometric and functional parameters in postmenopausal women (55).

4. Endogenous androgen and breast cancer in women

The mechanism by which estrogens can promote the growth of breast cancer has been clearly shown. However, the role of androgens is less clear, although it has been shown that androgens can directly stimulate the growth of human breast cancer cell lines (56). It has been reported that high levels of both testosterone and estradiol in serum precede breast cancer in postmenopausal women (57). An analysis of worldwide prospective studies showed strong associations of testosterone and DHEAS with breast cancer risk in postmenopausal women (58). Similar conclusions were obtained from a case-control study (59) and a large multicentric cohort study (60). A recent study has shown that high circulating levels of total and free testosterone are associated with the risk of developing breast cancer in postmenopausal women, while circulating estradiol level is not associated with the risk of breast cancer (61). High total testosterone was also significantly associated with increased risk of estrogen receptor-positive cancers. However, Danforth *et al.* reported that there were no significant associations between the score of breast cancer risk and levels of androgens such as testosterone, free testosterone and DHEA-S (62).

SUPPLEMENTATION OF TESTOSTERONE AND DHEA-S IN WOMEN

For women suffering from androgen deficiency, the option of exogenous testosterone therapy is available. Considerable progress has been made in recent years in the development of different modalities of testosterone therapy available to women. Transdermal testosterone patches as well as creams and gels are easily applied to the skin. Goldstat *et al.* reported that application of testosterone cream for 12 weeks improved well-being, mood, and sexual function without any adverse effects in premenopausal women with low libido and low testosterone level (63). It has been reported that transdermal

testosterone at a dose of 300 µg/day was effective for sexual desire in surgically and naturally menopausal women (64) and in women with hypoactive sexual desire disorder after surgically induced menopause (65, 66) without any relevant side effects. Davis *et al.* also reported that transdermal testosterone treatment resulted in a modest improvement in sexual function in postmenopausal women (67). Burger *et al.* reported that implants of estradiol and testosterone in postmenopausal women improved loss of libido, tiredness and lack of concentration (68). The results of Cochrane Review meta-analysis showed that hormone therapy (HT) plus testosterone improved libido, sexual function and sexual activity compared to the effects of HT alone (69). Barrett-Connor *et al.* reported that both estrogen alone and estrogen plus testosterone increased BMD at the hip and spine but that high-dose combination of estrogen and testosterone had the greatest effect in surgically menopausal women (70). Therefore, testosterone has a favorable effect on sense of well-being, increases BMD and improves general fatigue, sexual function and sexual activity. On the other hand, it has been reported that short-term testosterone treatment had no effect on verbal fluency and verbal memory in healthy postmenopausal women (71).

There is still considerable controversy regarding the use of testosterone therapy in women. Reported risks and side effects from testosterone therapy include the development of hirsutism, acne, alopecia, liver dysfunction, deepening of the voice, abnormal lipid changes, and virilization of a female fetus if pregnant. Another major concern of testosterone therapy is whether there is a stimulatory effect on the breast or endometrium. Proposed mechanisms include conversion to estrogen by the aromatase enzyme in breast tissue or direct stimulation of the androgen receptor. A prospective cohort study in the Nurses' Health Study showed that there was an increased relative risk for breast cancer in women using estrogen plus testosterone in comparison with that in women who had never used estrogen plus testosterone and that the risk was significantly greater than the risk of estrogen alone therapy (72). However, most of the available data do not support the concept of increase in the risk of breast cancer by testosterone but rather suggest that there is no effect or that testosterone reduces the risk of breast cancer by antagonizing the effects of estrogen on mammary tissue (73). On the other hand, there is a lack of data on endometrial safety. Panzer *et al.*

reported that testosterone replacement therapy for surgically and naturally menopausal women with low sexual desire can be used safely without increased risk of breast or endometrial cancer (74).

There does not appear to be an increase in cardiovascular risk through alterations in blood pressure, vascular reactivity, blood viscosity, hemoglobin concentrations, coagulation factors, or insulin sensitivity, with the exception of a lowering of HDL with oral testosterone (73). In addition, there does not appear to be an increased risk of hepatotoxicity. In particular, a transdermal patch or gel that avoids first pass has no related hepatic toxicity (75). The current recommendation for testosterone treatment is that therapy should be restricted to short-term therapy until long-term safety issues have been resolved. The number of adverse events associated with testosterone replacement treatment in women has been limited when protocols of treatment are optimized to achieve physiologic levels of circulating testosterone (67).

The physiological role of DHEA is poorly understood. Despite the wide use of DHEA as a dietary supplement, no well-designed study has established the efficacy and safety of DHEA therapy. None of the double-blind placebo-controlled studies have shown beneficial effects of DHEA administration on cognition, attention or memory (76). Wolkowitz *et al.* only reported that DHEA treatment had significant beneficial effects on depressive symptoms in patients with major depression (77). Cameron *et al.* suggested that doses of 30 to 50 mg of oral DHEA produce physiological androgen levels and that 50 mg of DHEA increases serum androgen levels within the physiological range as well as possible improvements of sexual function and mood and decrease in fatigue/exhaustion in women (78). A recent study has revealed that intravaginal administration of DHEA can be used to treat vaginal atrophy (79). However, since DHEA is converted not only into testosterone but also into small amounts of estradiol, DHEA treatment may have a risk for breast cancer in postmenopausal women. Thus, DHEA therapy should share the contraindications for use of estrogen replacement therapy in women.

EFFECTS OF TESTOSTERONE-DERIVED PROGESTOGENS IN WOMEN

Hormone replacement therapy (HRT) is available for women with menopausal symptoms. Addition

of progestogen is needed with estrogen for HRT in women with an intact uterus even if the dose of estrogen is low since it has been reported that endometrial hyperplasia and endometrial cancer occurred in women with an intact uterus when ultra-low dose estrogen alone was used (80). Progestogens, such as medroxyprogesterone, levonorgestrel and norethisterone acetate, which are older progestogens, have androgenic activities (81). Estrogen has favorable effects on insulin sensitivity, blood pressure and lipid metabolism, but androgenic activities of progestogens have unfavorable effects on these favorable effects of estrogen. In particular, testosterone-derived progestogens, such as levonorgestrel and norethisterone, have been reported to be associated with increase in the risk of breast cancer (82). Therefore, it is necessary to pay attention to lipid metabolism, insulin sensitivity and risk of breast cancer when using a testosterone-derived progestogen.

EFFECTS OF SHBG ON ANDROGEN

Consideration of only the total testosterone level is inadequate for assessing the androgen environment. Less than 2% of testosterone circulates in an absolute free state in the blood at any one time. Approximately 60-65% of testosterone is carried in peripheral blood bound to SHBG, and testosterone circulates in appreciable amounts bound to albumin (35-40%) and in small amounts bound to corticosteroid-binding globulin (CBG) (< 5%). Since the binding to albumin and CBG is relatively weak, testosterone can easily disassociate from these proteins to interact with the testosterone receptor. Essentially, SHBG has a function as a circulating reservoir of this potent androgen.

1. Change in SHBG

In women, the change in circulating SHBG with age is still controversial. SHBG has been demonstrated to decline steadily with age (7). However, it has been reported that SHBG was virtually unchanged in women, while SHBG in men increased more than 2 fold over the life span (5). Our population-based study showed that SHBG level in women gradually decreased around menopause and increased with age after menopause, while SHBG level was positively correlated with age in men (Figure 7). In addition, SHBG levels show a U-shape pattern in the 7 stages during menopausal

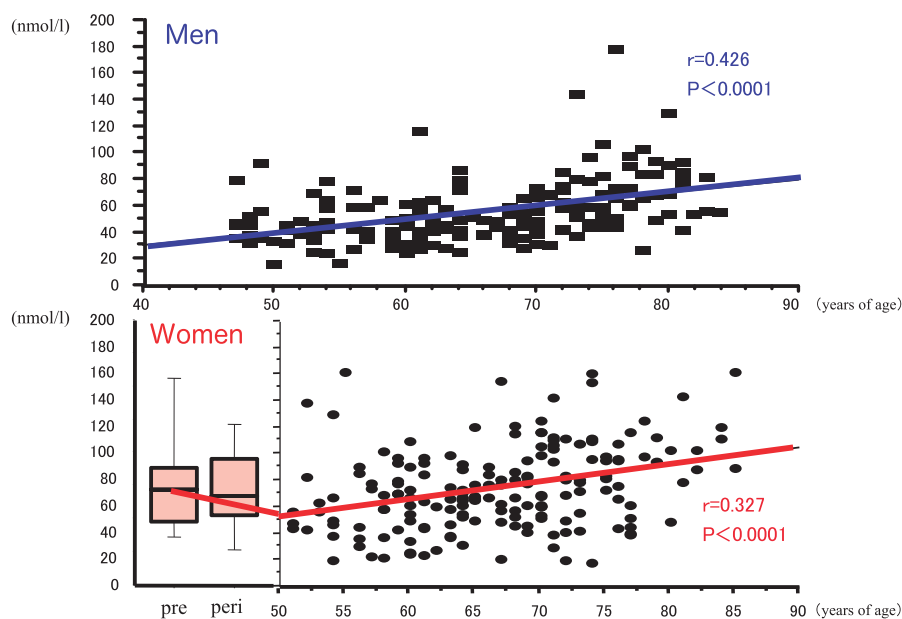


Figure 7. Changes in SHBG levels in men and women.
upper panel : men, lower panel : women

transition as can be seen in Figure 8.

2. Action of SHBG

Many studies have shown associations of SHBG with favorable effects on lipid profiles and insulin sensitivity in men (83, 84). In women, a high SHBG level was also associated with favorable lipid profiles decrease in the occurrence of cardiovascular

disease and metabolic syndrome. SHBG was shown to be negatively correlated with total cholesterol, LDL-C and TG and to be positively correlated with HDL-C (42, 85). Low SHBG level was associated with the occurrence of cardiovascular disease (43, 44). SHBG level was negatively associated with hyperinsulinemia (86) and risk of metabolic syndrome (16, 87). We also showed that SHBG level

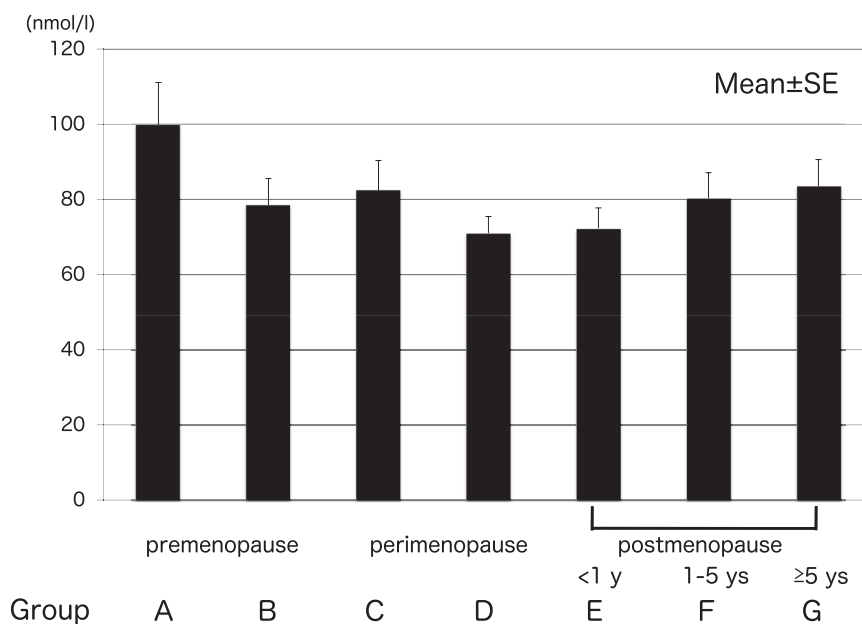


Figure 8. Changes in SHBG levels during the menopausal transition.
Group A : early reproductive stage, Group B : late reproductive stage, Group C : early menopausal transition, Group D : late menopausal transition, Group E : women for whom less than 1 year has passed since menopause, Group F : women for whom less than 5 years have passed since menopause, Group G : women for whom more than 5 years have passed since menopause

was negatively correlated with Homeostasis Model Assessment (HOMA) index in both men and women (88). In addition, SHBG level was negatively correlated with TG level in women but not in men. Therefore, SHBG may have biological functions beyond simply regulation of the level of free sex steroid hormones and may play important roles in lipid metabolism and insulin sensitivity.

SITE OF ANDROGEN PRODUCTION IN POSTMENOPAUSAL WOMEN

Whether ovaries produce androgens in postmenopausal women is a matter of debate. It has been reported that circulating androgens in postmenopausal women do not originate from the ovaries but from the adrenal gland since levels of androgens in postmenopausal women with natural menopause and those with surgical menopause were not different (89). It was later shown in a cross-sectional study that total and free testosterone levels in women aged 55 years or older with bilateral oophorectomy were significantly lower than those in age-matched women (90). A longitudinal study also showed a 42% decline in testosterone level in postmenopausal women who underwent oophorectomy, suggesting that the postmenopausal ovary is hormonally active and contributes significantly to the circulating pool of testosterone (91). Several studies also showed that women with bilateral oophorectomy had lower testosterone levels than those in natural postmenopausal women (92-94). Bui *et al.* reported that a significant decrease was found in testosterone levels after bilateral oophorectomy, whereas no significant difference was found after natural menopause by using the developed isotope dilution-liquid chromatography-tandem mass spectrometry (95). However, more recently, it has been shown that levels of testosterone and DHEA-S did not differ significantly between surgically and naturally menopausal women with a mean age of 52.4 years (96).

MEASUREMENT OF TESTOSTERONE

Ability to measure either total or free testosterone level accurately is essential for establishing the diagnosis of true androgen deficiency. The normal circulating level of testosterone in both reproductive-aged women and postmenopausal women still needs proper validation since methods for

measurement of testosterone have been inadequate in women until now (97). Recent advances with the use of ultrasensitive methods such as mass spectrometry coupled to either gas or liquid chromatography have improved the technology for measurement of testosterone. Advances in technology may allow clinicians to better define female androgen deficiency and may provide easier treatment options for testosterone replacement therapy.

CONCLUSION

Extreme levels of circulating androgens, whether high or low, may have negative effects on women's health. An excess endogenous testosterone level may be associated with unfavorable lipid profiles, insulin resistance and development of breast cancer in postmenopausal women. On the other hand, insufficiency of testosterone leads to an impairment in sexual drive, reduced libido, and depressed mood. For optimal physiological and psychological health in women, circulating testosterone levels should be within normal ranges (Figure 9). An appropriate level of androgen may play important roles in metabolic, psychological and sexual functions in women. Although testosterone level was not significantly low in postmenopausal women as shown in Figure 3, various symptoms and diseases due to insufficiency of testosterone in postmenopausal women might be caused by individual difference or SHBG level. In addition, very small changes in testosterone in postmenopausal women may influence on the symptoms and diseases. According to the estrogen threshold hypothesis proposed by Barbieri, tissues vary in their sensitivity to estradiol (98). As well as estrogen, sensitivity to androgen may be different in various tissues even if the range is narrow. In addition, the roles of testosterone and DHEA-S in women's health may be different. Further studies on testosterone, DHEA-S and SHBG in women are needed.

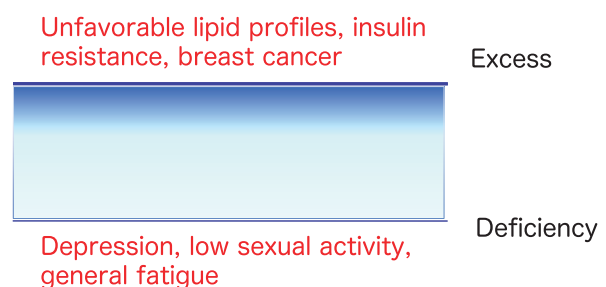


Figure 9. Optimal testosterone level in women.

CONFLICT OF INTERESTS

The authors have no conflicts of interest.

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