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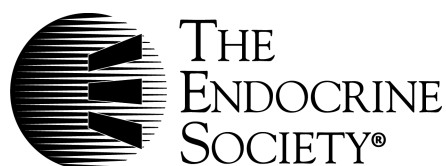
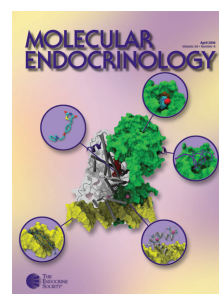
THE JOURNAL
OF CLINICAL
ENDOCRINOLOGY
& METABOLISM

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J. Clin. Endocrinol. Metab. 2003 88: 5076-5086, doi: 10.1210/jc.2003-030611

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CARDIOVASCULAR ENDOCRINOLOGY

Endogenous Sex Hormones and Cardiovascular Disease in Men

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Unlike women, men do not experience an abrupt reduction in endogenous sex hormone production. It has, however, become clear that an age-associated decrease in the levels of (bioactive) sex hormones does occur. Whether endogenous sex hormones have an impact on cardiovascular disease has for many years remained largely unknown, but during the last decade more attention has been drawn to the importance of testosterone, estrogens, and adrenal androgens in etiology, prevention, and treatment of male cardiovascular disease. The pur-

pose of this article is to summarize the evidence currently available on the association between endogenous sex hormones and cardiovascular disease in males. Published studies dealing with the relationship between circulating levels of sex hormones and cardiovascular disease in males were reviewed. The studies reviewed in this article suggest that circulating endogenous sex hormones and estrogens have a neutral or beneficial effect on cardiovascular disease in men. (*J Clin Endocrinol Metab* 88: 5076–5086, 2003)

ABUSE OF EXTREMELY high doses of anabolic steroids has been linked to sudden cardiac death, leading many to believe that the physiologically high levels of androgens in men may have a deleterious effect on the male cardiovascular system (1). However, recent reports contradict this theory, claiming that androgens may have cardiovascular benefits in men (2, 3).

The age-related decline in sex hormones in men (4) is hypothesized to promote age-related health problems. For many years, little was known about sex hormones and cardiovascular disease (CVD), but in the last decade the importance of testosterone (T) and dehydroepiandrosterone (DHEA), including its sulfate (DHEA-S), in CVD in men had been recognized.

This review summarizes current evidence on the association between sex hormones, endogenous as well as exogenous, and intermediate or clinically manifest indications of CVD and conditions in men.

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE and PubMed with the search terms “androgens” or “sex hormones” in combination with the terms “cardiovascular” and “males” or “men.” We then searched these publications using the terms “diabetes,” “cholesterol,” “obesity,” “atherosclerosis,” “hypertension,” and “vascular function.”

Abbreviations: BT, Bioactive (bioavailable) T; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein-a; MI, myocardial infarction; NO, nitric oxide; OR, odds ratio; PWV, pulse wave velocity; T, testosterone; tHcy, homocysteine.

We focused on publications in the past decade but did not exclude commonly referenced and highly regarded older publications. Relevant articles not identified with the search strategy described above but referenced in the bibliographies of these papers could also be included. Several recent review articles and book chapters were also included because they provide comprehensive overviews.

Sex hormone biosynthesis and metabolism

Circulating steroids of importance in men are T, dihydrotestosterone, and estradiol. T is mainly produced by the testicles, whereas DHEA and DHEA-S are mainly produced by the adrenal glands. Both organs produce androstenedione (5). Figure 1 presents the several pathways for androgen and estrogen biosynthesis.

Androgens and estrogens circulate either free (1–2% of T) or bound to the serum proteins, albumin (binds 40–60% of T) and SHBG (binds 40–80% of T, which is biologically inactive) (6). Bioactive (bioavailable) T (BT) includes both free and albumin-bound T. Androstenedione and DHEA circulate weakly bound to albumin. DHEA-S binds strongly to albumin.

Measuring hormone levels

Reported concentrations of sex hormones vary widely, which may in part be due to the choice of laboratory assays used (7). Although indirect methods have been the gold standard, direct assays can provide accurate relative results except for low concentrations (6) (Table 1).

There is no real consensus as to which forms of hormones should be measured to best evaluate androgen status, and there is a need to standardize the procedures used to measure

FIG. 1. Pathways for androgen and estrogen biosynthesis. Circled numbers represent the following enzymes: 1, 20,22-desmolase (P-450scc); 2, 3 β -hydroxysteroid dehydrogenase and Δ^5, Δ^4 -isomerase; 3, 17-hydroxylase (P-450c17); 4, 17,20-desmolase (P-450c17); 5, 17-ketoreductase; 6, 5 α -reductase; and 7, aromatase.

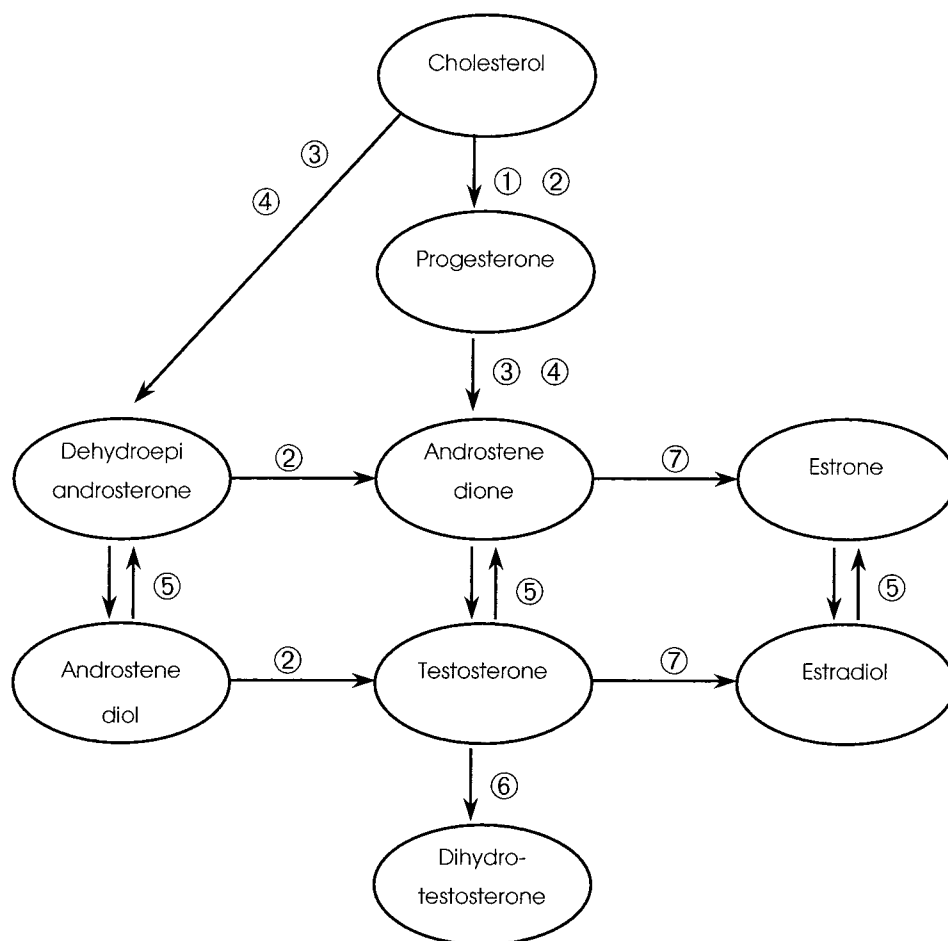


TABLE 1. Available assays of total T measurements

Assay	Pros	Cons
Direct immunoassay	• Use of small serum sample volumes • Reproducible at higher levels • Rapid and easy to use • Useful in research studies	• Cross-reactivity • Problems at low levels concerning reproducibility • Not standardized for EDTA plasma
Indirect immunoassay	• Reproducible at high and low levels • Useful in both clinical care and research studies	• Not easy to automate and laborious • Cross-reactivity (except if a chromatography separation step is included)
Chromatography and mass spectroscopy	• "Gold standard" • No cross-reactivity • Useful in both clinical care and research studies	• Laborious

these hormones (6). Recently several studies compared results of T assays. They have suggested that free T and BT are the most practical methods to determine hypogonadism. BT has been suggested to be the assay of choice in older persons in whom SHBG increases and substantial variation of albumin levels may occur (8,9). Due to episodic secretion, diurnal variation, and week-to-week variability of T and BT, the utility of a single value in making the diagnosis of hypogonadism is problematic (9). For epidemiological purposes a single value was found to be adequate (10).

Risk factors for CVD

During the past decades, several studies on the association between endogenous sex hormones and known cardiovascular risk factors have been conducted. It has been suggested that low levels of T and DHEA-S are associated with an unfavorable risk profile; however, the results have been conflicting. Table 2 summarizes the associations of observational studies between endogenous sex hormones and cardiovascular risk factors.

TABLE 2. Associations between endogenous sex hormones and cardiovascular risk factors: results from observational studies

Sex hormones	Cardiovascular risk factors	Direction of effect	Refs.
T ↓	Blood pressure, systolic	↑	38–40
	Blood pressure, diastolic	↑/=	38–40
	Cholesterol, total, LDL	↑	12, 13, 16, 19–22, 24, 35
	Cholesterol, HDL	↓	11–14, 17–23, 35
	Triglycerides	↑	16, 23, 35
	Body mass index, waist circumference	↑	12, 13, 27, 31, 35
	Insulin	↑/=	13, 29–36
	Glucose	↑/=	29–32, 34–36
	Fibrinolytic activity	↑	47, 48
	Blood pressure, systolic	↓/=	12, 15, 42
Estradiol ↓	Blood pressure, diastolic	↓/=	12, 15, 42
	Cholesterol, total, LDL	↑/↓/=	12, 19–22
	Cholesterol, HDL	↑/↓/=	12, 19–22
	Triglycerides	↑	12
	Body mass index, waist circumference	↓/=	12, 31
	Insulin	=	36
	Glucose	=	36
	Blood pressure, systolic	↓	44, 45
	Blood pressure, diastolic	=	44, 45
	Cholesterol, total, LDL	↑/=	13, 16
DHEA-S ↓	Cholesterol, HDL	↓/=	13, 16
	Triglycerides	↓/=	16
	Body mass index, waist circumference	↑/=	13, 31
	Insulin	=	13
	Glucose	=	13

↑, Significant increase; ↓, significant decrease; =, no significant association; ↑/=, both significant increase and no significant association has been reported; ↓/=, both significant decrease and no significant association has been reported; ↑/↓/=, all associations have been reported.

Lipids. High-density lipoprotein (HDL) cholesterol is inversely associated with the risk of CVD. Conversely, low-density lipoprotein (LDL) and lipoprotein-a (Lpa) are associated with a high risk of CVD. Cross-sectional studies have found high T levels to be associated with high HDL-cholesterol levels, low LDL-cholesterol, and low triglyceride levels (11–22). A longitudinal analysis of the Multiple Risk Factor Intervention Trial confirmed this relationship (23). Furthermore, this study showed that a decrease in endogenous T is associated with an increase in triglycerides. Smaller dense LDL-cholesterol particles were found to be associated with a low total T level and SHBG (24). Estradiol was found to be associated with apolipoprotein E (15). Correlations between physiological levels of total and free T, estradiol, DHEAS, and SHBG and Lpa have not been found (25), although supplementation with anabolic steroids may reduce Lpa (26).

Insulin, glucose metabolism, and body composition. It has been postulated that in hypogonadal states there is a preferential deposition of abdominal adipose tissue. Increased accumulation of adipose tissue leads to an increase in aromatase activity and hence a higher conversion of T to estradiol, which results in a further depression of T concentrations and an increased deposition of abdominal fat (27). Intervention studies demonstrated that correction of relative hypogonadism in men with visceral obesity seem to decrease the abdominal fat mass and reverse the glucose intolerance as well as lipoprotein abnormalities (28, 29). There is extensive experimental evidence showing that sex steroids and insulin interact in tissues. In cross-sectional studies of sex hormones and diabetes, the total T concentration was found to be lower in men with impaired glucose tolerance (29–32). The traditional view of sex hormones increasing insulin resistance has been challenged in women by studies showing that insulin

stimulates androgen production in the ovary (29). Furthermore, it has been suggested that insulin stimulates T production and suppresses SHBG production in men (33). On the other hand, results of prospective studies show that low levels of SHBG and T play a role in the development of insulin resistance and subsequently the development of type 2 diabetes (34–36). At physiological levels T and estradiol are thought to be involved in maintaining normal insulin sensitivity. However, outside these physiological levels, these steroids may promote insulin resistance (29, 37).

Blood pressure. Concerning the association between sex hormones and blood pressure, research findings suggest a relationship between essential hypertension and impaired T levels in men (38–40). This may be due to the use of anti-hypertensive medication, which can lower sex hormone levels (41). Another important caveat is that the lower T levels observed in the aforementioned studies may merely reflect increased stress. Other findings suggest that in men with hypertension, renin profile may be related to estradiol levels (42). It is hypothesized that sex hormones increase arterial pressure by causing a hypertensive shift in the pressure-natriuresis relationship, either by having a direct effect to increase proximal tubular reabsorption or by activation of the renin-angiotensin system (43). Furthermore, total and free estradiol levels were found to be associated with systolic and diastolic blood pressure (15); however, these results were not confirmed by other studies (12, 42). Inconsistent results have been found concerning the association between endogenous DHEA-S levels and hypertension status. Epidemiological observations of positive associations between DHEA-S and blood pressure levels have raised some concern (44–46). However, studies in experimental animals do not

suggest that DHEA-S administration causes hypertension (45).

Coagulation and fibrinolysis. Fibrinolytic activity is inversely associated with cardiovascular risk. Research demonstrated that because of the increase in several prothrombotic factors, men with lower androgenicity seem to be at greater risk for CVD (47, 48). Furthermore, T supplementation may increase blood fibrinolytic activity and produce clinical improvement in patients with occlusive vascular disease (49, 50).

Other risk factors. An elevated plasma level of homocysteine (tHcy) is an independent risk factor for CVD. There are indications that plasma tHcy is influenced by sex steroids. Androgen administration in transsexual (female) subjects increases tHcy levels (51). In contrast, short-term, high-dose T administration did not affect tHcy levels in normal men (52). There is increasing evidence for the role of inflammation in promoting atherogenic risk; elevated C-reactive protein levels have been shown to predict cardiovascular outcomes. Postmenopausal conjugated equine estrogen replacement leads to increased C-reactive protein levels in women (53); however, androgen supplementation does not alter serum inflammatory markers in men (54, 55).

Coronary heart disease [angina pectoris, myocardial infarction (MI)]

Published studies of the relationship between circulating levels of T and DHEA/ DHEA-S and coronary heart disease (CHD) in men were reviewed by Alexandersen *et al.* (56). Up to 1996, they retrieved one randomized intervention trial (57) and eight prospective (58–65) and 30 cross-sectional studies (11, 14, 44, 66–92). More recently, additional studies have been published and are summarized here (93–98). Of 33 cross-sectional studies, 21 reported lower concentrations of T, BT, and/or DHEA(-S) in patients with CHD than in healthy men (14, 66, 69–76, 79–86, 93, 96, 98). In 12 other studies (11, 44, 67, 68, 77, 78, 87–92), similar levels of these sex hormones were found in controls and patients with CHD, and one study (68) showed elevated levels of DHEA(-S) in patients. One study (97) reported hyperestrogenemia to be related to thrombotic occlusion of the coronary arteries in MI; the mean serum estradiol level in the men who had had an MI (38.5 ± 8.8 pg/ml) was higher ($P = 0.002$) than the level in men who had not had an MI (31.9 ± 7.1 pg/ml). However, a causal interpretation of these findings is inherently restricted by the cross-sectional nature of the design.

No significant association between serum T and CHD was observed in the prospective studies (58, 60, 62, 64), whereas either no (61, 63) or an inverse (59, 65, 94, 95) association was found between DHEA-S and CHD. One study (94) showed that men with serum DHEA-S in the lowest quartile at baseline (<1.6 μ g/liter) were significantly more likely to incur ischemic heart disease by follow-up [odds ratio (OR), 1.60; 95% confidence interval (CI), 1.07–2.39].

Most studies, however, have been carried out in selected populations generally involving small numbers (44, 61, 67–69, 71–74, 76, 79–81, 83, 84, 87, 88, 90, 92, 97, 98). Moreover, to assess the independent association between endogenous sex hormones and CHD, analyses should have been adjusted

for age and other cardiovascular risk factors; however, only a few studies adjusted their analyses properly (14, 44, 59, 60, 64, 65, 81, 93, 94). Results of the studies that presented adjusted ORs and relative risks of the association between endogenous sex hormones and CVD are joined together in Fig. 2. It would appear that there is a small beneficial effect of T and DHEA-S on CVD and a neutral effect of estradiol on CVD; however, presented studies used different end points and different study designs. Firm conclusions about the relation between endogenous sex hormones and male CVD cannot be drawn.

Generalized atherosclerosis (carotid intima-media thickness, aortic calcification)

Data on atherosclerosis and sex hormones are scarce, and those available have yielded contradictory results. In an Asian study (99), DHEA-S and DHEA concentrations were significantly lower in subjects with aortic calcification than in those without it (60 and 35%, respectively). However, in a large-scale cohort study, the development and progression of carotid atherosclerosis over 5 yr, monitored by high-resolution duplex ultrasound, was not related to age- and sex-adjusted endogenous DHEA(-S) concentrations (100); the OR of incident/progressive atherosclerosis comparing a 50% increase in DHEA-S levels was 0.99 (95% CI, 0.89–1.11). In one population-based study (13), an inverse association between levels of T and aortic atherosclerosis was observed, with a 60% reduced risk of severe atherosclerosis for men in the highest total T tertile, compared with the lowest tertile. Recently a study among independently living elderly men showed that lower serum T and estrone levels were found to be associated with increased carotid wall thickness (101); a decrease of total T with 1 nmol/liter was associated with an increase in intima-media thickness with 0.04 mm (95% CI, 0.01–0.08).

Vascular function (flow-mediated dilatation, pulse-wave velocity)

Impaired vascular reactivity is an important early event in atherogenesis and may determine dynamic plaque behavior in patients with coronary artery disease (102). Flow-mediated dilatation, measured in the brachial artery, has been used to investigate endothelium-dependent arterial dilatation. Arterial compliance or elasticity can be measured by pulse wave velocity (PWV). Decreased central arterial compliance decreases coronary artery perfusion and increases cardiac workload (103). There are several indications that low serum levels of androgens lead to deterioration of endothelial function, although reported associations have not always been in the expected direction. However, the Asian study reported low levels of DHEA and DHEA-S to be associated with a high PWV (with 2 m/sec increase in PWV for 50% decrement in DHEA or DHEA-S level), suggesting that high levels of DHEA(-S) have beneficial effects on vascular elasticity (99), which agrees with the data on clinically manifest cardiovascular end points. These adverse hemodynamic effects may increase cardiovascular risk in this patient group.

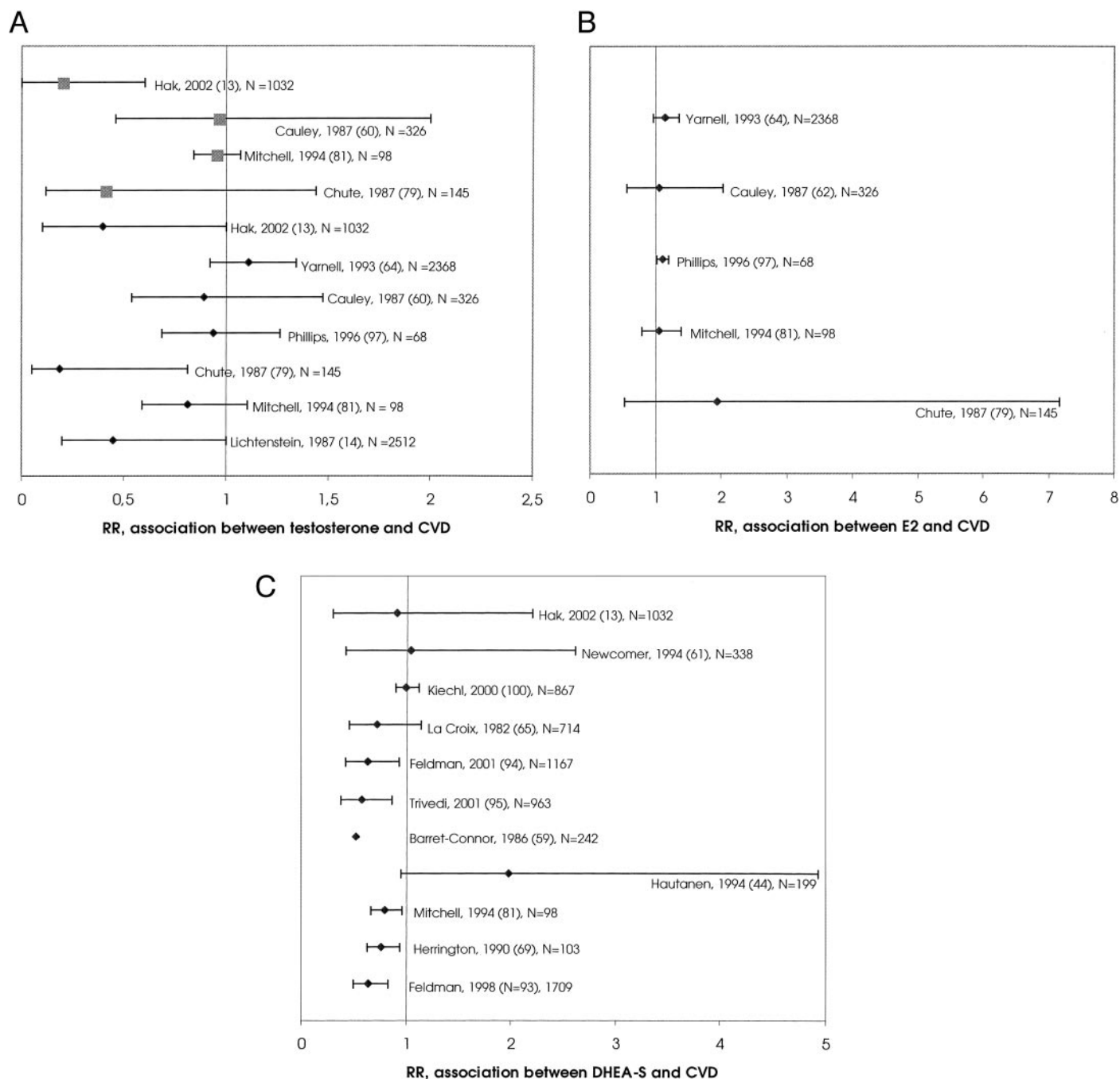


FIG. 2. Association between endogenous sex hormones and all cardiovascular end points in men of observational studies giving adjusted relative risk estimates (RR). In addition, sample sizes are presented. A, Studies of total (small squares) and free (large squares) T and CVD. B, Studies of estradiol (E2) and CVD. C, Studies of DHEA-S and CVD.

Peripheral arterial disease

To our knowledge, only one study (104) has been published on the association between endogenous sex hormones and peripheral arterial disease. The Edinburgh Artery Study, a large-scale prospective survey, found that after 5 yr of follow-up, 40 men had developed peripheral arterial disease. In a nested case-control study, total T, SHBG, and estradiol appeared to have a protective effect, whereas estrone appeared to have an adverse effect. None of the associations

reached statistical significance, but the power of the study may well have been too low to allow firm conclusions to be drawn (104).

Sex hormone supplementation

A possible role for sex hormone supplementation in men has been investigated in several studies. A few studies have shown that, in both young and middle-aged men, androgen administration is associated with a reduction in visceral fat

accumulation in the abdomen (28, 105). Several studies in the 1940s (106–110) showed beneficial effects of T therapy (± 25 mg/wk im during 1–11 months) on both ischemia and exercise tolerance. In one intervention study involving patients with CHD, orally administered T undecanoate significantly improved angina pectoris, as judged by patients' symptom records and electrocardiogram ST-T segment changes and Holter monitoring, compared with placebo (57). Moreover, short-term administration of T (2.5 mg iv in 5 min) induced a beneficial effect on exercise-induced myocardial ischemia in men with CHD (111). Compared with placebo, T increased time to 1-mm ST-segment depression with 12% and total exercise time with 19%. Similar results were observed in an intervention study of 22 patients treated with 2.5-mg T patches for 12 wk (2). In an intervention study involving 11 patients with CHD, acute iv administration of T (2.3 mg) enhanced endothelium-dependent flow-mediated vascular reactivity, compared with placebo ($6.86 \pm 3.72\%$ vs. $3.16 \pm 1.90\%$, respectively; $P = 0.005$) (3). However, in another study (112), acute T or placebo infusion in 32 men with stable CHD had neither a beneficial nor deleterious effect on the onset and magnitude of stress-induced myocardial ischemia.

Compared with age-matched controls, men with complete androgen deprivation had a significantly higher central PWV (14.2 ± 2.7 m/sec vs. 11.8 ± 1.6 m/sec, respectively; $P = 0.02$) (113), suggesting stiffening of the large arteries. Furthermore, androgen deprivation increased the augmentation index from 24% to 29% after 3 months (114), which indicated that induced hypogonadism increases cardiovascular risk. In contrast, men with androgen deprivation have markedly greater endothelium-dependent dilatation of the brachial artery, compared with a healthy control group ($6.2 \pm 3.0\%$ and $2.0 \pm 1.9\%$, respectively; $P < 0.001$), supporting a deleterious effect of T on vascular function (115). In accordance with this, transsexual genetic females, treated long term with high doses of androgens, had impaired endothelium-independent vasodilatation, compared with untreated healthy female subjects (116). The abuse of androgenic steroids in young male athletes had been associated with premature MIs and strokes (117).

Recently Price and Leng (118) published a Cochrane review on whether exogenous steroid sex hormones are an effective treatment for male patients with lower limb atherosclerosis. Only two, small-scale trials were available, in which T was administered over relatively short periods, and different methods for assessing peripheral arterial disease were used. The authors concluded that there is currently no evidence that male patients with peripheral arterial disease benefit from T treatment (118). Winther (49) showed that high doses of T increased blood fibrinolytic activity and produced clinical improvement in 30 patients aged 46–76 yr suffering from ischemic disease of the lower limb.

In an intervention study of 18 healthy elderly men, oral estrogen reduced tHcy, fibrinogen, and plasminogen activator inhibitor-1 concentrations and favorably influenced very low-density lipoprotein, LDL, and HDL subclass levels without increasing markers of thrombotic risk. Breast tenderness occurred in four men and heartburn in five but did not require discontinuation of treatment (119). Men with prostatic carcinoma had drastically decreased Lpa levels after

estrogen treatment but higher Lpa levels after orchidectomy (120), thus showing the role of androgens after aromatization but possibly only at supraphysiologic levels. In male-to-female transsexuals, long-term estrogen supplementation improves vascular function, compared with men [(mean $\pm$ SE) $11.5 \pm 1.3\%$ vs. $5.2 \pm 1.0\%$, respectively, $P < 0.005$] (121). The effect of high-dose conjugated estrogen (5 mg/d) was studied in the Coronary Drug Project, but estrogen treatment was discontinued because it nearly doubled the incidence of nonfatal MI in the treatment group (122).

It may be stated that estrogen as well as T administration had both beneficial and deleterious effects on cardiovascular functioning, depending on dose, population, and end point.

Mechanism of action

Most of the reviewed studies suggest that the naturally occurring adrenal and testicular androgens may have a beneficial or a neutral effect on cardiovascular diseases. The antiatherogenic mechanism of sex hormones is largely unknown, but several hypotheses have been proposed (Table 3).

Testosterone. Some data suggest that T may affect the development of CVD by modulating risk factors such as diabetes (36), insulin resistance (36), obesity (27), hypercholesterolemia (23, 24), and hypertriglyceridemia (23). It is hypothesized that an increase in triglycerides is mediated by changes in hepatic triglyceride lipase (123). Alternatively, T may directly affect HDL-cholesterol by increasing the hepatic production of apolipoprotein A-I, the major protein constituent of nascent high-density lipoprotein particles (23). Several lines of evidence support an association between hypogonadism and insulin resistance in men. Insulin resistance can be produced by castration of male rats and is reversed with subsequent T replacement (124). It is not known whether the observed relationship between low plasma T is direct or indirect because the relationship between T and insulin is not fully understood.

Androgen receptors are distributed throughout the cardiovascular system, having been found within human and animal systemic arteries, including aortic, coronary, pulmo-

TABLE 3. Mechanism of actions of endogenous sex hormones on the cardiovascular system

Sex hormone	Mechanism of action on cardiovascular system
T	• Favorably modulating cardiovascular risk factors • Androgen receptors in arteries, vascular cells • Vasodilatation through potassium channels, calcium antagonism • Vasoconstriction through thromboxane release
Estradiol	• Conversion to estradiol • Favorably modulating cardiovascular risk factors • Estrogen receptors in arteries and vascular cells • Local aromatase action • Increasing NO synthase activity in vascular endothelium • Direct effects on vascular smooth muscle

nary, and carotid arteries (125, 126). It is possible, in view of their location in the media, that steroids, acting through their receptors, modulate smooth muscle tone in some vascular beds (127). They may also in some way influence development of atherosclerosis because smooth muscle migration and proliferation appear to play a major role in the pathogenesis of this disease. Furthermore, androgen receptors have been found in peripheral vascular, ventricular, and atrial mammalian cells and normal human megakaryocytes and platelets (126, 128). The identification of androgen receptors on the megakaryocyte lineage may enable new strategies for investigating the prothrombotic effects of androgens (128). Vascular androgen receptors may mediate the effects of T on the arterial wall. T up-regulates the expression of arterial androgen receptor mRNA and is associated with a significant reduction in neointimal plaque development (129).

Furthermore, T has been shown to dilate the coronary, aortic, and brachial vasculature by both endothelial-dependent and independent mechanisms (130). Because genomic pathways typically mediate the hormonal effects of steroids, steroid hormone-induced responses generally take at least 1–2 h to occur. However, recent evidence has suggested that there are nongenomic pathways of steroid hormone action (130–132). It has been demonstrated that T induces endothelium-independent relaxation in isolated rabbit coronary artery and aorta and porcine coronary myocytes, a relaxation that is not mediated by prostaglandin I₂ or cyclic GMP (130). Potassium conductance and potassium channels may be involved in the mechanism of T-induced relaxation (131, 133). Furthermore, research findings (134) suggest that T acts as a coronary vasodilator by a calcium antagonistic action. T was recently found to impair coronary vasodilatation in response to adenosine in an isolated perfused rat heart model (135). Such effects were mediated acutely and most likely through thromboxane release. Thromboxane acts through membrane surface receptors to aggregate platelets and constrict vascular smooth muscle (136). Any vascular effect of T, therefore, is likely to be a balance of vasodilatation by endothelial and nonendothelial effects and vasoconstriction due to thromboxane and possibly other mediators. Another direct effect of androgens that should be considered is their anabolic effect on cardiac myocytes, which may lead to modulation of left ventricular mass (126, 137). T may attenuate early atherogenesis, at least in part, by being converted to estradiol by the enzyme aromatase, which is also expressed in endothelial cells. This resulted in increased local concentrations of estradiol without significant increases in circulating estradiol levels (138). The relevance of these mechanisms in relation to physiological levels of androgens remains to be elucidated (Table 3).

Estrogens. In men estrogen is not solely an endocrine factor but instead is produced in a number of extragonadal sites and acts locally at these sites. These sites include the vascular endothelium, aortic smooth muscle cells, and numerous sites elsewhere in the human body. Within these sites, aromatase action can generate high levels of estradiol locally without significantly affecting circulating levels (139). The following hypothesis has been postulated concerning the role of es-

trogens in men: Estrogen interacts with the vascular endothelium, causing an increase in nitric oxide (NO) synthase activity and the release of NO, which is now considered to be beneficial to the vascular system (140). The effects of estrogen on hemostasis and thrombosis, however, appear to be dose dependent. Estrogen at high concentrations has direct effects on smooth muscle in the blood vessel wall via a number of ion channels such as calcium channels (140). It has been shown that low-dose oral estrogen in men favorably influences very low-density lipoprotein, LDL, and HDL subclass levels and reduces tHcy, fibrinogen, and plasminogen activator inhibitor-1 concentrations without increasing markers of thrombotic risk (119). Estrogens may particularly limit lipid accumulation in the presence of an intact endothelium, which synthesizes and releases NO, which in turn relaxes the vessel wall and inhibits platelet aggregation, leukocyte adhesion to endothelium, vascular smooth muscle cell migration and growth, and LDL-cholesterol oxidation, *i.e.* estrogens prevent atherosclerosis (121). Estrogen decreases tHcy levels in women by direct or indirect mechanisms (119).

So-called “experiments of nature” have revealed the importance of estrogens to male cardiovascular functioning. A point mutation in exon 9 of the gene encoding aromatase (CYP19) is associated with an inability to convert androgen to estrogen (141). Estrogen insensitivity caused by a disruptive mutation in the estrogen-receptor gene has also been described (142). The absence of a functional estrogen receptor appears to be associated with structural abnormalities of the coronary vasculature and an impaired flow-mediated endothelium-dependent peripheral vasodilatation (143, 144). Furthermore, glucose intolerance, hyperinsulinemia, and lipid abnormalities are present in patients with either estrogen deficiency (aromatase deficiency) or estrogen resistance (estrogen receptor mutation) (145) (Table 3).

Adrenal androgens. Several plausible mechanisms for a beneficial effect of DHEAS on cardiovascular morbidity or mortality have been postulated; these include prevention of platelet aggregation (146), inhibition of macrophage accumulation in the intima as well as proliferation of smooth muscle cells from the media into the intima (147), interference with arterial uptake of cholesterol (148), suppression of superoxide radical formation (149), conversion of DHEA to estrogen (150), and binding of DHEA metabolite (androstenediol) to vacant estrogen receptors, and enhanced estrogen-like effects in men (151).

Clinical implications and conclusions

The cross-sectional and prospective studies reviewed in this article suggest that natural circulating androgens and estrogens have a neutral or beneficial effect on CVD in men. As stated before, firm conclusions about the relation between endogenous sex hormones and male CVD cannot be drawn. Many studies have been carried out in selected populations generally involving small numbers. Moreover, few studies investigated physiological levels of sex hormones, and not all studies adjusted their outcome for age and other cardiovascular risk factors.

With respect to the potential of sex hormone supplement-

tation in elderly men, existing data do not suggest that this is associated with a high risk of adverse events with an unacceptable risk (152, 153). The principal issues surrounding androgen administration include an increased risk of prostate carcinoma, precipitation of benign prostatic hyperplasia, an increased hematocrit, sleep apnea, gynecomastia, and water retention (153, 154). The scientific basis for these concerns is scarce. The literature available about the association between androgens and prostate cancer indicates that caution has to be taken with supraphysiological levels of androgens (152). Moreover, concerns about the effect of supplemental T on cardiac mass and blood pressure, especially when supraphysiological concentrations are reached, need to be carefully considered (46, 137). Studies of men undergoing T replacement should include prospective measurements of hematocrit, prostate-specific antigen, and cardiac mass.

Taking the results of the reviewed data and the possible side effects of androgens into account, we would, for the time being, advise against androgen therapy unless male patients have both the presence of clinical symptoms (155) and reduced (bioavailable) T levels (in combination with high LH levels), indicating hypogonadism. When previously mentioned conditions are fulfilled, clinicians could consider measuring the androgen status of men with a high cardiovascular risk profile. It is, however, too early to consider low serum levels of androgens as an important risk factor for CVD. Furthermore, in today's clinical and research settings, there is a lack of consistency in the term "androgen status" (6). Morley *et al.* (155) developed and validated a questionnaire for androgen deficiency in aging males that may be useful in identifying males in need for hormonal measurements for hypogonadism.

There is a need for studies of the possible benefits of high levels of endogenous androgens in the prevention of heart disease in men, especially large-scale prospective studies and randomized trials involving men with low serum levels of androgens, to firmly establish their role in the prevention and treatment of CVD.

Acknowledgments

Received April 8, 2003. Accepted August 1, 2003.

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This work was supported by the International Health Foundation, Geneva, Switzerland.

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