Significance of oestrogens in male (patho)physiology

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INTRODUCTION

Oestrogens in men, which are largely a product of peripheral aromatization of androgens, receive increasing attention. Traditionally conceptualized as ‘female hormones’, oestrogens appear to have unexpected but important effects on the male reproductive system; (for review see Couse and Korach) [17]. Oestrogen receptor knockout mice show abnormalities of the testis and accessory sex organs; (for review Luconi et al.) [55].

It is becoming increasingly clear that oestrogens have an important effect on the final phases of skeletal maturation and bone mineralization in puberty. In addition, some studies in aging men show that oestrogen levels have a higher correlation with bone mineral density (BMD) than androgen levels; (for review see Riggs et al.) [67]. Impaired oestrogen action in men leads to dyslipidaemia and to impaired flow-dependent vasodilatation in peripheral arteries in response to an ischaemic stimulus probably resulting from endothelial dysfunction [79]. Evidence suggests that the effects of oestrogen on the vascular system are not entirely receptor-mediated [44]. Oestrogen effects on the brain are also becoming increasingly recognized [60]. In view of the effects of oestrogen on many important organ systems in the (aging) male, further research into the role of oestrogens is necessary. A better understanding of oestrogen recep-
tor physiology and its two subtypes may allow for possibilities in terms of selective effects of oestrogens in men. This may also be significant for the potentially negative effect of oestrogens on prostate disease in old age. The relevance of oestrogens in bone, the cardiovascular system, the brain and prostate will be discussed further below.

Oestrogen physiology in men

In men, androgens (androstenedione, dehydroepiandrosterone produced by the adrenal, and testosterone (T) produced by the testis) serve as precursors for chemical conversion to oestrone and oestradiol via the enzyme aromatase. The testis itself produces approximately 10-15 µg from peripheral conversion of androsterone [56]. The blood transfer constant amount of oestrone is produced mainly by the adrenal [92]. Aromatase is the enzyme responsible for the conversion of androgens to estrogens.

The total quantity of E\textsubscript{2} which is formed in peripheral tissues may however be significantly higher since part of the peripherally formed E\textsubscript{2} is further metabolized in situ (to oestrone, oestriol or 2-hydroxy oestradiol) and hence does not enter the peripheral circulation.

The adipose tissue is the most important source of oestrogens in men, but muscles, the brain, mammary tissue, skin, the liver and bone are also capable of synthesizing oestrogens from precursors. Circulating E\textsubscript{2} levels in young men are about 70±15 pmol/L, which is equivalent to the levels in the early follicular phase in women.

Estrogens in men and aging

Several studies have indicated that while plasma T levels show an age-related decline, plasma oestrogen levels remain relatively constant with aging in men resulting in an increased oestrogen/androgen ratio [37, 91, 92]. Factors accounting for the relatively stable levels of plasma E\textsubscript{2} in old age are the very common relative increase in fat mass with aging and the increase in aromatase activity with aging. This corresponds to the clinical observation of the occurrence of gynecomastia in aging men. Vermeulen and coworkers [92] studied three age groups of men: young males (age 24-31 yr., n = 90), middle aged men (37-46 yr., n = 46) and elderly men (age 70-79 yr., n = 283). Regardless of age they found a highly significant correlation between total plasma T and total plasma E\textsubscript{2} (r = 0.56, P < 0.01) and free T and free E\textsubscript{2} (r = 0.53, P < 0.01). Since it is controversial whether there is an age-related decline of circulating E\textsubscript{2}, the effect of aging in relation to plasma E\textsubscript{2} levels was analyzed in to greater detail in the three age groups. Vermeulen and coworkers did not observe any significant decrease of total plasma E\textsubscript{2} levels with age, with mean (±S.D.) concentration being 84±22.4 pmol/l in young males (age 24-31 yr.), 81.5±23.1 pmol/l in middle aged men (37-46 yr. old) and 88.1±24.6 pmol/l in elderly men (age 70-79 yr.). As fat mass was significantly higher in elderly men, a potential age-associated decrease in plasma E\textsubscript{2} could be obscured by this age-associated increased fat mass providing a larger substrate for the aromatisation of androgens, but after correction for fat mass, the correlation coefficient was only – 0.0035! This implies that aging in itself has no strong impact on circulating E\textsubscript{2} levels.

SHBG not only binds dihydrotestosterone (DHT) and T but also E\textsubscript{2}. As a consequence of the age-associated increase in sex hormone binding globulin (SHBG) binding capacity, the mean bioavailable (non-SHBG-bound) E\textsubscript{2} levels were 46.5±15.7 pmol/l in the young, 40.3±11.1 pmol/l in the middle-aged and 37.5±10.8 pmol/l in the oldest group and this constitutes a small though statistically significant lower level of bioavailable E\textsubscript{2} in the oldest group compared to the youngest. The mean T and free T (FT) levels were 20.2±5.0 and 0.46±0.11 nmol/l, respectively, in the youngest group and 19.0±5.2 and 0.25±0.07 nmol/l in the elderly. The ratio FT/FE\textsubscript{2} was 323±82 in the youngest group and 197±55 in the elderly group, indicating that the FT/E\textsubscript{2} is relatively higher in old age than in young age, very likely explained by the fact that in old age a larger proportion of FT is aromatized to FE\textsubscript{2}. This is best explained by an age-associated increase in aromatase activity. So, the age-related decline in plasma total T and free T is not paralleled by a decline in plasma total and free E\textsubscript{2} (FE\textsubscript{2}), partly explained by the common increase in fat mass associated with aging, and partly due to an increase in aromatase activity with aging. Indeed, the ratio FT/FE\textsubscript{2} appeared highly significantly negatively correlated with body mass index (BMI) (r = – 0.51 p < 0.01), with percentual fat (r = –0.55) as well as with insulin levels (r = – 0.58).

What are the factors determining E\textsubscript{2} levels?

With T being the major precursor of E\textsubscript{2} in males, it is not surprising that a highly significant correlation between T and E\textsubscript{2} levels (r = 0.56) and between FT and FE\textsubscript{2} (r = 0.53)
was observed even though T and FT themselves were negatively correlated with BMI and fat mass [92]. To further define the role of fat distribution on hormone levels, body composition was determined in a subgroup of 57 elderly men (70-80 yrs). Abdominal fat appeared to be a more important determinant of (F) T levels than gluteal fat (abdominal fat: r = −0.56 and −0.37, respectively; gluteal fat r = −0.42 and 0.26, respectively). To further define the role of fat distribution on hormone levels, subcutaneous and visceral fat was determined by CT scan in a group of obese men 30-60 yrs old. Whereas (F) T levels were not significantly associated with either total, subcutaneous or visceral fat, E2 and free E2 were significantly associated with total fat mass (r = 0.55 p < 0.01) and subcutaneous abdominal fat (r = 0.71; p < 0.001) but not with visceral fat. This fits with the observation of Killinger et al. [42] that the aromatase activity in omental fat is only 1/10th of the activity in gluteal fat, corresponding to the finding in women that gluteal fat is the major site of aromatisation [20].

The men studied participated in a weight loss program and the effects of this reduction in weight on hormone levels was measured. After weight loss (mean loss 9.6±6.6 kg with a decrease of BMI from 34.1±2.65 to 30.3±2.47), total E2 and free E2 decreased significantly (total E2 from 81.3±18.4 pmol/L to 63.2±19.8 pmol/L and FE2 from 2.54±0.63 to 1.94±0.59pmol/L) notwithstanding an increase in total T levels (p < 0.01 by 10% from 12.8±3.6 to 13.9±3.5nmol/L), while the increase in FT levels was non significant, probably due to the rise of SHBG levels associated with weight loss.

The above data show the important role of fat mass in aromatisation of testosterone. Whereas total T and FT levels decreased significantly with age, total E2 levels did not change whereas the FE2 levels decreased marginally, partly due to the increase in fat mass and partly a consequence of the age associated increase in aromatase activity. The increase in fat mass concerned essentially gluteal fat, which appeared to be the more important determinant of the decrease in T levels.

Other studies, however, have found a decrease of bioavailable T and E2 with aging [27, 40, 74, 88]. Part of this discrepancy might be explained by the different measures of levels of total and free E2 used in these studies. E2 also binds to SHBG though less strongly than testosterone. SHBG levels increase generally with aging in men and this may explain why bioavailable and free E2 levels fall with aging as is also the case with free testosterone, of which the decline is more extensive than that of total testosterone.

**Intracrinology**

Since the majority of oestrogen production from the androgenic precursors occurs locally in the tissues, where their biological action is required, measurement of circulating oestrogen levels does not provide a reliable assessment of the quantitative aspects of its biological activity and metabolism of oestrogens in men. For the latter process the term ‘intracrinology’ has been coined [47]. The locally-required concentrations of bioactive androgens and oestrogens are determined by the local concentrations of aromatase, thus avoiding the overexposure of the organism as a whole to inappropriately high oestrogen levels [48]. In addition, there are two oestrogen receptor types, the α and β subtypes, which allow the local modulation of oestrogen effects in tissues depending on the distribution of receptor subtypes. Interestingly, in the male reproductive system Leydig cells, Sertoli cells, ductus deferens, the prostate and even the spermatogonia and spermatocytes show the presence of oestrogen receptors; (for review Luconi et al.) [55]. Their biological significance, however, in the male reproductive system, has not yet been elucidated.

**BRAIN**

**Oestrogen and brain function**

Receptors of neuroactive steroid oestrogens can be found in several brain areas including cerebral cortex, hypothalamus, pituitary and the limbic system (amygdala and hippocampus) [13]. And, indeed, effects of oestrogen on the brain are increasingly being recognized [60]. Studies have mainly been carried out using animal models. During the period of central nervous system development in fetal life, oestrogens influence the sexual differentiation of tissues in specific areas of the brain. Oestrogens are involved in promoting outgrowth of neural processes, neuronal differentiation, and formation of synaptic connections [85]. Oestrogens have been observed to influence many processes in many regions of the brain throughout the entire life span. These effects include those on cognitive function, co-ordination of movement, pain and affective state, involving both the ER α (oestrogen receptor α) and ER β genes. Only some of the oestrogen actions on the brain are intracellular receptor-mediated, while others take place on the cell membrane, mediated via second messenger mechanisms, neuronal excitability and ion channels [72].

As men are more at risk of cardiovascular disease than women, brain dysfunctions on the basis of vascular pathology affect men more frequently, though less frequently than one would expect on the basis of the gender difference in vascular disease. With regard to Alzheimer’s disease, men are relatively protected in comparison to women. One intriguing possibility is the putative neuroprotective effect of oestrogens in preventing or retarding Alzheimer’s disease [60]. Post-
menopausal women seem to enjoy protection from Alzheimer’s disease when they receive oestrogen replacement therapy. Oestrogens increases choline acetyltransferase, the enzyme needed to synthesize acetylcholine. This suggests that oestrogen enhance cholinergic function, which is known to be deficient in Alzheimer’s disease, the disease notorious for its memory deficits [9]. Estrogen reduces the generation of 40- and 42-amino acid beta-amylloid peptides that accumulate to compose cerebral plaques in vulnerable brain regions and which are responsible for Alzheimer’s disease [73]. This represents probably another mechanism by which oestrogen confers protection from Alzheimer’s disease. Recently, it was reported that in female rats E2 increases the expression of genes for the 5-hydroxytryptamine receptor and the serotonin transporter in regions of the brain that, in humans, are concerned with cognition, mental state and memory [28]. In male rats castration decreased, while oestrogens and androgen, but not the non-aromatizable DHT, increased the density of 5 hydroxytryptamine receptors in the forebrain. This strongly suggests that this action of T on the brain is mediated by its aromatization to oestradiol. Oestrogens interact with acetylcholinergic, serotonergic (5-HT), monoamine oxidase activity and catecholaminergic systems of the brain, but also through estrogen-induced synapse formation [59]. The latter two are implicated in depression and schizophrenia. With aging, men show declining T levels, and for men T is the precursor for oestrogens [52].

There is also evidence that androgens confer protection from Alzheimer’s disease in their own right [31]. So there may be an advantage in supplementing androgens in aging men whose T levels have fallen below a certain limit, thereby in fact substituting both androgens and oestrogens. Not all studies in aging men are in agreement, however. A recent study [94] found only a link between cognition and oestrogens in women but not in men, whereas Yaffe et al. [96] found a correlation between cognitive functioning and bioavailable T, but not E2.

Oestrogen contributes to explicit (or declarative) memory function through its action on hippocampal neurons. The implication of this oestrogen effect is improved (conscious) recall of facts, events and autobiographical memories [49, 60]. Explicit memory is considered the cognitive function that is most vulnerable to loss of oestrogen [87]. Women receiving oestrogen replacement and men whose estrogen levels are above those of postmenopausal women score better on explicit memory tasks [12]. The hippocampus is presumed to play a key role in the estrogen dependent cognitive function. Recently evidence emerged that estrogens have also effects on prefrontal cortex functions (working memory, attention). Keenan and co-workers hypothesized that a low estrogenic state first leads to a defect in executive (frontal) functions and then affects explicit memory (hippocampal) function [38]. This clearly needs further investigation. A recommendation of two recent meta-analyses is that different estrogen preparations and different psychometric tools preclude firm conclusions of estrogen related effects on memory, therefore the cognitive effects of estrogens need better designed investigations [35, 50].

It may be expected that estrogen, via neurotransmitter pathways, may have effects on mood, declarative memory, motivation and cognition such as verbal fluency. Women have an advantage over men in the outcome of acute neurological injury, suffering less post-ischaemic and post-traumatic brain injury. It is theorized that oestrogens act as anti-oxidants and that progesterone has a membrane-stabilizing capacity. In the future, the potential therapeutic role of non-feminizing selective oestrogen receptor modulators will be better defined. These are drugs designed to exert oestrogen-like effects selectively in one or more target tissues, while simultaneously blocking oestrogenic effects in others [19].

Earlier studies have questioned the relevance of oestrogens in human male sexuality [5, 30]. A recent study found that oestrogen replacement in an aromatase-deficient man increased libidinous aspects of sexuality [11].

**BONES**

From different lines of investigation there is increasing evidence that estrogens protect women from osteoporosis [40, 66]. In men, recently, three cases have been described with a severe impairment of the biological effects of estrogens. They presented with delayed epiphyseal closure and osteopenia. These four remarkable cases have stirred up attention for the role of estrogens in acquiring and maintaining bone mineral density (BMD) in men [10, 34, 61, 68, 75]. The role of estrogen in bone metabolism was demonstrated in a man with a type α estrogen receptor (ERα) abnormality and in another man with aromatase deficiency. It was shown in two men with aromatase deficiency that estrogen administration had a significant beneficial effect on skeletal growth and bone maturation, providing evidence that estrogens do indeed play a role in male bone (patho) physiology; (for review see Faustini-Fustini et al.) [26]. In normal elderly men estrogen seems to play a more dominant role than T in regulating bone resorption. In elderly men lower than normal levels of estrogen appeared to be associated with vertebral fractures [8]. Age related decreases of estradiol, especially levels...
below 40 pmol/l, may be the major cause of bone loss in elderly men [3, 39, 41]. For review, see Riggs et al. [67] and Khosla et al. [67]. But apart from estrogen, T itself appears to be important in maintaining bone formation [21, 24, 83].

The effects of estrogens (and androgens) exerted on bone turnover are likely to be mediated via the growth hormone-insulin like growth factor axis [89]. In male-to-female transsexuals orchiectomized in adulthood, administration of relatively high dosages of estrogens appear capable of maintaining BMD [90].

THE CARDIOVASCULAR SYSTEM

Oestrogen and cardiovascular disease

Traditionally, it is thought that the relationship between sex steroids and cardiovascular disease is predominantly determined by the relatively beneficial effects of oestrogens and by the relatively detrimental effects of androgens on lipid profiles. The findings in men with aromatase deficiency show that oestrogens and androgens indeed do matter for these variables. In men with aromatase deficiency [34, 61] a metabolic profile is encountered with similarities to the profile found in the metabolic syndrome: elevated triglycerides, low HDL, an elevated LDL/HDL ratio and insulin resistance; these elements show improvement upon administration of estrogens. The increase in HDL may be due to estrogens but can also very well be explained by the fall in androgen levels as a result of an increased negative feedback signal of the supplemented estrogens to pituitary LH secretion; LH is elevated in men with a diminished biological action of estrogens. But recent research shows that the impact of endogenous estrogens on the cardiovascular risk profile is not limited to metabolic factors such as lipids, glucose and insulin but also to the effects of sex steroids on other biological systems, such as fat distribution, endocrine/paracrine factors produced by the vascular wall (such as endothelins, nitric oxide), blood platelets, inflammatory factors and coagulation, must also be considered; (for review: Cushman) [18]. It is now generally believed that women, in comparison to men, are protected against cardiovascular disease up until menopause. Traditionally this sex difference has been attributed to the beneficial effects of premenopausal levels of estrogens on the cardiovascular system. It is then paradoxical that in cross-sectional studies of men, elevated levels of oestrogens [64] and relatively low levels of T [7, 64, 82] appear to be associated with coronary disease and myocardial infarction. Some studies in aging men have shown results that seem to contradict the overall notion that androgens, by their influence on the lipid profile, increase the risk for coronary artery disease. In a study of men with type 2 diabetes, patients showed lower levels of total and free testosterone, however their high density lipoprotein (HDL)-cholesterol levels were lower and triglyceride levels were higher than in controls [7]. The common denominator of the above correlational studies may be the so-called syndrome X: a set of cardiovascular risks associated with visceral obesity and low plasma T levels. The large fat mass as a site of aromatization of androgens to estrogens may be a factor in the high E2 levels found in these men [92].

There is growing evidence that there is a relationship between levels of circulating oestrogens and risk factors for cardiovascular disease. The reduction of circulating oestrogens [6] or impaired oestrogen action (for review see Faustini-Fustini et al.) [26] in men leads to dyslipidaemia. Oestrogens also directly affect the vascular wall. Impaired oestrogenic action leads to poor flow-dependent vasodilatation in peripheral arteries in response to an ischaemic stimulus [78], possibly resulting from endothelial dysfunction, perhaps a decreased vascular synthesis/release of nitric oxide [77, 79].

Low concentrations of estrogens lead to poor flow-dependent vasodilatation in peripheral arteries in response to an ischemic stimulus distal to the brachial artery probably resulting from endothelial dysfunction [78, 95], possibly by means of a decreased vascular synthesis/release of nitric oxide [77, 79]. In healthy young (eugonadal) males low dose E2 implants significantly enhanced arterial endothelium dependent dilatation without altering vessel size or smooth muscle dependent responses [69]. In vitro studies showed a direct effect of low doses of estrogen on neuronal-type nitric oxide synthase in neutrophils in men [29]. Studies in hypogonadal men and in men with coronary artery disease reported beneficial effects of estrogens and selective estrogen receptor modulators (SERM’s) on endothelial function. These effects were assessed by means of forearm vascular reactivity measurements of endothelial dependent and independent responses to ischemia [14, 45]. The investigators claim that the effects of E2 on endothelial function in these experiments are not to be ascribed to cholesterol lowering effects of E2 or tamoxifen.

There is much progress in understanding the molecular mechanisms underlying the diverse reproductive and non-reproductive effects of E2 and the multitude of (synthetic) estrogen receptor ligands [33]. In human endothelial cells, which reportedly have a high density of estrogen receptors (20 to 80 000 per cell), the intensity of immunostaining for estrogen receptors is similar in male and female donor cells, and neither electrophoretic mobility shift assays nor ligand-binding studies show reproducible gender differences in estrogen receptor expression [43]. A recent study found that coro-
nary atherosclerosis is related to estrogen receptor 1 gene polymorphism [51].

There is evidence that the ERα does not only mediate vascular effects of estrogens but other, nongenomic, pathways are also involved in estrogen signaling. These effects of estrogens, as has been shown on cutaneous vasculature, show a rapid onset and rapid offset mechanism that is specific to the endothelium. These effects do not involve nitric oxide effects on vascular smooth muscle [44].

When androgen replacement is given, it must be remembered that part of its beneficial action on the cardiovascular system may be due to the effects of its aromatization products [63].

PROSTATE

Oestrogen and prostate disease

It has been argued above that estrogens in men of all ages are very relevant for their beneficial effects on bone, the cardiovascular system and maybe the brain. So it seems pertinent that in old age not only androgens but also estrogens remain with normal limits. The counterpart is that not only plasma levels of androgens but also estrogens play an important role in prostate development and prostate pathology [84]. Recent knowledge indicates that prostate development depends on the synergistic effect between androgens and estrogens [80, 81]. Furthermore, this synergistic effect characterizes the different stages of prostate development in human life.

In aging men, plasma T and, in particular, free T levels decline while plasma E2 remains fairly constant [37, 91, 92]. Since benign prostatic hyperplasia (BPH) occurs typically in the aging male, the resultant increase in the oestradiol/testosterone ratio has been implicated in its pathogenesis, mainly on the basis of observation in dogs. Histologically, BPH is more a stromal disease than an epithelial disease. For example, one study found that concentrations of E2 and oestrone increased in the stroma but not in the epithelium, as a function of age [46]. In the normal situation, as opposed to BPH, the concentration of E2 and oestrone are higher in the epithelium of the prostate than in the stroma. The stromal dihydrotestosterone (DHT) level shows no correlation with age [46]. One hypothesized mechanism for the effects of oestrogens on the prostate is that oestrogens can induce transcriptional activity of the androgen receptor [98]. Another hypothesis states that SHBG (which rises with increasing age) facilitates the generation of intracellular cyclic adenosine monophosphate (cAMP) in the prostate, which promotes growth [25]. From this, it would seem that the inhibition of the biological effects of E2 might have a beneficial effect on stromal hyperplasia, but one study showed that the reduction of oestrogen level, using the aromatase inhibitor atamestane, has no effect on clinically established BPH [65]. Interruption of the negative feedback of oestrogens on the hypothalamo-pituitary axis, however, caused an increase in the level of circulating androgens, which may be an undesired effect.

The relationship between oestrogens and prostate cancer has received less attention. A recent study indicates that E2 levels were lower while cortisol levels were higher in men with prostate cancer compared to age-matched men with lower urinary tract symptoms [71].

POTENTIAL THERAPEUTIC SOURCES OF OESTROGENS IN MEN

In eugonadal men the androgens secreted by the testis and the adrenal serve as precursors for peripheral aromatization to estrogens. In hypogonadal men exogenous testosterone, regardless the mode of administration (parenteral, oral or transdermal) lead to a 50-150% rise in plasma estrogen levels.

Phyto-estrogens

A modern Western diet is high in fat and protein, whereas a traditional Asian diet is low in fat and protein but high in carbohydrates. An important part of the Asian diet consists of soy and vegetarian foods with high amounts of isoflavonoids, flavonoids and lignans. These are metabolized by the gut microflora to produce phyto-oestrogens such as enterolactone, daidzein and genistein [32]. Phyto-oestrogens are plant chemicals that resemble steroidal oestrogens in structure or function. Most phyto-oestrogens are isoflavonoids or lignans. A wide range of biochemical actions of phyto-oestrogens has been reported. These actions include their capacity to bind to oestrogen receptors, elucidate a variety of non-receptor-mediated actions, act as antioxidants and exert an inhibitory action on enzymes involved in the biosynthesis of E2 and other steroids, such as 17β-hydroxysteroid dehydrogenase, 5α-reductase or aromatase. Both coumestrol and genistein appear to have a higher affinity for the newly discovered oestrogen receptor variant ERβ (present in the prostate) than for the classical ERα [93].

There have only been a few non-clinical studies examining the effects of phyto-oestrogen on testicular function, and results are somewhat contradictory [93]. In a study in pre-pubertal mice who were fed with 900 – 3600mg/kg of the genistein glycoside genistin for 6 weeks, testicular weight and spermatogenesis were suppressed [57]. However, an oral dose of 300 – 1000 mg/kg genistein or
Phyto-oestrogens may also have an important effect on 5α-reductase. It has been found that isoflavonoids and lignans inhibit 5α-reductase activity [23]. The effect of phyto-oestrogens on T metabolism has been noted. Vegetarians and Asian men seem to have higher plasma levels of SHBG and lower levels of free and total T than men on a Western diet [32]. This is in agreement with a recent study [53] which reports that diets low in protein, especially if consumed by older men, may lead to elevated SHBG levels and decreased T bioactivity. Total caloric intake, carbohydrate and fat did not have a significant influence. An increase in SHBG levels has been reported when a diet low in fat and high in fiber is consumed in addition to a daily exercise regimen [86]. These effects may be a result of the action of phyto-oestrogens which, as weak oestrogens, stimulate the synthesis of SHBG in the liver [2, 32]. Sex hormone-binding globulin may protect against the progression from a latent to clinically apparent prostate cancer by modulating androgen action. A study by Jin and colleagues [36] observed that the level of SHBG was higher in Chinese men living in China compared to Chinese migrants in Australia. No difference in serum total and free T levels between Asian and Caucasian men could be demonstrated [54], while another study indicated low levels of total plasma T in Chinese residents in the USA compared to recent Chinese migrants [70].

Finally, an interesting study investigating the influence of ethnic differences reported higher concentrations of isoflavonoids, daidzein and equol in the plasma and prostatic fluid of men from Hong Kong compared with those from the United Kingdom and Portugal [62]. Diets high in soy protein may also lower total cholesterol, low density lipoprotein (LDL)-cholesterol and triglycerides and may thus be cardio protective [4].

In conclusion, isoflavonoids and lignans may have very interesting properties, and may in part be responsible for the lower incidences of cardiovascular disease and prostatic neoplasm in Asian men. In a recent review information was presented that the cardiovascular benefits of soy protein for men are questionable [15]. The isoflavonoids from soy may be protective against prostate disease [1, 32]; though a recent nested case-control study provided no evidence for this assumption [76], so more concrete data are needed before definitive conclusions can be drawn.

**Selective oestrogen receptor modulators (SERMs)**

The observation that the non-steroidal oestrogen-receptor antagonist tamoxifen preserved bone mass in post-menopausal women with breast cancer [16] invites one to reconsider the concept of the biological action of both oestrogens and oestrogen-receptor blockers. In addition, the potential clinical uses of both their anti-oestrogen action (on breast and uterine tissue) and their oestrogenic action (on bone), need to be considered. Raloxifen, a compound closely related to tamoxifen but with less potency to stimulate the endometrium, has been developed. A study by Yang et al. [97] has elucidated the mechanism (s) of action of oestrogens and anti-oestrogens. The mechanism of action is as follows: the oestrogen receptor has two distinct domains that are both activated by E2 in the body. Compounds such as tamoxifen and raloxifen selectively activate one of these two domains of the receptor and this explains the tissue selectivity of the latter. Selectivity is also enhanced by hormone receptor action involving activators and suppressors. Hence the term ‘selective oestrogen receptor modulator’ (SERM) has been introduced. This mechanism allows opportunities to produce tissue-specific oestrogens; for men this would mean oestrogen action on bone, the brain and the cardiovascular system but not, for instance, not on mammary tissue or fat distribution or on the prostate. For a recent review of tissue specific responses: Diel P [22].

**Adrenal androgens (DHEA and androstenedione)**

Dehydroepiandrosterone (DHEA) and androstenedione are actively converted into other hormones, such as E2 [47]. The majority of oestrogen production from the androgenic precursors occurs locally in the tissues where their biological action is required [47]. The concentrations of bioactive androgens and oestrogens required locally are determined by the local concentrations of aromatase. As mentioned previously, this avoids the over-exposure of the organism as a whole to inappropriately high androgen or oestrogen levels [48]. This use of DHEA for estrogen replacement awaits further investigation.

**CONCLUSION**

There is now strong evidence that oestrogens are important for a man’s sexual and non-sexual functioning. The reason that this role has only recently become evident is that as long as circulating androgen levels are normal or only modestly decreased in men, a sufficient amount of oestrogens can be derived from these androgens. In old age, some of the symptoms (loss of bone mass, cardiovascular problems) appear to be associated with low androgen levels, which, in turn, has increasingly shown a powerful correlation with oestrogen status in men. Several treatment modalities are potentially...
available: T replacement therapy if plasma (free) T levels are subnormal, dietary oestrogenic products, selective oestrogen receptor modulators and locally-converted adrenal androgens. All await corroboration in studies.

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