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The role of androgen therapy

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The concept of a female androgen insufficiency syndrome, although not new, remains somewhat controversial. Androgens are quantitatively the predominant sex steroid in women, circulating in the micromolar and nanomolar concentration range, compared with picomolar levels of oestrogens. The most significant biologically active androgen is testosterone (T), which circulates bound tightly to sex-hormone-binding globulin (SHBG) and loosely to albumin. It is generally held that the non-SHBG-bound fraction is the bioavailable moiety. Hence, clinically useful T measurements require data on total concentrations as well as SHBG level. Testosterone insufficiency occurs in a number of circumstances, including hypopituitarism, premature ovarian failure, adrenal failure, exogenous corticosteroid use and oral oestrogen therapy (causing elevation of SHBG and suppression of gonadotrophins). Clinical symptoms of androgen insufficiency include loss of libido, diminished well-being, fatigue and blunted motivation and have been reported to respond well to T replacement, generally without significant side-effects.

Key words: testosterone; dehydroepiandrosterone sulphate; sex hormone binding globulin; free testosterone; hypopituitarism; premature ovarian failure; libido; well-being.

CHARACTERISTICS OF ANDROGENS

The term 'androgens' refers to a group of 19-carbon steroid hormones which are associated with maleness and the induction of male secondary sexual characteristics. They are the most abundant circulating sex steroids in both men and women. In women, androgens circulate in the concentration range nanomolar to micromolar, in contrast with the oestrogens, whose circulating concentrations are in the picomolar range. Androgens are obligatory precursors in the biosynthesis of oestrogens. Thus, oestrone

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is formed by the aromatization of androstenedione (A) and oestradiol by the aromatization of testosterone (T).

A consideration of the role of androgen therapy in the context of a text on 'Menopausal Medicine' implies the existence of an androgen insufficiency state, potentially remediable by the administration of androgens. We will address the overall concept of female androgen insufficiency, without a particular focus on the peri- or post-menopausal periods, as androgen insufficiency is not a consequence of natural menopause. We have reviewed the sources and circulating levels of androgens during reproductive life, the clinical features of androgen insufficiency, its biochemical diagnosis and the indications for androgen therapy and potential issues involved. The present authors have published several recent reviews discussing aspects of this topic.[1–3]

ANDROGENS—THEIR SOURCES, CIRCULATING LEVELS AND PHYSIOLOGY

In descending order of their serum concentrations, the major androgens found in women include dehydroepiandrosterone sulphate (DHEAS), DHEA, A, T and dihydrotestosterone (DHT). Giving T a reference potency of 100, the relative androgenic activities of the other members of the class are DHT 300, A 10 and DHEA and DHEAS 5.[4] Data on androgen biosynthesis, circulating levels and physiology have been reviewed recently.[5]

Biosynthesis of the androgens takes place in both the adrenal gland and the ovary and is modulated by two cytochrome P_{450} enzymes, P_{450} Scc, which catalyses cholesterol side-chain cleavage, and P450 C_{17}, which catalyses 17-hydroxylation and 17–20 bond cleavage (17/20 lyase), which is required for the production of DHEA and A from pregnenolone and progesterone, respectively. The further metabolism of androgens involves other important enzymes, including 3β-hydroxy steroid dehydrogenase (3β-HSD), catalysing the conversion of pregnenolone to progesterone and DHEA to A, and 17β-hydroxy steroid hydrogenase (17β-HSD), which catalyses the conversion of A to T. While adrenal androgen secretion is stimulated by ACTH and ovarian androgen secretion by LH. The existence of a physiological negative feedback system which regulates androgen homeostasis has not been demonstrated in the female.

Dehydroepiandrosterone sulphate

DHEAS is a unique secretory product of the adrenal zona reticularis, with a production rate of 3.5–20 mg daily during reproductive life and circulating concentrations in the range of 3–12 μmol/l. Its serum concentrations increase from about age 7 to 8 (the adrenarche), reach a peak in the third and fourth decades and then decline steadily with age.[6] There are no significant changes during the menstrual cycle, nor is there any significant change in concentration specifically related to the menopausal transition or the menopause.[7] Clinical insufficiency of DHEAS is seen in Addison's disease, following bilateral adrenalectomy, hypopituitarism with adrenal involvement[8], glucocorticosteroid therapy, chronic illness and oral oestrogen replacement. Whether the decline in DHEAS with age qualifies as an insufficiency state that merits treatment is extremely controversial. Both DHEAS and DHEA are important precursors for peripheral biosynthesis of both T and oestrogen.

Dehydroepiandrosterone

DHEA is produced by the adrenal (50%) and the ovarian stroma and theca interna (20%), with 30% being derived from circulating DHEAS under the action of steroid sulphatase. Daily production rates are 6–8 mg/day and circulating concentrations are in the range 3–35 nmol/l. The decline in DHEA with age parallels that of DHEAS.

Androstenedione

Androstenedione (A) is produced approximately equally by the adrenal zona fasciculata and the ovarian stroma and theca interna. Daily production rates are in the range 1.4–6.2 mg and circulating concentrations are in the range 2–8 nmol/l. Oophorectomy in post-menopausal women results in an approximately 30% fall in circulating levels. Androstenedione shows diurnal variation and a midcycle elevation in concentrations parallel with the midcycle peak of oestradiol. Its circulating concentrations are reduced substantially in hypopituitarism[8], and exogenous glucocorticosteroid administration also suppresses its levels.

Testosterone

The major biologically active circulating androgen in both males and females is T. Testosterone is secreted by the adrenal zona fasciculata (25%), the ovarian stroma and theca interna (25%), with the remaining 50% being produced from peripheral conversion of circulating A. Total female daily production rates are in the order 100–400 μg and circulating levels are in the range 0.6–2.8 nmol/l (although this may vary significantly between different assays). Levels of T fluctuate during the normal menstrual cycle, with the lowest concentrations being found in the early follicular phase. There is a midcycle peak approximately parallel to the midcycle oestradiol peak, and luteal phase concentrations are higher than those in the early follicular phase. This steroid also shows diurnal variation, peaking in the early morning. Oophorectomy either before menopause results in an approximately 50% fall in circulating levels. The effect of oophorectomy in older women is less dramatic. DHEAS is an important precursor of intracellular T production, so that T levels are suppressed by the systemic administration of oral glucocorticosteroids. Concentrations of T in the ovarian vein of post-menopausal women have been shown to be higher than those in systemic venous blood, suggesting that the post-menopausal ovary continues to be an androgen-secreting organ. However, in a recent series of experiments assessing the steroidogenic potential of the post-menopausal ovary Couzinet and others have demonstrated that this tissue is not a significant source of post-menopausal androgens.[9] This apparent paradox remains unresolved. T circulates in peripheral blood with approximately 66% bound to sex steroid-hormone-binding globulin (SHBG) and about 33% loosely bound to albumin. Only 1–2% of total circulating T is in the free form. Bioavailable T is a term used for that part of total T not bound to SHBG and includes the albumin-bound moiety. However, the clinical relevance of measurement of bioavailable T is not clear. The levels of both total and free T are markedly reduced in hypopituitarism.[8] The levels of T do not change significantly in relation to the menopausal transition.[7] When circulating concentrations are assessed as a function of age, there is an approximately 50% fall in both total and free T between the ages of 20 and 40 to 45, with only a very slight fall in circulating concentrations thereafter.[10] It should be noted that this description of circulating T concentrations should be interpreted in the knowledge that

most available T assays show poor reliability at the lower end of the circulating female concentration range. Across the menopausal transition, without exogenous oestrogen therapy, circulating SHBG levels fall and as a result free androgen levels rise.[7] Of great importance is the fact that oral oestrogen therapy substantially increases circulating SHBG levels as well as suppressing pituitary LH, with a consequent fall in free T concentrations, a phenomenon not observed with physiological doses of parenteral oestrogen.[11,12]

The potential significance of androgen therapy in relation to menopausal medicine should not be limited to women whose ovaries have been removed but should include naturally menopausal women and younger women who have been treated with systemic chemotherapy, radiotherapy, or those who have experienced premature ovarian failure.

Dihydrotestosterone

DHT is a product of peripheral conversion from T catalysed by 5α-reductase. This occurs primarily in androgen-sensitive tissues such as the skin. A small quantity is directly secreted by the adrenal zona fasciculata and daily production rates are between 4 and 12 mg, derived almost entirely by peripheral conversion. Measurement of circulating DHT is not a reliable indicator of total DHT production, as, once synthesized, DHT is further metabolized intracellularly to 3α-androstenediol glucuronide and 3β-androstenediol glucuronide which appear in the circulation.

Δ5-Androstenediol

For the sake of completion, mention should also be made of androstenediol, a moderately androgenic steroid which is intermediate in the conversion of DHEA to T. Its circulating concentrations reflect DHEA and DHEAS metabolism.

ANDROGEN ACTIONS

Androgens may act directly according to classic concepts of steroid hormone action, binding to a specific androgen receptor and initiating a series of biological responses in the target tissue. Androgens may also act after conversion to oestrogens in peripheral tissues and then via the oestrogen receptors. Androgen receptors and oestrogen receptors are widely distributed and are found in the central nervous system, bone, breast, skeletal muscle, the heart and blood vessels, adipose and genital tissues and the pilosebaceous unit.

The consequences of androgen excess in women are well recognized, with high levels inducing features of virilization and mildly raised levels capable of causing hirsutism, acne, and androgenic alopecia.

Physiological roles for androgens in women have been more difficult to define and the current evidence relates mainly to their effects on libido, bone mineral density and lean body mass [13] Bilaterally oophorectomized women are clearly at risk of androgen insufficiency. When treated with T they have been found to have an improved sense of well-being, higher energy, improved sexual arousal and increased sexual fantasy levels, in comparison with women receiving oestrogen or placebo.[14–16] Mood and sexual functioning were restored to levels similar to those in intact pre-menopausal controls. Doses used in these studies may be considered pharmacological.

Burger et al[17] treated 17 patients with combined subcutaneous implants of oestradiol (40 mg) and T (100 mg) because oral oestrogen (conjugated equine oestrogen 1.25 mg daily or oestradiol valerate 4 mg daily) had not adequately relieved decreased libido in

particular. Significant improvements were noted in libido, enjoyment of sex and tiredness ($P < 0.01$) without significant changes in flushes, sweats and depression. Libido increased from a mean basal level of 13.5 to a maximum of 86.1 (on an analogue scale, maximum 100) at 3 months and increased in all evaluable subjects. Symptomatic improvement was maintained for 4–6 months. No significant changes were seen in total serum cholesterol, triglyceride or cholesterol subfractions. Total T plasma concentration rose from 2.3 (measured at the point of discontinuing oral oestrogen) to 6.7 nmol/l at 1 month, and had returned to baseline at 5 months. Again, this dose of T can be considered pharmacological.

The same authors[18] undertook a single blind controlled study of androgen administration in 20 post-menopausal women complaining of loss of libido and unresponsiveness to adequate oestrogen replacement. The women were treated with implants of either oestradiol alone (40 mg) or oestradiol in combination with T (50 mg) at concentrations raising the total T level to just above the upper limit of normal (3.5–3.7 nmol/l). Women receiving oestradiol implants alone showed no improvement in sexual function after 6 weeks, and were treated with T also. Those receiving combined implants showed a marked improvement in the various sexual measures recorded, similar to that observed in the earlier study. That group of women who initially received oestradiol alone showed marked improvement in sexual functioning when subsequently treated with combined implants. The dose of T used here could be considered to be in the high physiological or low pharmacological range. Again, no significant changes were seen in serum lipids. Davis et al[13] conducted a randomized trial of 34 post-menopausal women over a 2-year period. Women received either oestradiol implants 50 mg alone or oestradiol 50 mg with T 50 mg. The combined treatment increased serum T concentrations to high in the normal range and improved all parameters of sexual function measured using the Sabbatsberg Sexual Self-rating Scale as compared with oestradiol alone.

More recently Shifren and colleagues[19] studied 75 hysterectomized and oophorectomized women, all of them receiving conjugated equine oestrogens in a dose of at least 0.625 mg daily. They were randomized to treatment with transdermal patches of T delivering either 150 or 300 μg daily or placebo. The higher dose of T which produced circulating free T concentrations close to the upper end of the normal female range produced some improvement as compared with placebo in the frequency of sexual activity, masturbation, sexual fantasies, pleasure-orgasm, as well as improved well-being, which showed the largest effect. The treatment duration of the study was 12 weeks.

Results of DHEA administration in comparison with placebo have been reported in 24 women with primary or secondary adrenal insufficiency.[20] Serum T was increased from below normal to the lower part of the normal range by the therapy and there was improvement in several parameters of sexual function compared with placebo.

Evidence is available for the role of androgens in maintaining bone turnover and bone mineral density in women. Raisz et al[21] randomized 28 post-menopausal women to treatment with conjugated equine oestrogens alone, or combined with 2.5 mg oral methyltestosterone daily for 9 weeks. Only the group treated with androgen showed an increase in bone formation markers, whereas both groups showed decreases in markers of bone resorption. Watts et al[22] studied 65 oophorectomized women, again randomized to treatment with esterified oestrogens only, or combined with the same dose of oral androgen for 2 years. Data on bone density were available on 48 of the 65 women—the figures were not significantly different after 2 years of treatment. In the study of Davis et al[13] 34 post-menopausal women received either oestradiol alone or oestradiol plus T by implant for 2 years, the androgen-treated group showing significantly greater increases in bone density in both the spine and the hip, as compared with those treated with oestradiol alone.

Thus there is evidence of potentially physiological effects of androgens on overall well-being, mood, sexual function and bony health in women.

CLINICAL FEATURES OF ANDROGEN INSUFFICIENCY

The proposed clinical features of female androgen insufficiency have been based largely on the results of studies in which usually pharmacological, but more recently physiological androgen replacement has been undertaken and observations made on the responsiveness of a number of clinical features. A recent consensus conference[23] agreed that symptoms of androgen insufficiency which had been most commonly reported in the literature include a diminished sense of well-being, dysphoric mood and/or blunted motivation, together with persistent unexplained fatigue and changes in sexual function, including decreased libido, sexual receptivity and pleasure. Other possible features include bone loss, decreased muscle strength and changes in cognition or memory. There are, however, to date no clinical data to support the latter. It is clear that all these symptoms are non-specific and are therefore insufficient in themselves to diagnose androgen insufficiency. Many of the features can be symptomatic of other common disorders such as depression and are subject to marked variability, particularly as a result of varying socio-economic and environmental circumstances. Further, it is well known that the effects of oestrogens are strongly linked to well-being, mood and sexual functioning and thus a diagnosis of androgen insufficiency should be made only in women who are adequately oestrogenized i.e. normally cycling pre-menopausal women or post-menopausal women receiving oestrogen replacement. To verify the diagnosis, the free T concentration should be at or below the lowest 25th percentile of the normal range for 20–40-year-old women of reproductive age, a clinically useful but somewhat arbitrary criterion. The consensus conference[23] emphasized the urgent need for further research to determine the normal ranges of androgens in women, particularly at different phases of the reproductive life cycle.

The responsiveness to T administration of some of the symptoms mentioned has been described above. Another level of evidence which should be able to support the diagnosis of androgen insufficiency is that from observational studies of women presenting with the proposed symptom complex. A major limitation in the interpretation of such studies has been the unreliability of most T assays in the concentration range required for this purpose. A number of observational studies have been reported, but have often been on very small sample sizes, thus limiting their generalizability. Where sexual function has been assessed, validated rating scales have often not been used and the statistical methods have often been questionable. With these reservations it is important to note that most small observational studies agree that there is a correlation between free T or total T and certain aspects of female sexual functioning, including sexual frequency and libido. For example, Kaplan and Owett[24] noted markedly reduced sexual desire or fantasy, orgasm and the presence of global sexual symptoms in a group of 11 women with low androgen levels following chemotherapy or bilateral oophorectomy, in comparison with 11 who were similarly hypo-oestrogenic, but had normal androgen levels. A number of studies have not found any association between androgen levels and sexual functioning.[25–27]

A major longitudinal study of sexual functioning in relationship to the menopausal transition is the Melbourne Women's Midlife Health Project.[28] This prospective observational study involved 438 Australian-born women aged 45–55 and still menstruating at baseline of whom 197 have been studied for effects of the natural menopausal transition on sexuality.[29] The early menopausal transition was defined as the period of onset of menstrual cycle irregularity and the late menopausal transition as

a state in which menstrual cycles were still occurring, but the cycle prior to observation was at least 3 months earlier. In passing from the early to the late menopausal transition, the percentage of women with sexual dysfunction, assessed using the short personal experiences questionnaire (SPEQ) rose from 42 to 88%, whereas there were no significant changes in mood scores. Those who showed low SPEQ total scores in the early transition had lower oestradiol levels, but similar androgen levels to those with higher scores, and decreasing scores correlated to decreasing oestradiol, but not to T. Hormone levels did not correlate with mood scores. It was concluded from that study that 'the dramatic decline in female sexual functioning with the natural menopausal transition, relates to decreasing oestradiol rather than androgens'. A limitation of this study is that total T was measured with an assay that had poor sensitivity at the lower end of the female range. Thus, in terms of correlations between actual low T and sexual function, this study is inconclusive.

Androgen insufficiency has been demonstrated to occur in women with hypopituitarism[8] and is also seen in primary adrenal insufficiency, ovarian failure and following oophorectomy in pre-menopausal women. Androgen insufficiency is not a specific consequence of the menopause, but may result from a continued decline of circulating androgen as occurs during late reproductive life. Androgen insufficiency may occur at any age during reproductive life, or after the menopause. Whether androgen insufficiency can be a consequence of depression, or alternatively a cause of that disorder, remains controversial and requires further study.

THE BIOCHEMICAL DIAGNOSIS OF ANDROGEN INSUFFICIENCY

The major circulating androgen in women is T, of which the important biologically active fraction appears to be the free fraction. The biological activity of the albumin-bound fraction is not known. The diagnosis of androgen insufficiency therefore requires measurement of free T as the gold standard with SHBG to guide clinical management, or total T plus SHBG, allowing the calculation of a free T index (T nmol/l ÷ SHBG nmol/l × 100). The free T index is a clinical approximation and has been shown in one study to correlate well with free T measured using equilibrium dialysis.[8] A major difficulty in this field has been the lack of routinely available sensitive assays for both total T and free T. It is likely that the normal female range for total T concentration is in the vicinity of 0.5–2.8 nmol/l. However, the coefficients of variation of most commercial assays are above 10% at T concentrations of 1.5–2 nmol/l and rise to 20% or more at 1 nmol/l. Below that concentration standard curves in most T assays have shallow slopes and T concentrations cannot be reliably measured in the concentration range of interest. The consensus conference referred to previously[23] emphasized the need for accurate and reliable androgen measurements. This conference recommended that clinical assessment of androgen status should include either free T and SHBG (as the gold standard), total T and SHBG, or free T and total T. This is because SHBG can be independently influenced, particularly by orally administered oestrogen (or by thyroxine), so that women on oestrogen replacement may have markedly elevated SHBG levels, which, in turn, may give rise to apparently normal T levels. Correction to calculate free T index will approximate the true androgenic status.

The place of DHEAS assay is less certain for clinical diagnosis. While assays for this steroid are robust and not subject to diurnal variation, the relationship to the most common causes of clinical androgen insufficiency syndrome is less clear-cut, although in adrenal insufficiency this measure is a useful one.

INDICATIONS FOR ANDROGEN THERAPY

Testosterone therapy is indicated for women who present the classical clinical symptoms, with the diagnosis being substantiated by a free T concentration arbitrarily in the lowest quartile of the relevant female reference range.

A common clinical scenario is the presentation of a woman in her late 30s or early 40s with progressive loss of libido and sexual enjoyment, associated with non-specific tiredness, drive, motivation and a lack of sense of well-being. If such a patient is otherwise cycling normally, is not clinically depressed and has no other explanation for her symptoms (including the lack of partner problems), the diagnosis must be confirmed by finding a low free T concentration and a cautious trial of T therapy could be justifiably initiated.

More clear-cut circumstances of androgen insufficiency include hypopituitarism, primary and secondary adrenal insufficiency, ovarian failure (due to natural menopause, premature menopause, Turner's syndrome, radiation, chemotherapy or surgical removal), and exogenous oral glucocorticosteroid therapy, leading to ACTH and some gonadotrophin suppression. Oral oestrogen therapy can also induce androgen insufficiency—which may be seen in women being treated with the oral contraceptive pill, or with menopausal hormone therapy. Other conditions that have been associated with androgen insufficiency include anorexia nervosa and certain immunological disorders such as rheumatoid arthritis, systemic lupus erythematosus and human immunodeficiency virus infection. An adrenal cause of androgen insufficiency is likely in the latter circumstances, although the pathophysiology of these conditions is uncertain.

Adrenal insufficiency represents a specific indication to consider DHEA replacement. A controlled trial has indicated clinical benefit from DHEA replacement in this situation.[20]

METHODS OF ANDROGEN ADMINISTRATION

A major deterrent to more widespread use of androgen therapy at the present time is a lack of preparations specifically suitable for use in women. The only generally available preparation in the USA is an oral preparation which contains a small dose of methyltestosterone. Oral androgen therapy is associated with a suppression of circulating HDL and is not ideal for long-term administration, although, as noted above, it can be clinically effective. Other than this preparation no formulation specifically designed for women is currently available, although some new therapeutic agents are in development. The situation has been recently reviewed.[30]

For women with clear-cut T insufficiency, i.e. symptomatic plus total T below the lower limit of detection by a reliable assay, or free T below the lower limit of normal with a normal SHBG, therapy can be initiated. Women with normal T, elevated SHBG and low free T on oral oestrogen therapy should be switched to non-oral oestrogen therapy for at least 12 weeks and then reviewed. The fall in SHBG may obviate the need for T therapy. In Australia therapy is commonly initiated with T pellets implanted subcutaneously under local anaesthetic. The authors use a dose of 50 mg, obtained by cutting into halves a 100 mg implant made specifically for males under sterile conditions. These implants remain effective for periods of 4–6 months. Repeat implantation should not be undertaken without confirmation that total T, corrected for SHBG, or free T has fallen back into the lower quartile of the normal female range. When the diagnosis is in doubt, a therapeutic trial of one to three

intramuscular injections of T-esters 50–100 mg each given 3–4 weeks apart can be considered. This may or may not result in a clinical response over 1–2 weeks or more. A positive response supports the initiation of longer-term therapy. As peak levels are very super-physiological, T esters should not be considered a long-term treatment option.

Testosterone undecanoate is an oral formulation available as 40 mg capsules for men which is absorbed via the intestinal lymphatics and thus avoids the first-pass effect in the liver. There are neither efficacy data nor safety data for this therapy in women. This method of administration causes short-lived and very variable serum concentrations[31] and the authors do not recommend this mode of therapy.

Testosterone transdermal patches have been used experimentally in studies referred to above and are currently in a large-scale clinical trial. Other therapeutic possibilities include T gels or creams. Certain pharmacists prepare T for buccal administration in the form of troches, but there are no published pharmacokinetic or safety data or efficacy studies to validate this method of administration.

Another agent which can be conceived as an androgen (in addition to having properties as an oestrogen and a progestin) is tibolone, which has been recently reviewed elsewhere.[31] In a dose of 2.5 mg daily, it improves libido and well-being. There are no studies of its use specifically for androgen insufficiency.

As far as the use of DHEA is concerned, the major difficulty for the prescriber is the lack of well standardized preparations for oral use. There are reports which indicate that the administration of DHEA 50 mg to women will produce physiological increases in circulating T and oestradiol, but such therapy does lead to some suppression of circulating HDL.

SIDE EFFECTS AND RISKS OF ANDROGEN THERAPY IN WOMEN

Contraindications to T therapy include pregnancy and lactation, androgen-dependent neoplasia, severe acne and/or hirsutism, androgenic alopecia and, of course, situations where increased libido is an undesirable consequence.

Providing that circulating androgen concentrations are kept within, or close to, the upper limit of the normal physiological range, masculinizing effects are extremely unlikely. Those for which careful monitoring should be undertaken include increasing hair growth, acne, temporal balding and/or deepening of the voice. Maintenance of pharmacological levels will lead to clitoral hypertrophy. Oral androgens lead to unfavourable changes in circulating lipid concentrations, but these do not appear to occur with parenteral T administration. In some women increases in sexual thoughts and fantasies may cause distress and in those circumstances doses should be substantially lowered or therapy stopped.

There is almost no evidence that parenteral T administration is likely to have adverse cardiovascular consequences, and in fact it has been suggested that it may be beneficial.[32,33] There is evidence also that endogenous androgen levels are inversely related to carotid artery wall thickness, a marker of atherosclerosis.[34] The relationship of T administration to breast cancer is not established, but evidence from a primate model suggests the possibility of a protective effect.[35]

Practice points

- female androgen insufficiency is characterized by diminished well-being, dysphoric mood, unexplained fatigue and decreased sexual interest
- confirmation of the diagnosis requires demonstration of a low morning free T concentration
- there is a lack of suitable therapeutic agents to treat female androgen insufficiency and compromises must be made with preparations primarily designed for use in the male

Research agenda

- the characteristics of female androgen-insufficiency syndrome require further validation
- improved methods of T measurement in the female concentration range are urgently needed
- generally available methods for determination of free or bioavailable T in the female range are needed
- development of preparations specifically designed for use in women is an urgent necessity
- long-term safety of exogenous T in women requires study

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