

The impact of testosterone imbalance on depression and women's health

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Abstract

Women suffer more often from depression than males, indicating that hormones might be involved in the etiology of this disease. Low as well as high testosterone (T) levels are related to depression and well-being in women, T plasma levels correlate to depression in a parabolic curve: at about 0.4–0.6 ng/ml plasma free T a minimum of depression is detected. Lower levels are related to depression, osteoporosis, declining libido, dyspareunia and an increase in total body fat mass. Androgen levels in women decrease continuously to about 50% before menopause compared to a 20-year-old women. Androgen levels even decline 70% within 24 h when women undergo surgical removal of the ovaries. Conventional oral contraception or HRT cause a decline in androgens because of higher levels of SHBG. Hyperandrogenic states exist, like hirsutism, acne and polycystic ovary syndrome. Social research suggests high androgen levels cause aggressive behavior in men and women and as a consequence may cause depression. Higher androgen values are more pronounced at young ages and before and after delivery of a baby and might be responsible for the “baby blues”. It was found that depression in pubertal girls correlated best with an increase in T levels in contrast to the common belief that “environmental factors” during the time of growing up might be responsible for emotional “up and downs”. T replacement therapy might be useful in perimenopausal women suffering from hip obesity, also named gynoid obesity. Abdominal obesity in men and women is linked to type 2 diabetes and coronary heart diseases. Testosterone replacement therapy in hypoandrogenic postmenopausal women might not only protect against obesity but also reduce the risk of developing these diseases. Antiandrogenic progestins might be useful for women suffering from hyperandrogenic state in peri- and postmenopause. Individual dosing schemes balancing side effects and beneficial effects are absolutely necessary. Substantial interindividual variability in T plasma values exists, making it difficult to utilize them for diagnostic purposes. Therefore a “four-level-hormone classification scheme” was developed identifying when estradiol (E) and T levels are out of balance. (1) Low E–low T levels are correlated with osteoporosis, depression, and obesity; (2) high E–low T with obesity, decreased libido; (3) high T–low E levels with aggression, depression, increased libido, and substance abuse; (4) high E–high T with type II diabetes risk, breast cancer and cardiovascular risk. Testosterone delivery systems are needed where beneficial and negative effects can be balanced. Any woman diagnosed for osteoporosis should be questioned for symptoms of depression. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Depression; Postmenopausal women; Hormone replacement therapy; Osteoporosis; 17 β -Estradiol; Testosterone; Weight reduction; Obesity

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1. Introduction

Mood disturbances including depression will lead to an epidemic of disease in the 21st century in the western world (Fig. 1), the increase of depression in persons older than 65 years seems to be particularly of concern [1]. The NIH asks for a decade long research to reduce mental health problems especially in postmenopausal women, since they are suffering twice as much as males from depression and mood disturbances [1]. Gender research may suggest that different work loads create differences in coping, however, as will be outlined, depression in females has not only social causes but might have a biological component as well. It may be judged as premature aging and therefore is accompanied by other diseases commonly seen in the aging processes.

Treatment of depressed women is an unmet medical need [1,2] as during menopausal transition 50–70% of women experience all kinds of somatic and emotional symptoms [2–6]. In Germany a population based analysis showed that symptoms as depressive mood, sad, and being tearful in women increased from 20% in 18–29 years old, to 48% for 50–59 year old and remains at this level after the age of 60 years [2]. In men compared to women about half of the percentages in all age groups report depressive symptoms and

being tearful but interestingly men over 60 years seem to suffer as much as women from depression, since in this age group a steep increase to 45% is reported.

The benefits of traditional hormone replacement therapy (HRT) in women with estrogens or estrogens plus progestins are well documented [3–6]. While vasomotor symptoms (flushing) and urogenital (vaginal dryness) symptoms are widely recognized as being a direct consequence of the declining estrogen production during menopausal transition, there is much debate concerning the cognitive, vegetative and emotional symptoms of the climacteric [7,8]. While exogenous estrogens are successful in relieving vasomotor symptoms, reducing the heart attack rate in women and decreasing the risk of osteoporosis, estrogens are not as successful in improving mood and emotional state [8]. Also the usual weight gain in this age group is of major concern [8]. Although much has been achieved within the last half century, there are major diseases which are not treated well like cognitive, vegetative and emotional issues, including major depression, dysthymia, decreased libido, weight gain, or body composition, and urogenital aging. Therefore current HRT was recently criticized by Maartens et al. [8], indicating that depression might be an underlying and underestimated problem.

There is increasing evidence to suggest that many postmenopausal women experience symptoms which may be secondary to androgen deficiency [1,10–14]. Huber calls androgens “the forgotten female hormones” [7] but use of androgens as a routine component of HRT has been limited in part because of misconceptions regarding the risk benefit ratio associated with androgen administration [15]. In earlier studies androgen-only HRT was given at high doses resulting in masculinization [15]. Newer oral formulations contain lower doses of androgens avoiding overdosing [15] and therefore in the last 10 years androgen replacement in peri-and postmenopausal women has gained more and more attention [9,16–18]. Only recently it was highlighted that oral administration of estrogens causes a reduction of active androgens by increasing SHBG concentrations [19].

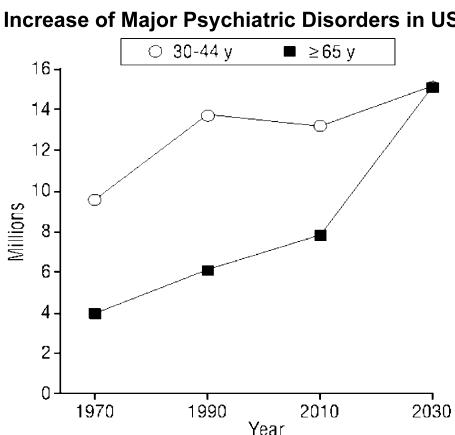


Fig. 1. Estimated prevalence of major psychiatric disorders in younger (aged 30–44) vs. older age (age 65 years or older) adults from 1970 to 2030: see the text for explanation of the estimates used. Taken from Ref. [1].

Hyperandrogenic states in women are related to polycystic ovarian syndrome (PCO), hair loss, acne, a possibly increased breast cancer risk, type-2 diabetes and depression. High androgen levels make women and men aggressive and may lead to antisocial behavior, which might lead to depression.

It is a controversial finding that depression in women might be raised by too low or too high androgen levels, which raises questions like:

1. do females with specific testosterone levels have an increased risk for depression,
2. does testosterone replacement lead to an improvement in depressive symptoms,
3. are other diseases linked to depression (as pre- or co-morbidity like osteoporosis) and to an testosterone imbalance,
4. will testosterone replacement alter depression and other diseases, and
5. which delivery systems are needed?

2. Testosterone physiology

During embryonic development testosterone in women is involved in the differentiation of the brain and sexual organs [20]. After puberty about half of the testosterone is produced in the ovaries [20] and, in contrast to estrogens, this synthesis remains constant for up to 15 years after menopause [20]. In peripheral tissues the majority of androgens will be metabolized from DHEA and androstenedione [23,24,28] and therefore testosterone replacement can be achieved by DHEA or testosterone. Testosterone is the most active androgen. It binds to the androgen receptor, which is distributed widely throughout the body including the central nervous system, the limbic and cortical tissue [24,25].

Within the male brain testosterone is metabolized regionally to estradiol via the enzyme aromatase, present in higher amounts in hypothalamus than in cortex [25,26,30]. Aromatase is abundant in CNS, liver and adipose tissue. The daily production of testosterone in healthy young premenopausal women is approximately 300 µg per day, about 5% of the daily production in men [27]. In the circulation 98% of

testosterone is protein bound, about half is weakly bound to albumin and the remainder is tightly bound to sex hormone binding globulin (SHBG) [29]. The bioactive fraction of circulating testosterone, considered to exist of the non-protein bound fraction plus the fraction that dissociates readily from albumin, can diffuse into the target cell and bind to the androgen receptor [24]. The steroid receptor complex binds to specific sequences of genomic DNA and thereby influences the production of messenger RNA, which modulates protein synthesis in the cell [24]. In many of the target cells testosterone is metabolized to dihydrotestosterone (DHT) which also binds to the androgen receptor. DHT is required for the effects of testosterone on external genitalia and sex glands, the required 5 α -reductase is abundant in reproductive tissues and skin.

Androgen receptors have been identified in cortex, pituitary, hypothalamus, preoptic region, thalamus, amygdala and brain stem [31]. Androgen effects in the brain are sexual behavior, libido, temperature control, sleep control, assertiveness, cognitive function, learning capacities, visual spatial skills and language fluency. It has been shown that aggressiveness typically occurs with an androgen excess and not with androgen levels within normal ranges [31].

3. Testosterone levels in women throughout life

Although substantial interindividual variability exists in testosterone levels in females a decline with age can be detected [32,33]. In the years to the menopausal transition levels of circulating androgens begin to decline as a result of age related reduction of both ovarian and adrenal secretion [9] and after menopause testosterone levels are reduced by 50% to about 0.6 nmol/l. A bilateral ovariectomy reduces testosterone by 70% to 0.3 nmol/l [9]. Although between 40 and 60 years of age there seems to be virtually no change in testosterone levels, a steep decline between 20 and 40 years can be seen (Fig. 2a): at age 40 testosterone has declined to about half of its value at age 20 (Fig. 2a). Between 40 and 60 years androgen levels are relatively constant (Fig. 2b)

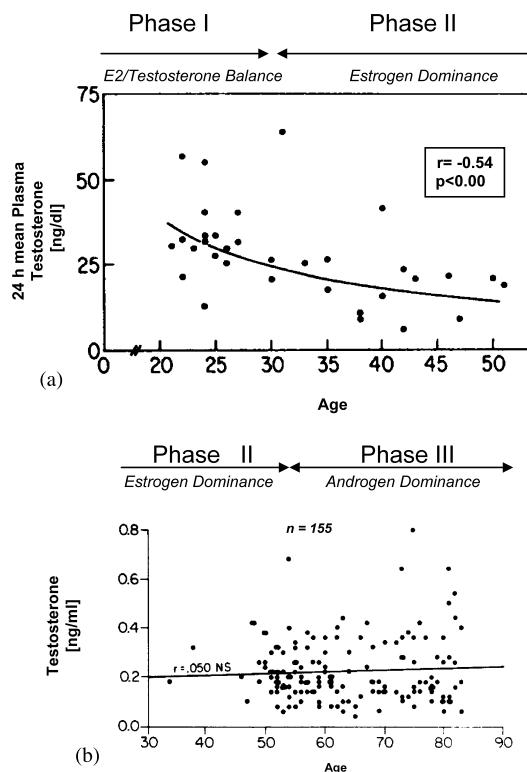


Fig. 2. (a) Age-dependent decline of bioavailable testosterone in women. Taken from Ref. [32]. (b) Age-dependent decline of free testosterone in women. Taken from Ref. [33].

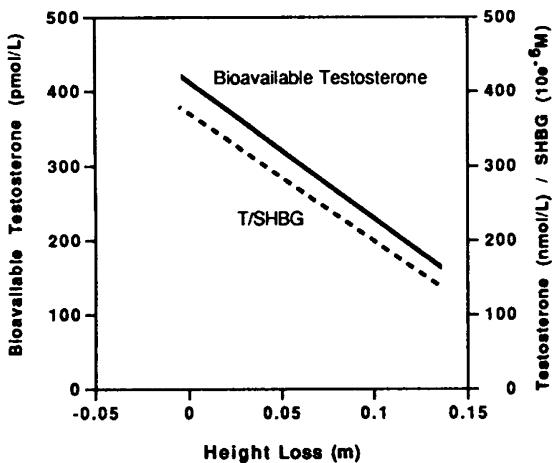


Fig. 3. Height loss over 16 years by measured and estimated bioavailable testosterone in postmenopausal women. Taken from Ref. [43].

and in contrast to the dramatic decrease in estradiol production, the decline in testosterone production is smaller, from 250 to 180 µg per day [20], with considerable interindividual variability (Fig. 2a; b).

4. Reduced testosterone plasma levels after ovariectomy

Hysterectomy is a common surgical procedure and in the USA 600 000 hysterectomies are performed annually, about half with bilateral oophorectomy [34]. Although the production of estrogens is one of its main functions, the ovary also is a source of androgens and surgical removal causes a dramatic decreases in estrogen, progesterone and testosterone [34,35]. The levels can drop to about 50% within 24–48 h after the operation [34,35]. Women who have undergone removal of the ovaries are the prime candidates for estrogen plus androgen therapy [34,35]. The positive effects in androgen replacement therapy are increased energy [35], libido [30], sexuality [30] and sense of well-being [34].

5. Testosterone and osteoporosis

Decreased estrogens are related to bone loss in men and women and estrogen replacement in women has been shown to reduce bone loss [36–38]. Men suffering from mutations in the estradiol receptor or in aromatase show less growth during puberty and deficits in bone mass [39,40]. Osteoporosis as a consequence of hypogonadism in males is very well documented [41]. Decreased testosterone plasma levels are markers of osteoporosis in women [42]. A relation of endogenous testosterone to loss of height in postmenopausal women, a surrogate for osteoporotic vertebral fractures, has been shown [42] (Fig. 3), based on measurements 16 years apart. These women lost an average of 0.22 cm/year in height. Neither estrone nor estradiol levels were significantly and independently related to height loss but bioavailable testosterone levels predicted future height loss independent of age,

obesity, cigarette smoking, alcohol intake, and use of thiazides and estrogen. These data on height loss are compatible with a direct effect of testosterone on bone mineral density or bone remodeling [42,43].

Davis et al. investigated the effects of estrogen-androgen therapy on bone density in a prospective 2 years single blind trial in 34 menopausal women [44] (Fig. 4), randomly assigned to either estradiol implants (50 mg) or estradiol plus testosterone (50 mg) implants once every 3 months. Both treatment groups showed significant increases in total body, lumbar vertebral and hip bone density but the authors concluded that estrogen-androgen therapy was more effective in increasing bone mineral density in the hip and lumbar spine than estradiol alone [44].

A very interesting model for testosterone and its effect on bone markers are individuals suffering from complete androgen insensitivity syndrome (CAIS), genotypically XY women who are unresponsive to androgens [45,46], because of mutations in the androgen receptor. CAIS women tend to be tall but they show deficits in their spinal bone mass index, averaging 1 SD from normal [45,46] which means a 2–3 fold long-term increase in fracture risk. Although more evidence

suggests that androgens might be an important factor for maintenance of female skeletal integrity, this area is open for more research.

6. Osteoporosis and depression

Osteoporosis, indicated by decreased BMD, has recently been reported in older women suffering from several mental disorders, including schizophrenia and major depression [47]. Findings suggest that chronic stressors are associated with significant elevations in IL-6 over and above the elevations associated with normal aging, but that moderate stressors may not be related to appreciable elevations in IL-6 [48]. Although the link between osteoporosis and depression in women has been well established, the treatment options are not very well worked out. Since relief with application of testosterone in depression might be much more successful than estradiol in postmenopausal women, treatment with testosterone would result in both an increase in BMD and mood elevation [9].

7. Sexual behavior of women and testosterone

In the USA approximately 40% of women across the age range 18–59 years report a lack of interest in sex [49,50]. The nature and determinants of sexual desire in women are poorly understood. Although their androgen levels are lower than in younger women, older women exhibit the same level of sexual desire and arousal as the younger ones, however, intercourse frequency and self-rated sexual gratification scores were significantly lower than younger women [51].

Sexual desire in women correlates with endogenous androgens [44,49,52], sexual response decreases in 33–46% of women after ovariectomy [53]. It is known that testosterone improves the well-being of women suffering from decreased libido [9–13,30,31,53]. Estrogen-androgen therapy significantly improved sexual sensation and desire after double-blind treatment in comparison to previous estrogen therapy and baseline assessments. A transdermal patch was successfully ap-

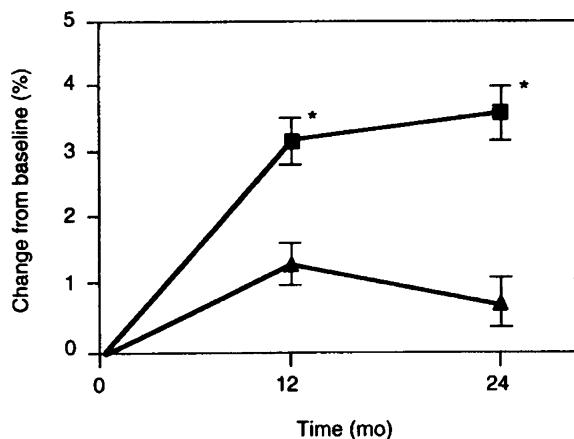


Fig. 4. Mean percentage change from baseline in spinal bone mineral density (L1–L4) in 60 surgically menopausal women treated with 1.25 mg esterified estrogens plus 2.5 mg/d methyltestosterone (filled squares) or 1.25 mg esterified estrogens (filled triangles). Error bars represent SD. Asterisks represent $P < 0.01$. Taken from Ref. [43].

plied in women with impaired sexual function after oophorectomy [54]. Except for local vaginal changes, which relief of pain and increased vaginal lubrication during intercourse, studies have failed to detect a significant improvement in sexual function by estrogen alone therapy [55]. Estrogens do not play a significant role in improvement of sexual-drive and enjoyment in women.

Davies compared injectable estrogens with injectable androgens and found significant increase in sexual desire only in the androgen treated group [44]. However, while certain amounts of testosterone appear to be beneficial for sexual motivation, there is no evidence that androgens in women with normal or hyperandrogenic state are associated with improvements in sexual motivation [38].

8. Testosterone and body composition in men and women

Obesity is a health hazard and its epidemic increase places a tremendous burden on health-care systems in western societies, since it has been linked to diabetes, dyslipidaemia, and hypertension [56,57]. Lean body mass declines with age as a result of an increasingly sedentary lifestyle [56]. It is believed that excess fat and not excess weight is linked to cancer risk, diabetes, and cardiovascular problems [57], already recognized by Vague in the forties of the last century, who described the high risk of "android obesity" [57]. Today "android obesity" or male type obesity with increase in visceral fat, which accompanies postmenopause, is distinguished from "gynoid obesity", with accumulation of body fat in the gluteofemoral region, commonly found in premenopausal women [58] (Figs. 9 and 10).

Interestingly, gynoid obesity is not linked to cardiovascular health [58]. Abdominal obesity, however, is a major clinical and public health issue; it is a major risk factor for coronary heart disease, type 2 diabetes, and related mortality [59]. Frequently the waist/hip ratio is used to describe obesity. However it is recommended to measure the waist circumference, because it is linked to android obesity with high concentration of vis-

ceral fat. The WHO defined a cut off with a critical waist circumference of 102 cm in men and 88 cm in women [59]. Weight loss programs with gynoid women therefore do not necessarily lead to an improvement in health, however men and women suffering from android obesity gain tremendously from weight loss programs.

Visceral fat dramatically raises the risk of developing coronary heart diseases: viscerally obese man have a 20 fold increased risk of developing coronary heart diseases over a period of 5 years compared to a matched group with similar weight without visceral obesity [60]. Studies in women are critically needed to determine the risk of visceral fat on coronary heart disease.

Androgens modulate abdominal fat deposition [61]; studies in men investigating hormonal parameter showed a direct correlation between the increase in body fat mass with a decline in testosterone [62] independent of estradiol concentration. Jensen pointed out that low testosterone levels in men are related to adverse metabolic effect of predominantly visceral body fat distribution [63]. Intramuscular treatment with testosterone over 2 years led to a clear improvement in well-being, bone mass and reduction in visceral fat mass in a cryptorchid male [21] (Fig. 5).

In women suffering from PCO and ovarian hyperandrogenism, an increase in visceral fat is found, on the other side subcutaneous abdominal fat is found in obese postmenopausal women suffering from low androgen levels. In hypogonadal men testosterone replacement leads to a decline in visceral fat, however not in subcutaneous fat. In women testosterone replacement leads to a reduction in abdominal fat as well as visceral fat [64].

Not only peri- and postmenopausal women show associations between hormones and obesity: Recently Huber et al. conducted an investigation on relations between body composition in young women (< 30 years) and endogenous hormone levels [65]; associations between estradiol, testosterone, SHBG and FSH were found with body fat, bone mass and fat distribution. They concluded that body composition was related to androgens or to estrogens: women with low androgen levels exhibit postmenopausal charac-

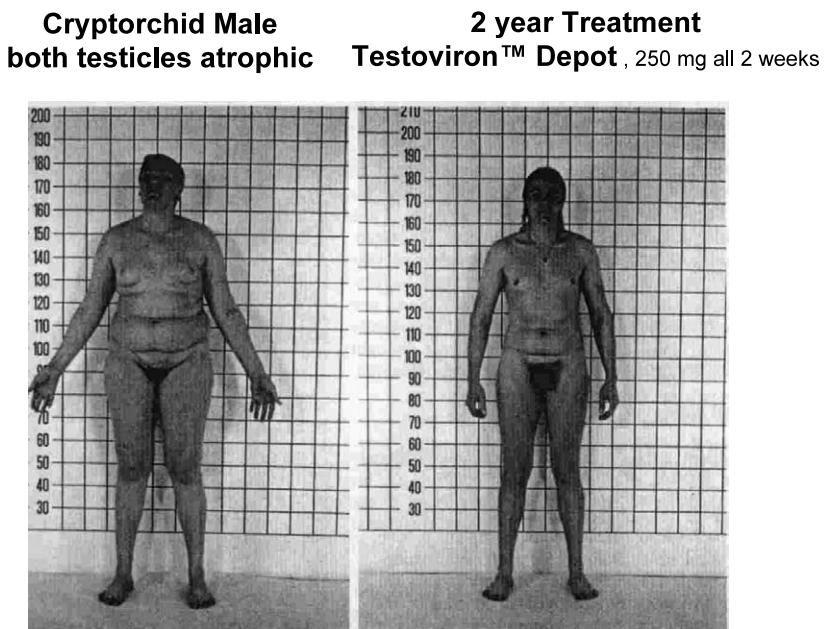


Fig. 5. Influence of testosterone treatment on physical appearance in a cryptorchid man. Taken from Ref. [21].

teristics with an increased hip/body fraction [55]. Bulimia nervosa is associated with low estradiol and high testosterone and cortisol values [24] and it has been reported that these patients show aggressive behavior [24]. In a recently conducted study, it was found that increased testosterone and cortisol plasma concentration correlated with depression and aggression rates [24].

From these observations the following model emerges: a 20-year-old women is considered in “hormonal balance”, since estrogen as well as androgen are relatively high (Phase I, Fig. 2A). Between 20 and 45 years testosterone declines continuously, resulting into an estrogen dominance (Phase II in Fig. 2a,b). Around menopause a decline in estrogens takes place but testosterone remains constant, resulting into a testosterone dominance (Phase III in Fig. 2B). These phases are depicted in Fig. 10, where at young age and normal testosterone concentrations no obesity occurs. Due to natural decline in testosterone at ages between 20 and 40 years or during pregnancy an increase in estradiol occurs, estrogen dominance results in gynoid obesity (Fig. 10). Also oophorectomy, with a surge of estradiol when

estrogen is replaced, results in “gynoid obesity”. This is reversible in young women, because after pregnancy the fat depot can be reduced by exercise and reduction of caloric intake, via increases in testosterone and growth hormone. At perimenopause many women show decreased androgen levels, resulting in gynoid obesity. This opens an interesting possibility for testosterone replacement in perimenopausal women suffering from gynoid obesity to reduce excess fat.

The picture at higher testosterone levels in women is less clear, since at higher androgen levels, e.g. in PCO, many women are lean and non obese whereas many women are obese from the android type [131–133] (Fig. 10). Since obesity at higher testosterone levels is not fully understood and scientists are at the stage of data collection, it can currently only be speculated why these differences exist. A strong association between testosterone and leptin in non-obese men and women is lost with increasing (central) adiposity [133,134]. Differences in races in obesity exist: African American women show much more pronounced insulin resistance from central obesity than Caucasian women [135].

9. Testosterone and cognitive function in elderly women

Sex steroid hormones are implicated in the cognitive processes of the adult brain [66] but the effects of testosterone are not very clear. Some studies indicate that the administration of testosterone to non-demented subjects is associated with better visuospatial functioning and deterioration of verbal skills [19]. Studies comparing cognitive performance between conditions with different hormone levels, such as phases of the menstrual cycle, surgical menopause, and estrogen replacement therapy, suggest that higher levels of estrogen are associated with better verbal memory and worse visuospatial ability [18,66]. High estradiol levels were associated with delayed verbal memory and retrieval efficiency, whereas low levels were associated with better immediate and delayed visual memory; levels of testosterone were related positively to verbal fluency. Levels of progesterone and androstenedione were unrelated to cognitive performance.

In older women, higher endogenous estrogen levels were not associated with significantly better performance on any cognitive function test. In contrast, higher levels of testosterone predicted better categorical performance on several cognitive tests [67].

Table 1
Signs of depression [1]

Persistent sad, anxious, or “empty” mood
Loss of interest or pleasure in activities, including sex
Restlessness, irritability, or excessive crying
Feelings of guilt, worthlessness, helplessness, hopelessness, pessimism
Sleeping too much or too little, early-morning awakening
Appetite and/or weight loss or overeating and weight gain
Decreased energy, fatigue, feeling “slowed down”
Thoughts of death or suicide, or suicide attempts
Difficulty concentrating, remembering, or making decisions
Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain

10. Testosterone levels in children

A recent study investigating the influence of testosterone on social behavior in female and male preschool children [68] revealed a positive relationship in boys between testosterone and giving and receiving aggression in the context of social interaction [68]. Testosterone can therefore be a useful biological marker for serious aggression (and behavioral patterns reflecting different levels of sociability) in preschool boys [68]. It is interesting to note that in preschool children depression is rather rare, however boys seem to be slightly more affected than girls.

11. Depression and wellness in old age

There are three types of depression [1]: unipolar major depression, manic-depressive illness (also known as bipolar disorder) and dysthymia (a less severe form of depression). Women in the USA are more frequently (12%) affected by depression, at roughly twice the rate of men (7%). Women and men are equally likely to develop manic-depressive illness but women are more likely than men to suffer from major depression and dysthymia. Unipolar major depression is the leading cause of disease burden among females ages 5 and older worldwide. Before adolescence and late in life, females and males experience depression with the same frequency [1], no gender difference is seen until puberty and following menopause. Scientists hypothesize that hormonal factors are involved in women’s greater vulnerability at other ages. Stress due to psychosocial factors, such as multiple roles in the home and at work and the increased likelihood of women to be poor, at risk for violence and abuse, and raising children alone, plays a role in the development of depression and other mental disorders (Tables 1 and 2).

The relationship between mood and menopause has been studied extensively [22,66,67], and several theories have emerged relating mood disorders with menopause and hormonal changes. The Massachusetts Menopause Study suggests that there is an increase in the rate of depression after surgical menopause [69]. The domino theory sug-

Table 2
Well-being according to the General Health Questionnaire (GHQ 30) [124,129,130]

Negative items	Positive items
Lost sleep over worry	Able to concentrate
Restless nights	Busy and occupied
Constantly under strain	Getting out of the house
Could not overcome difficulties	Managing as well as most people
Life a struggle	Doing things well
Taking things hard	Satisfied with task performance
Scared or panicky	Feeling warmth and affection
Everything getting on top of you	Able to get on with people
Unhappy and depressed	Chatting with people
Losing confidence	Playing a useful part
Feeling worthless	Capable of making decisions
Life is hopeless	Enjoying normal activities
Nervous and strung-up	Able to face up to problems
Life is not worth living	Hopeful about the future
Nerves very bad	Feeling reasonably happy

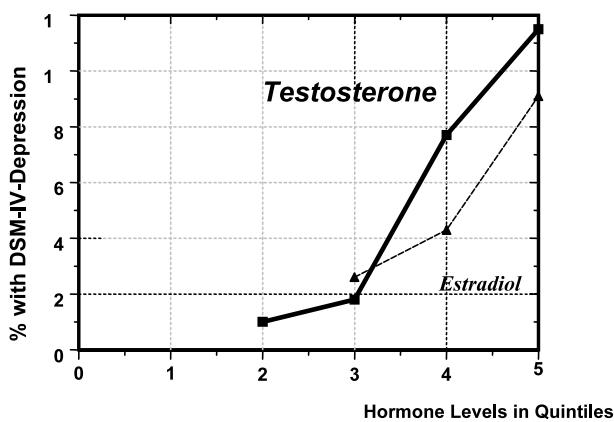


Fig. 6. Relationship between depression, measured on the DSVM-IV Scale and hormone levels in girls in puberty at various Tanner stages. Triangles: estradiol; squares: testosterone. Taken from Ref. [73].

gests that an improvement in mood and behavioral symptoms is a consequence of a reduction in somatic symptoms [70,130], while other factors like the empty nest syndrome might add up to this picture [70].

Estrogens have a limited capacity to improve well-being of postmenopausal women [30,103,

104]. Very often elderly women complaining of fatigue, low libido and diminished well-being symptoms are misdiagnosed to psychosocial and environmental factors [9]. There is increasing evidence to suggest that many postmenopausal women experience symptoms alleviated by androgen therapy and that such symptoms may be secondary to androgen deficiency [31], with low circulating bioavailable testosterone. Testosterone replacement results in significant improvement in symptomatology and quality of life for the majority of women [30,31,53,55,66,67,71,72]. Notelowitz et al. compared the effect of oral estrogen formulations with and without androgens in an array of symptoms in postmenopausal women and showed that only addition of testosterone was able to increase well-being [35].

12. A model for depression in women: depression in girls

Recent findings in 9–15 years old girls argue against theories that explain the female excess of depression in adulthood in terms of changes in body morphology and their effects on social interactions and self-perception [73]. They suggest that causal explanations of the increase in depression in females has to focus on factors associated with changes in androgen and estrogen levels rather than the morphological changes of puberty (Fig. 6) [73]. Hormones like testosterone might be responsible for depression in puberty. Additionally it was shown in this study that alcoholism in teenage girls is strongly related to elevated testosterone plasma levels [73].

12.1. Testosterone and depression in men: the Vietnam veterans study

Testosterone has positive effects on mood and well-being in men [21,66,74–85]. In contrast to this, social science suggests that high plasma levels of testosterone are associated with antisocial [86], wife beating behavior [87], health risk behavior [88], unemployment [89] and being unmarried [90]. Aggressive and competitive behavior is largely dependent on testosterone levels [91,100]

and this might contribute negatively for depression. Athletes using high doses of anabolic-androgenic steroids suffer substantially more from depression than the general population: 23% of steroid users reported major mood syndromes, mania, hypomania, or major depression [88]. These steroids represent a health problem for athletes using steroids causing irritability and aggression [88].

In a recent study a parabolic association was identified between testosterone and depression in a large sample of 4393 Vietnam veterans (Fig. 7) [90]. Men who do not enjoy the integrative benefit of marriage and especially when engaged in anti-social risk behavior are more likely to be depressed [90]. However the benefits of testosterone in preventing depression among those with average or below average levels are unaffected by these behavioral and social factors [90]. A linear relationship was identified for testosterone levels below average, regardless of social status. This observation may help to explain some discrepancies on the role of testosterone in depression in medical and social literature; it may help to lay the ground for testosterone replacement therapy (TRT). Men with testosterone levels of less than 5 ng/ml plasma may benefit from replacement therapy.

13. Testosterone and depression in women

A link between depression and testosterone in women has been suggested [91–98], but reports are conflicting; low testosterone levels may cause depression in oophorectomized women, high testosterone levels may also cause depression [97].

Women with endometriosis treated with GnRH-agonists experience considerable reductions in estradiol, testosterone and progesterone levels and they show dramatic increases in depression (about 60%) [137]. Some of these patients respond to SSRI-treatment, indicating that estrogen might be involved [137], but systematic studies are missing. They suffer from weight increase from the gynoid type, loss of sexual desire, loss of energy and incapability to interact in social situations. They frequently report that they “cannot defend themselves”. All these parameters can be linked to testosterone deficiencies.

This author suggests a model for women on the relationship between testosterone levels and depression (Fig. 8). Studies correlating circulating androgens levels to hirsutism revealed a linear relationship between testosterone plasma concentrations and depression [99]; the correlation was higher between hirsutism and depression. There is a direct link between testosterone and criminality in men [100] and women [101]; it was related with

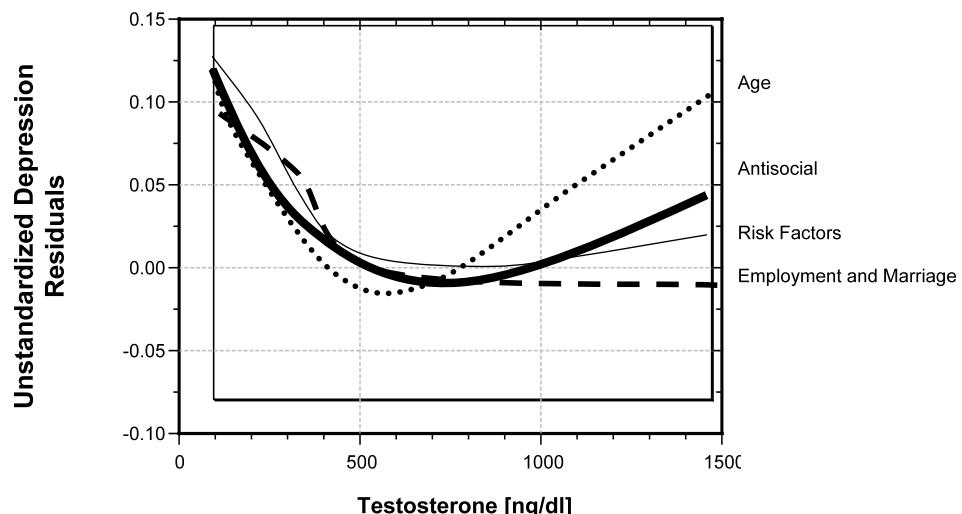


Fig. 7. Testosterone and depression in men. Taken from Ref. [91].

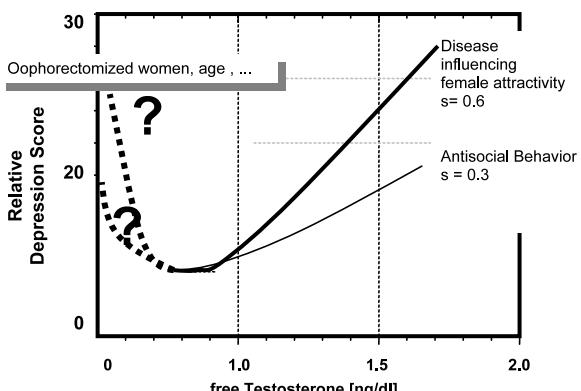


Fig. 8. Testosterone and relative depression risk in women.

criminal violence and aggressive dominance in prison among women [102]. Changes with age are partly explained by the decline in testosterone levels [101]. Depression as a consequence of criminal behavior was identified to be strongly related to testosterone in women. A recent study showed that testosterone levels in pregnant women peri- and postpartum correlated with depression and anger observed later [136].

Fig. 8 depicts hypothetical relationships between depression and testosterone plasma levels in women under different conditions resulting into a parabolic curve, similar to those seen in men. Increases in depression at high testosterone levels seem to be related with antisocial behavior, when women are prison inmates. Hirsutism severely disturbs the attractivity and self perception, reducing the social status in women, causing higher depression and anger rates.

14. Dehydroepiandrosterone (DHEA)

DHEA can be seen as a precursor of testosterone [116]. In the Rancho Bernardo Study it was shown that DHEAS levels were significantly and inversely associated with depressed mood, independent of age, physical activity, and weight change [105]. Several investigators evaluated the efficacy of the adrenal androgen DHEA in the treatment of midlife-onset dysthymia [22,105]. In

one study a significant response in women was seen after 3 weeks of treatment, the symptoms that improved significantly were anhedonia, loss of energy, lack of motivation, emotional numbness, sadness, inability to cope and worry [22]. DHEA showed no specific effects on cognitive function or sleep disturbance. Another study found that DHEA reduced SHBG and produced modifications in steroid levels in plasma with an increase in allopregnanolone, anabolic and estrogenic steroids, a decrease in cortisol and an increase in β -endorphin production [105].

15. Side effects of testosterone

15.1. Coronary artery disease

Renewed interest in the cardio-protective effects of estrogens has led to re-examination of the effects of androgens [106,107]. Androgens lower total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides but also decrease high-density lipoprotein (HDL) cholesterol levels [107]. Androgens affect arterial-wall effects by maintaining mechanisms involved in vasodilatation. Androgens alone appear to promote atherosclerosis but when administered with estrogens have opposite effects on the arterial wall. Preliminary clinical findings in women using postmenopausal estrogen/androgen treatment indicate a good safety profile [106]. Oral application of androgens has more pronounced negative effect on plasma lipids and cholesterol than injectable forms [106,107].

The lower doses administered to women compared to men have not resulted in significant hepatic events [106]; Davis found no negative effect on lipids when testosterone was delivered parentally to women [53] and Huber could not identify negative effects on plasma lipids when testosterone was delivered transdermally [65]. In men, testosterone has beneficial effects on fibrinolysis and blood vessel endothelium, on blood sugar and insulin metabolism and in maintaining coronary artery circulation [108]. Studies on the potential effects of physiologic levels of testosterone in women are critically needed.

The increased evidence of coronary artery disease in men compared with premenopausal women suggests a detrimental role of male hormones on the cardiovascular system [109]. It was recently found that men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms [110]. Experimentally, low dose supplementation of testosterone in men with chronic stable angina reduced exercise-induced myocardial ischemia. In contrast to common belief, the use of anabolic steroids in male bodybuilders is not associated with significant abnormalities of arterial structures or function although impaired vascular reactivity and increased arterial thickening has been reported [111].

15.2. Breast cancer

There is a theoretical concern that menopausal androgen replacement therapy may increase the risk of breast cancer but this has not been demonstrated in clinical practice. In an animal model it was observed that additional administration of testosterone to estradiol reduced the risk of breast cancer [112]. These results show that an estrogen–progestin–androgen combination has an antiproliferative effect in mammary glands of experimental animals [112].

15.3. Diabetes

There is evidence for an inverse association between type 2-diabetes and androgens in men and a positive association in women [113]. Additionally, in women suffering from type-2 diabetes the estrogen levels were higher [108]. Overall, the safety profile of androgen replacement therapy appears to be acceptable using doses avoiding supraphysiologic testosterone levels [106].

15.4. Virilizing effects

While all androgens are potential virilizing agents in women, alkylated compounds have an additional risk of inducing hepatic consequences, regardless of their route of administration. Virilizing and cutaneous side effects in women remain

the primary concern; some observational studies described acne in up to 38% of male patients treated with oral methyltestosterone; other studies suggest a much lower incidence of approximately 5% [106]. These effects in women clearly are dose-dependent.

16. Reduction of testosterone by drugs

16.1. Progestins

Sex hormone-binding globulin (SHBG) levels increase and free testosterone levels decrease by the use of contraceptives and HRT [114,115]. ERT decreases serum DHEA-sulfate and testosterone by 23 and 42%, respectively [19]. Whereas the decline in testosterone is likely due to a decreased LH-driven ovarian steroidogenesis, the declining levels of DHEAS also imply an adrenal effect of estrogens [19]. Thus, ERT may induce relative androgen deficiency, creating a rationale for concurrent physiologic androgen replacement. Also HRT in postmenopausal women with estrogen and progestins causes a decrease in testosterone and consequently a reduction in libido and well-being [117]. Therefore in the USA a combination of an estrogen plus testosterone formulation was introduced, targeted to increase well-being and libido.

16.2. Corticosteroids

Treatment with glucocorticoid drugs (asthma and auto-immune diseases) is a valuable therapy, but the use of these drugs is associated with major side effects, including osteoporosis, muscle wasting, and obesity [118]. In men who take glucocorticoids, circulating testosterone concentrations are reduced, and this might contribute to the changes in bone and soft-tissue mass [118]. Testosterone treatment reverses the deleterious effects of glucocorticoids on skeletal and soft tissues in men [119] and increases BMD in hypogonadal men regardless of age [119,120]. The greatest increase is seen during the 1st year of treatment in previously untreated patients with low initial BMD.

16.3. Antiandrogenic progestins

In contraceptives, antiandrogenic progestins are utilized for acne prevention and protection of the breast [115]. The most widely used antiandrogens in clinical practice are the progestins chlormadinone acetate, cyproterone acetate and dienogest [122]. The mechanisms of these potentially beneficial therapeutic effects are

1. increase of SHBG by stimulation of the synthesis and consequently a reduction of free testosterone [19],
2. competitive inhibition of 5 α -reductase, the enzyme that converts testosterone to DHT in the skin [115,122],
3. decreased production of ovarian androgens (androstenedione and testosterone) [118], and
4. decreased production of DHEA-S [115].

Varying effects on SHBG have been observed with oral contraceptives and in HRT containing different progestins. Cyproterone acetate is the strongest antiandrogenic progestins, dienogest, reaches about 40% and chlormadinone acetate about 30% of the antiandrogenic potential of cyproterone acetate. Antiandrogenic progestins are believed to improve the lipid profile and to prevent atherosclerosis and to improve mood in hyper-androgenic women [123].

17. Testosterone delivery for treatment of deficiency

17.1. Oral delivery

Natural testosterone is readily metabolized in a first pass effect in the liver and therefore testosterone-17 β esters have been synthesized and solubilized in oil for oral delivery in men. Maximal plasma peaks are attained at 2–6 h after application, so that 2–4 capsules per day must be applied in men and 1–2 in women [27]. Disadvantages of oral delivery systems are: (1) fluctuation of plasma levels during the day, (2) high frequency of drug intake, and (3) poor predictability of individual plasma profile.

The only orally active testosterone preparation currently available in the USA is a fixed combina-

tion of methyltestosterone and esterified estradiol [30], but for most women the amount of androgen is rather high [30]. Although the main use of this preparation is sexual dysfunction, the label indicates relief of postmenopausal hot flashes. Also this formulation should cause high interindividual variability.

17.2. Transdermal delivery

Limited data are available on the kinetic and dynamic performance and the side effects of transdermal testosterone matrix patches in women [114]. Generally transdermal delivery faces major problems caused by individual skin type, for estradiol women with high hormone and with low hormone passage have been found. The interindividual variability in achievable plasma values is quite substantial; the intra-individual variability however is relatively small.

It is technically feasible to develop patches for transdermal testosterone delivery in women, since the doses needed are 1/20 of the doses required in men [54,114]. The advantage of transdermal drug delivery is that the patient can remove the patch and that individual dosing can be achieved by varying the contact area. Since the exact dose and indication in women has not been defined yet, it is not clear for how many days these patches can be designed.

In France a gel is on the market, containing 5 α -DHT [27] in alcohol, but unfortunately 5 α -DHT is not metabolized to testosterone and therefore not all effects of testosterone are seen, such as improvement of libido. On the other hand, 5 α -DHT may be more relevant for weight reduction than testosterone, because testosterone can be converted to estradiol [121]. Sometimes this gel is also used for therapy of Lichen, a local skin disease, affecting men and women [27]. The relation of dose to blood level has not been standardized, and some women get full male-range blood levels when using these preparations.

17.3. Subcutaneous and intramuscular drug delivery

Testosterone intramuscularly has a short half life and to increase this testosterone has been

esterified. The most frequently used injectable testosterone delivery system for men in Europe is testosterone enanthate solubilized in ricine oil or peanut butter oil [27]. Repeated application results in a “saw-tooth” like testosterone profile, inducing substantial disturbances in the patients because of this profile [27].

Implanted pellets have also been employed [27]. Doses used in some studies have been in the range used for male replacement, which is obviously inappropriate for women. These implants are the oldest delivery systems for testosterone [53]; they consist of pure testosterone pressed to a cylinder of 12 mm and a diameter of 4.5 mm. The implants are inserted by an incision in the abdominal range. If the implants are applied, slightly declining testosterone levels over a period of 4–6 months will be achieved. Limiting factors for use are the surgery, danger of infection, scars, and bleeding; they are on the market in Australia and in Great Britain.

18. Discussion

Steroid hormones seem to play an important role in mood functioning and behavior. The fact

Table 3
Four-level hormone classification scheme

	Low testosterone	High testosterone
Low estradiol	(e.g. Endometriosis patients under GnRH-treatment) Depression Fatigue Obesity Osteoporosis Decreased libido	Bulimic risk Depression Aggression and substance abuse Smoking Increased libido Cardiovascular risk
High estradiol	Gynoid obesity Decreased libido Breast cancer risk	Breast cancer risk Type II diabetes risk? Android obesity Cardiovascular risk PCO risk

that women are affected at twice the rate of men with depression, suggests that hormones may be involved in protection as well as in etiology. The increase with age suggests a lesser production of beneficial hormones with age [1,2]. Estrogens have mild antidepressive actions, however their effects on well-being are limited [136]. Oral application of estrogen bears the risk of reducing testosterone plasma levels, since SHBG increases [122] and the reduction in free testosterone might benefit some women and cause negative effects in others.

Testosterone seems to have an impact on women's health, well-being and sexuality but supraphysiological levels have traditionally been related to diabetes, PCO and breast cancer risk (Table 3). Social science suggests that supraphysiological testosterone levels in women are associated with antisocial behavior, drug abuse, and depression. Only recently it was reported that high testosterone levels can be found in women suffering from postpartum “baby blues”, arguing against estradiol or progesterone involvement [136]. Higher testosterone levels in women are more likely to occur in young women, where depression, substance abuse as well as acne can be related to testosterone. Low estrogen levels with high testosterone levels in bulimic women can be related to their aggression and depression, supporting detrimental effects of a testosterone imbalance. It was hypothesized in this outline that there is an optimum for testosterone plasma concentrations in women; minimal side effects occur in the range of 10–20 nmol/l free testosterone (Fig. 8). The hypothesis suggests a parabolic association between testosterone and depression, similar to findings recently reported in males (Fig. 7) [91]. The suggested model of testosterone and depression rates in women needs confirmation by clinical investigation.

The finding that low as well as high testosterone levels can be related to depression in women is of importance for diagnosis and treatment. Low androgen levels in women might cause low self esteem, low well-being and depression; high androgen levels cause conflicting behavior and depression. Figs. 7 and 8 suggest that cut-off

lines exist, but Fig. 2a and b illustrate substantial inter-individual variability and thus the use of absolute testosterone levels as a demarcation line for hyper or hypo-androgenic state seems to be difficult. The hypothesis, that a parabolic relation between plasma testosterone and well-being exists, suggests that individual dosing has to be established for optimal treatment. TRT for hypo-androgenic women as well as antiandrogenic treatment for hyperandrogenic women should be considered. In both options, the delivery systems for TRT should avoid plasma peak values. A decision should be made on the clinical pictures: the “four-level-hormone classification scheme” might be useful, since an experienced clinician can identify hyper- or hypo-androgenic states (Table 3) on an individual base. Osteoporosis might be related to low estradiol and testosterone levels, whereas hypermineralisation of bones is frequently related to breast cancer, because it might be related to high estrogen [125].

Progestins with antiandrogenic compounds are currently evaluated and favored by some clinicians [122]. They are useful as a means to reduce testosterone in patients with hyperandrogenism, in mood disturbances with aggressive behavior, prevention of arteriosclerosis, hirsutism, acne, hair loss, etc. Controlled clinical trials with progestins during HRT for women with mood disturbances and high testosterone levels are missing.

Testosterone deficiency in women cannot be related to a single symptom, but might lead to a cascade of symptoms, like mood disturbances, sexual disinterest and osteoporosis as a long-term consequence (Table 3). The case reported by Ehrenreich et al. [21], although conducted in a male, is valuable as it showed the interrelationship between mood, body composition and bone density (Fig. 5). Any women diagnosed for osteoporosis should therefore be questioned for symptoms of depression as this is mostly seen in women with low estradiol and testosterone plasma values (Table 3).

Although the majority of patients with depression respond well to treatment, as many as 30–45% fail to achieve an adequate response [70,85,92]. In addition to the more traditional

lithium and thyroid hormone augmentation strategies, a number of new approaches are being used to manage refractory depression: addition or a switch to another antidepressant. In particular, several studies have suggested that depressed patients refractory to selective serotonin reuptake inhibitors (SSRIs) may show a good response to agents with a pharmacological profile distinct from the SSRIs [85]. Several studies have shown that testosterone in men might be a potentially interesting agent for augmentation therapy in depression [79]; testosterone and/or estrogens might play a role in the fight against mood disorders, dysthymia and/or depression [80]. These observations, although sometimes based on single case reports or limited studies, provide strong evidence that testosterone may exert powerful antidepressant action in the absence of concomitant antidepressant agents. Many women with depressed testosterone levels might benefit from a replacement therapy with testosterone similar to men.

Whether TRT is successful in improvement of reduced sex drive in women with reduced testosterone values is under discussion. The recent study of Shiffren et al. [54] suggests that in some women sex drive can be restored, however the improvement in sex drive was moderate and the achieved plasma levels were supraphysiological, where side effects can be expected [126].

An important aspect in older women is that low estradiol as well as low androgen levels may lead to dyspareunia. Traditionally it is believed that dyspareunia can be treated with estradiol, since thickness of vagina mucosa might be improved. However it is frequently overlooked that dyspareunia and aging of sexual organs as well as incontinence are not only related to estrogen deficit in women: incontinence might be related to degradation of muscle. Since the clitoris is a muscle and androgens build muscle tissue, dyspareunia by androgen deficit might cause a degradation of the clitoris. Androgens are therefore applied directly on the clitoris.

Obesity is a very important risk factor in the western world and in particular abdominal obesity should be listed as a disease [58]. This form of obesity, frequently seen in postmenopausal

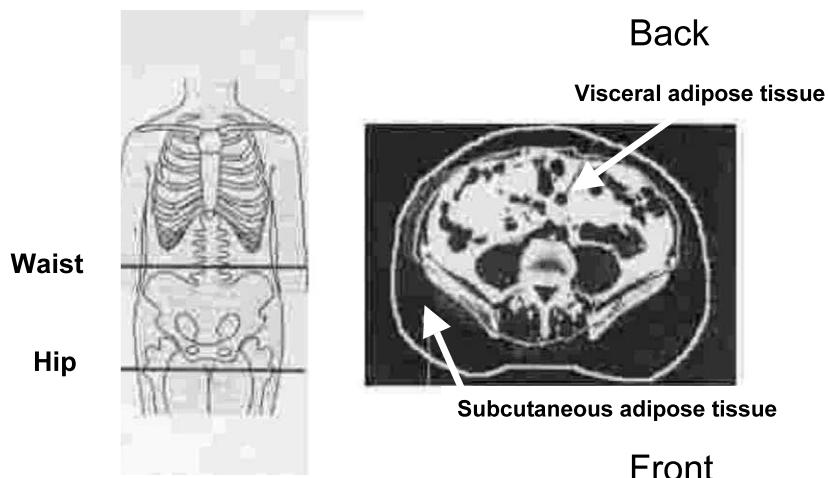


Fig. 9. Assessment of accumulation of abdominal fat by measurement of waist at mid-distance between bottom of rib cage and iliac crest. Amount of visceral adipose tissue that can be assessed by computer tomography and can be estimated by waist measurement.

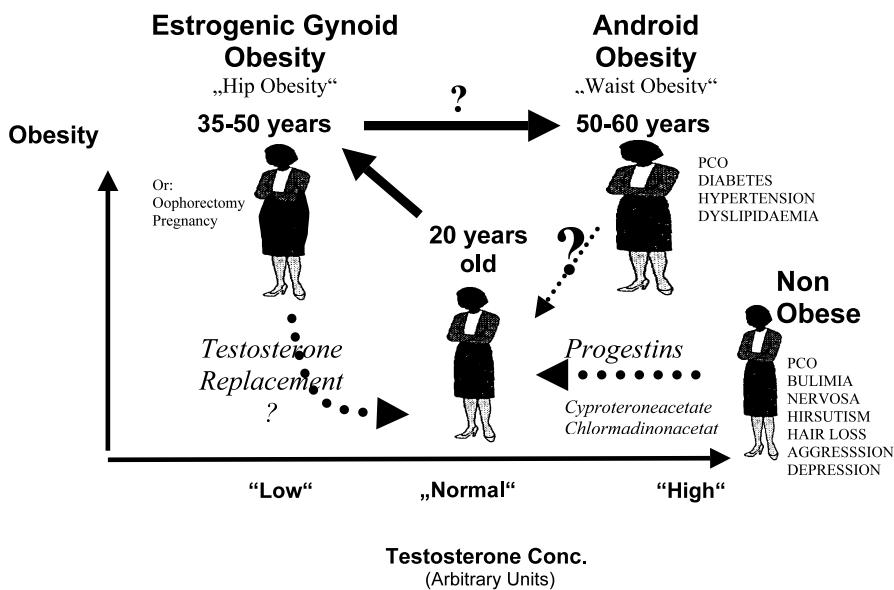


Fig. 10. Schematic of testosterone involvement in obesity in women. Management of the disease may be done by prevention with testosterone or treatment of obesity, the complications (hypertension, dyslipidaemia, diabetes) or the disease itself. Modified from Ref. [59].

women and in males, is related to cardiovascular risk, dyslipidaemia, and type 2 diabetes; it is not a cosmetic problem [59]. Testosterone suppresses not only appetite, especially the need for eating sugar, but also increases lipolysis [56]. Testosterone was successfully applied for reduction of

abdominal obesity: Fig. 10 depicts prevention possibilities of gynoid obesity. Whether testosterone reduction might reduce the risk of developing abdominal obesity and as a consequence might reduce type-2-diabetes and dyslipidaemia has to be investigated (Fig. 11).

Testosterone treatment in women should be developed as a serious means to prevent diseases, rather than treat obesity, because it might raise awareness to women that obesity is treatable.

The Canadian Task Force on Preventive Health Care recommended highest priority for research to develop methods for prevention of obesity. Weight loss in postmenopausal women should not be seen only for improvement of physical appearance but also for general health and well-being [127]. The risks of high testosterone values make it necessary that medication should be applied and supervised by trained physicians.

As only 7% of women are able to maintain a reduced body weight once they have achieved it, the ideal drug to lead to a reduced body weight should (1) reduce appetite, (2) reduce fat by metabolic changes, and (3) maintain an achieved success over a longer period of time. Physical exercise, and lifestyle adapted eating habits should be first on each prevention strategy. Long-term replacement with low doses of testosterone might help to maintain body mass and might help to prevent obesity.

For a long time a high testosterone level was believed to be a negative factor for cardiovascular problems in males [107]. Latest findings [109] seem to support evidence that normal testosterone plasma levels protect against coronary heart dis-

ease, if kept in the normal range. In females the doses for testosterone replacement will be substantially smaller, therefore the cardiovascular risk should be substantially smaller as well [109]. Higher testosterone and estradiol levels than normal have been associated with type II-diabetes in women but not in men [128]. It has been speculated that testosterone administration might lead to an increase in breast cancer risk and therefore the investigation in an animal model [112] is interesting in that breast cancer risk is reduced by additional testosterone. Furthermore, concern has been expressed related to risks of endometrial hyperplasia when menopausal androgen replacement therapy is used in conjunction with estrogens. Fortunately, concomitant progestin administration is protective.

All these new findings make testosterone replacement in women an interesting area. However, in contrast to estradiol delivery, testosterone requires less fluctuating delivery systems. Stable plasma profiles over extended periods of time are difficult to achieve with conventional dosing forms. Individual dosing seems to be necessary and this can be achieved with matrix patches and with gels by adjusting the skin surface area of application. Injectables with improved delivery technique and pharmacokinetic profiles are necessary as well.

Management of Coronary Heart Disease

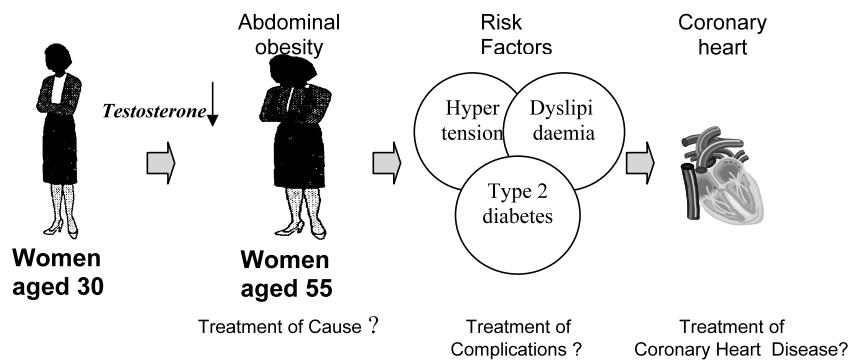


Fig. 11. Contribution of abdominal obesity to coronary heart disease. Management of the disease may be done by prevention of obesity or treatment of obesity, the complications (hypertension, dyslipidaemia, diabetes) or the disease itself. Modified from Ref. [59].

Whether circadian testosterone plasma profiles can be achieved and are important for therapy has to be explored. Delivery systems specifically developed for female needs of testosterone do not exist. An ideal testosterone delivery system for women should follow the parental route of application (transdermal, injectable), give stable plateau-like plasma levels over an extended period of time, and individual dosing should be achievable (by injection volume, patch size).

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