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Male sex is an acknowledged risk factor for many forms of cardiovascular disease, and vascular disease prevalence patterns appear to be different in men versus women. The vascular properties of the principal mammalian androgen, testosterone, are complex and linked to dose, duration of exposure, presence of underlying vascular disease, and, possibly, biological sex. Data from isolated vessels and animal models suggest that pharmacological doses of testosterone, or its potent intracellular metabolite dihydrotestosterone, produce vasodilation. Testosterone's major effect on vascular beds at physiologic concentrations remains unclear, with documentation of both vasodilatory and vasoconstrictive actions. Results of various studies suggest that testosterone can alter vascular tone through both endothelium-dependent and endothelium-independent mechanisms in a variety of vascular beds and vessel types. Testosterone's endothelium-dependent effects are likely mediated at least in part through nitric oxide (NO) elaboration, whereas mechanisms of endothelium-independent effects involve 1 or more types of smooth muscle ion conductance channels. Data from clinical studies indicate that, in men, androgen replacement may provide beneficial effects when coronary artery disease is present. Conversely, in women, testosterone may augment existing hypertension, increase risk for cardiovascular events, or promote atherogenesis. However, it should be emphasized that most of these observations are anecdotal or come from small-scale clinical studies, and limited information is available in women. New research is required to understand the potential efficacy of androgen therapy, or lack thereof. This review focuses on current understanding of testosterone's physiological effects on vascular behavior and of testosterone's putative role in vascular health and disease.

Key words: *androgens, blood flow, sex biology, testosterone, vascular behavior, sexual dimorphism*

Male sex is an acknowledged risk factor for many forms of cardiovascular disease, and vascular disease prevalence patterns appear to be different in men versus women. However, a substantial knowledge gap exists concerning the vascular consequences of androgen decline in aging men (the so-called andropause). Similarly, little is known about the effect of supranormal androgen levels in men or women. In comparison to female sex hormones, relatively few studies of androgens as vascular mediators have been conducted in humans, and in vivo work in animal models is limited. Furthermore, androgen-specific effects on vascular targets can be difficult to isolate because testosterone and estrogen share biosynthetic pathways. Recent compelling clinical observations and anecdotal reports suggest that men with existing cardiovascular disease derive benefit from testosterone therapy, but the long-term consequences of such therapy remain unclear. This article is a review of the current understanding of

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testosterone's actions within blood vessels and of the steroid's putative role in vascular health and disease.

Testosterone Levels and Receptors

In men, normal circulating testosterone levels range from 10 to 30 nM (Winters 1999), whereas much lower levels (0.6 to 2.5 nM) are found in women (Burger 2002). Although the adrenal gland can synthesize small quantities of testosterone, testicular Leydig cells are the primary source of androgens in men (Winters 1999). Ordinarily, plasma luteinizing hormone (LH) interacts with Leydig cell surface receptors to regulate pulsatile testosterone release in a diurnal pattern, with peak levels occurring in the morning. However, other hormones, including prolactin, cortisol, insulin, insulin-like growth factor, and estrogen, are known to influence circulating testosterone (Winters 1999). In women, peripheral sites such as liver, skin, and adipose tissue provide approximately half of the circulating testosterone, whereas adrenal (25%) and ovarian sources (25%) produce the remainder (Burger 2002).

As members of the steroid superfamily, androgens originate from the cholesterol-derived precursor, pregnenolone (Fig. 1). Both estrogen and testosterone are derived directly from pregnenolone's by-product, androstenedione. In addition, androstenedione can be formed indirectly from the progesterone degradation product 17 β-hydroxyprogesterone. The enzyme 17 β-hydroxysteroid dehydrogenase (17 β-HSD) catalyzes this metabolism to testosterone and is also requisite for 17 β-estradiol production (the principal and most potent mammalian estrogen). Testosterone can be converted to 17 β-estradiol via a cytochrome P450 aromatase. Alternatively, testosterone can be metabolized to 5 α-dihydrotestosterone (DHT) via the enzyme 5-α-reductase, a step that then does not permit aromatization to estradiol.

Testosterone interacts with a single known cognate androgen receptor (AR) to initiate gene transcription (known as the "classical" steroid mechanism). However, testosterone has also been shown to produce rapid vascular effects that clearly do not involve genomic mechanisms. ARs have been identified in several human cell types, including aortic and mammary arterial cells (Chung and others 1988; Williams and others 2002) and umbilical vein epithelial cells (Ling and others 2002). In the vasculature, it is not known if testosterone's activity is transduced though genomic or nontranscriptional mechanisms. Recent characterization by X-ray crystallography (Sack and others 2001) reveals that the AR shares structural similarities with estrogen receptors. As in most steroid receptors, the AR possesses both a ligand-binding and a DNA-binding domain (Elder and others 2001). Because most circulating testosterone is tightly bound to sex hormone-binding globulin (SHBG) or other proteins such as albumin, it is the free portion that is bioactive. Biologically active testosterone is thought to readily traverse plasma membranes of target cells. Intracellularly, androgen binds to cytoplasmic ARs, and then the receptor complex translocates to the nucleus (for reviews, see Winters 1999; Schwertz and Penckofer 2001; Gelmann 2002). The ligand-receptor complex binds to a hormone response element within target DNA in the promoter of the target gene, altering transcription and consequently protein translation. Recently published data describe a nontranscriptional pathway located in or near the plasma membrane (Benten and others 1999; Rubio-Gayosso 2002; Wunderlich and others 2002). Because androgens can cause rapid vasomotor responses (Yue and others 1995; Teoh and others 2000b; Tep-areenan and others 2002) that are clearly uncharacteristic of genomic pathways, nonnuclear AR signal transduction mechanisms may be important.

Direct and Indirect Effects of Testosterone on Vasomotion

Ex Vivo Studies

The picture of how androgens affect blood vessels is far from complete and is complicated by methodological issues and potential species and sex differences. Hormone systems are complex and integrative, and vessels may respond differently at supraphysiologic versus physiologic drug concentrations (Schwertz and Penckofer 2001). Classic pharmacologic studies use single vessels or vessel rings to control variables and evaluate vascular behavior, and most recent studies of testosterone have employed such techniques. Because such vessels are tested ex vivo, only a cautious generalization of the data to intact vascular beds is possible.

Table 1. Summary of Vasorelaxant Effects of Testosterone in Animal Models

Model (Sex)	Vessel Type	Vessel Effect	Reference
Rat (m, f)	Pulmonary and coronary artery sections	Dilation	English and others 2001
Dog (m, f)	Coronary artery in vivo	Dilation of epicardial and microcirculatory vessels	Chou and others 1996
Pig (m)	Coronary artery rings	Relaxation of precontracted rings	Deenadayalu and others 2001
Pig (m)	Coronary artery strips	Relaxation of precontracted strips	Crews and Khalil 1996b
Rabbit (m, f)	Coronary and aortic artery rings	Relaxation of precontracted rings	Yue and others 1995
Rat (f)	Coronary artery	Vasodilatation, but attenuated in aged animals	English and others 2000a
Rat (m)	Thoracic aorta rings	Dose-dependent relaxation of precontracted rings	Costarella and others 1996
Rat (m)	Thoracic aorta rings	Dose-dependent relaxation of precontracted rings	Honda and others 1999
Rat (m)	Thoracic aortic rings	Relaxation	Ding and Stallone 2001
Rat (m)	Isolated mesenteric arterial bed in vivo	Dose-dependent dilation	Tep-areenan and others 2002
Rat (f)	Hind limb arterial bed in vivo	Vasodilation to Ach greater in testosterone-treated rats	Tatchum-Talom and others 2002

NOTE: m, male; f, female; Ach, acetylcholine.

Testosterone can induce direct vasodilation (Yue and others 1995; English and others 2001) or direct vasoconstriction (Matsuda and others 1994; Farhat and others 1995) or can indirectly change vessel diameter by depressing responsiveness to agents that are vasodilators (Quan and others 1999). Virtually no direct studies have been conducted on human blood vessels. In other species, testosterone has been shown to dilate vessels (Table 1). An important caveat in interpreting these findings is that the testosterone concentrations required to induce vasorelaxation are often in the supraphysiologic range. Therefore, extrapolation to normal male plasma testosterone is not easy, leaving open the question of how potent physiological testosterone is as a dilator of normal blood vessels.

One potential mechanism for testosterone's vasodilating capacity is via intraconversion of testosterone to estradiol by vascular aromatase (Fig. 1). However, it is unlikely that this mechanism alone accounts for vasodilation, as inhibition of P450 aromatase fails to prevent testosterone-induced vasodilatation (Yue and others 1995; Teoh and others 2000a; Deenadayalu and others 2001; Tep-areenan and others 2002). Alternatively, testosterone could elicit vasorelaxation by stimulating nitric oxide (NO) release from endothelium. NO is a potent vasodilator liberated by the vascular endothelium by a process involving the enzyme NO synthase. Endothelial denudation or inhibition of NO synthase attenuates but does not fully abolish testosterone-induced vasodilation (Costarella and others 1996; Honda and others 1999; Ding and Stallone 2001; Tep-areenan and others 2002). These observations suggest that testosterone's action is only partially mediated through endothelial NO. Because endothelium-denuded coronary and aortic arteries (Crews and Khalil 1999b; Ding and Stallone 2001) relax in response to testosterone, an important mechanism likely involves vascular smooth muscle (VSM). Numerous ion channels within VSM have been implicated but not proven as the site of testosterone's action. These include large conductance calcium-activated potassium channels (Deenadayalu and others 2001), as well as voltage-dependent and adenosine triphosphate–sensitive (Chou and others 1996; Honda and others 1999) ion channels (for review, see Jones and others 2003). Data strongly suggest that testosterone antagonizes calcium influx through voltage-gated as well as receptor-operated calcium channels (Jones and others 2003).

Despite much evidence to support testosterone's vasodilatory properties, several studies report direct vasoconstrictive effects or suppression of vasodilatory capacity (Table 2). Such data provide evidence that testosterone replacement therapy in humans could re-

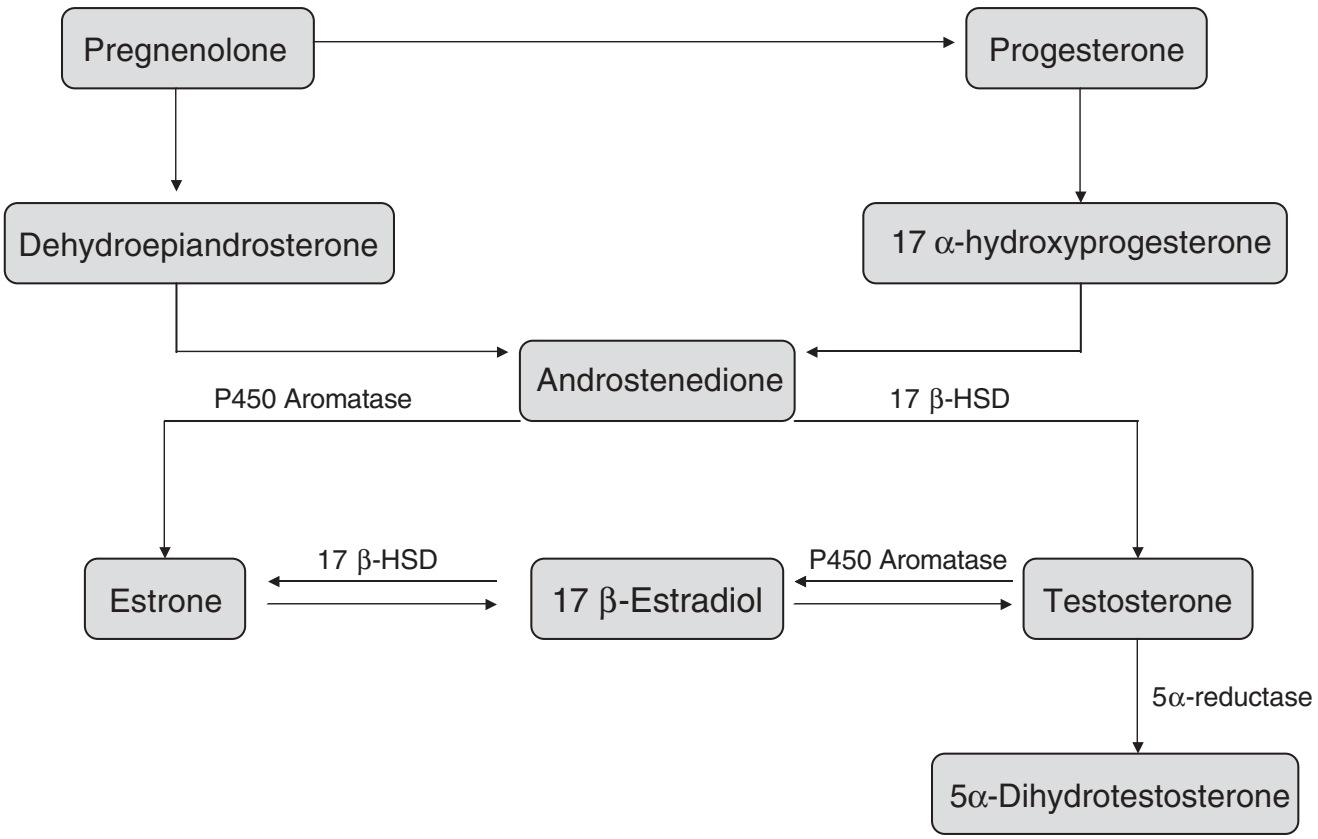

Figure 1. Simplified synthetic pathways for progesterone, estrogen, and testosterone (17 β-hydroxysteroid dehydrogenase: 17 β-HSD).

sult in unfavorable vascular consequences. For example, incubation with testosterone potentiates maximal contractile responses in coronary vessels to vasoconstrictors prostaglandin $F_{2\ alpha}$ (Farhat and others 1995) and U46619 (Karanian and Ramwell 1996). Furthermore, androgen deprivation lowers middle cerebral artery tone (Geary and others 2000), whereas testosterone repletion reverses the effect, suggesting that restoring androgen levels to normal after a period of depletion may adversely raise vessel tone in the brain. In addition to direct vasoconstriction, testosterone decreases coronary artery responsiveness to endogenous vasodilators (e.g., bradykinin) (Quan and others 1999; Teoh and others 2000a) and/or pharmacological agonists (e.g., adenosine) (Ceballos and others 1999). Impaired vasodilation is one of the earliest vascular defects associated with atherosclerosis. Therefore, reduction of vasodilatory capacity by androgens could adversely affect vascular behavior in cardiovascular disease. Mechanistically, it remains unclear how testosterone increases vascular responsiveness because relatively few studies have observed vasoconstriction per se. However, some evidence suggests that testosterone can suppress the vascular mediator prostacyclin (Nakeo and others 1981), increase vascular tone by potassium channel inhibition (Geary and others 2000), or increase vascular receptor density for the vasoconstrictor thromboxane (Matsuda and others 1994).

Clearly, testosterone's major effect on vascular reactivity is subject to a certain amount of controversy. One variable that must be considered in these ex vivo studies is the concentration used to test vessel reactivity. In a recently published paper, Teoh and colleagues (2000b) describe a variable dose-dependent effect of testosterone that may be the source of some of the conflicting data reported in previous studies. At concentrations far exceeding physiologic levels (1 μM), testosterone elicits non-endothelium-dependent relax-

Table 2. Summary of Vasoconstrictive Effects of Testosterone in Animal Models

Model (Sex)	Vessel Type	Vessel Effect	Reference
Rat (m)	Coronary arteries in isolated perfused heart	Dilation in response to adenosine inhibited	Ceballos and others 1999
Dog (f, m)	Coronary arteries	Enhanced contraction in response to U46619 and greater EC50	Karanian and Ramwell 1996
Pig (m, f)	Coronary artery rings	Inhibited relaxation in response to bradykinin and A23187. Physiologic range relaxed in precontracted rings	Quan and others 1999
Pig (m, f)	Coronary artery rings	Blunted relaxation in response to bradykinin and A23187 and was reduced when estradiol added	Quan and others 1999
Pig (m, f)	Coronary artery rings	Increased contraction in response to U46619, 5-HT, and endothelin	Teoh and others 2000b
Pig (m, f)	Coronary artery rings	Increased contractile responses	Farhat and others 1995
Rat (m, f)	Aorta	Increased maximal contractile responses	Matsuda and others 1994
Rat (m)	Aortic rings	AR receptor inhibition improved dilation to Ach	Zheng and others 2001

NOTE: m, male; f, female; Ach, acetlycholine; 5-HT, 5-hydroxytrypamine; A23187, calcium ionophore; AR, androgen receptor.

ation (Teoh and others 2000b); physiologic concentrations, however, actually potentiate contraction (Quan and others 1999; Teoh and others 2000b).

Few studies have addressed testosterone's sex-specific effect on vascular reactivity. Accumulating evidence points toward a sexually dimorphic effect in some regional vascular beds, but species is an important intervening variable. For example, dilation in response to testosterone is more pronounced in coronary and pulmonary vessels of male dogs relative to females (Karanian and others 1996; English and others 2001), but the same difference is not evident in rats (English and others 2000a). In female rats, incubation with testosterone amplifies mesenteric artery dilation responses to estradiol, and the response is more exaggerated when plasma estradiol levels are lowest (Shaw and others 2001), suggesting increased aromatization of testosterone to estradiol. Data obtained from studies in cultured vascular cells also suggest sex-specific effects of testosterone. In female but not male aortic cells, incubation with testosterone inhibits synthesis of the endogenous vasodilator prostacyclin (Wakasugi and others 1989). Parenthetically, testosterone is not the only agonist that is sexually dimorphic in the vasculature. Phenylepherine generates a more intense contractile response in the male rat than in the female (Crews and Khalil 1999a), whereas vasopressin produces greater contractile responses in females compared to males (Stallone and others 1991). Clearly, the concept of sexual dimorphism in vessel behavior is quite complex and may or may not be linked in any way to testosterone.

In Vivo Studies

In contrast to ex vivo studies of isolated vessel preparations, few studies have been conducted in intact animal models that allow assessment of vascular behavior in situ. Although data from the intact vascular network can be difficult to interpret because of multiple neuronal, biochemical, and metabolic input variables, such data more closely approximate the clinical actions of androgens. At physiologically relevant concentrations, testosterone acutely relaxes mesenteric blood vessels in the male rat (Tatchum-Talom and others 2002) and improves coronary vasodilatory capacity in response to endothelium-dependent vasodilators in the female monkey (Adams and others 1995). At supraphysiologic concentrations, the androgen decreases coronary arterial resistance and triggers rapid dilation in canine vessels via NO mechanisms (Chou and others 1996). Therefore, at least in the coronary circulation, testosterone lowers vascular tone via endothelium- and NO-dependent mechanisms ex vivo and in vivo (Chou and others 1996; Tep-areenan and others 2002).

In vivo data also more directly address the androgen's potential role in vascular disease. Increasing evidence suggests that exogenous testosterone modulates atherosclerosis and that sex is an important variable in these actions. In the male rabbit, exogenous testosterone attenuates neointimal atherosclerotic plaque formation, up-regulates arterial androgen receptor density (Hanke and others 2001), and reverses aortic atherosclerosis produced by castration (Alexandersen and others 1999). In contrast, 2 separate studies report that in females, chronically high testosterone levels may produce undesirable augmentation of atherosclerosis (Adams and others 1995) and hypertension (Tatchum-Talom and others 2000). One elegant study of female nonhuman primates demonstrated a proatherosclerotic effect of hypertestosteronism but a paradoxical reversal of the impaired vasodilation that accompanies atherosclerosis (Adams and others 1995). Genetically hypertensive female rats treated with chronic testosterone experience increases in mean blood pressure and vascular resistance (Tatchum-Talom and others 2002). However, there is again a paradoxical benefit conferred by the treatment because endothelium-dependent dilation was augmented, which would mitigate hypertension-induced pathology. As discussed below, these data are consistent with clinical data showing that testosterone treatment can be detrimental to females with cardiovascular disease, particularly if a preexisting injury to the endothelium is present.

Androgen involvement in cerebrovascular disease remains unclear. In experimental stroke models, plasma testosterone levels correlate positively with expansion of the ischemic lesion size in rats (Hawk and others 1998). Castration reduces both ischemic brain damage and attenuates abnormalities of cerebral blood flow during recovery from ischemia (Hawk and others 1998; Yang and others 2002). Conversely, other studies show that castration has little effect on brain damage from experimental stroke in young male rats (Toung and others 1998). It is important to note, however, that there are no data available in aging animals. Because aging men are at greater risk for stroke than their younger counterparts, such data could be important to understanding clinical cerebrovascular disease. Last, there is a suggestion that testosterone moderates vasomotor function in animal models of complex pathophysiological states such as hemorrhage. In male rodents, administration of a testosterone-receptor antagonist prevents cardiac dysfunction after systemic trauma and hemorrhage (Remmers and others 1997; Ba and others 2001). AR antagonists spare kidney and splanchnic organ blood flow, restoring endothelium-dependent arterial dilation (Zheng and others 2001).

Clinical Studies in Adult Men and Women

Studies on the vascular effects of testosterone in normal human volunteers are limited. In studies of blood flow within the male reproductive system, testosterone has potent effects on genital perfusion. Blood levels of testosterone obtained from the penile cavernous body correlate with surges in blood flow during sexual arousal, increasing during erection and rapidly falling during detumescence (Becker and others 2001). The importance of testosterone in sexual function is well known and illustrated by the fact that testosterone therapy augments cerebral blood flow to the midbrain and the superior frontal gyrus (Azad and others 2003) in hypogonadal men. These data are notable because they emphasize that androgen-induced changes in vascular tone can be widespread in the clinical setting.

Anecdotal evidence suggests that testosterone is beneficial in men with cardiovascular disease through its actions on blood pressure, reduction of atherosclerotic pathology, and enhancement of coronary perfusion. Recent studies show that testosterone levels in men are inversely related to mean arterial and diastolic blood pressure (Muller and others 2003; Rosmond and others 2003) and to arterial wall thickness (van der Beld and others 2003). Men with established coronary artery disease (CAD) exhibit lower free testosterone levels as compared to healthy controls (English and others 2000b). In this same clinical setting, androgens enhance coronary arterial vasodilatation and improve myocardial performance. For example, testosterone or its metabolite DHT lowers coronary artery tone and subsequently augments myocardial perfusion (Rosano and others 1999; Webb and others 1999a; Webb and others 1999b; English and others 2000c). Intracoronary testosterone infusion triggers relaxation of coronary arteries and augments blood flow in men with diagnosed CAD (Webb and others 1999a). Testosterone may also affect exercise-induced myocardial

ischemia. Both acute intravenous and chronic transdermal testosterone therapy delay the onset of exercise-induced S-T segment depression in men with chronic, stable angina (Rosano and others 1999; English and others 2000c). The steroid also extends total exercise time before development of myocardial ischemia and shortens return of the S-T segment to the isoelectric line (Rosano and others 1999).

The mechanism(s) by which testosterone produces these salutary actions is not clear. Aggregate data suggest that the steroid improves vascular tone with consequent impact on clinical disease parameters. One important question is whether vascular endothelium versus smooth muscle cells are key players in testosterone's effect on tone. Classically, investigators have employed flow-mediated brachial artery reactivity (FMR) as a noninvasive measure of endothelium- and non-endothelium-dependent activity (Anderson and others 1995). Studies using FMR to evaluate testosterone demonstrate that dose, route, and duration of administration are important to mechanism of action. For example, men with preexisting CAD display few changes in endothelium-dependent FMR when treated acutely with low-dose testosterone, whereas those receiving high concentrations demonstrate large increases in FMR (Ong and others 2000). Healthy postmenopausal women receiving parenteral testosterone/estrogen/progestin drug regimens demonstrate higher FMR and better endothelium-dependent vasodilation relative to controls treated solely with ovarian steroids (Worboys and others 2001). In men, chronic low-dose oral testosterone augments both endothelium-dependent and endothelium-independent FMR (Kang and others 2002). However, no benefit was observed with chronic transdermal testosterone treatment of otherwise healthy men with low testosterone (Kenny and others 2002).

Not only are route and duration of therapy important factors in interpreting clinical studies of testosterone, but the presence or lack of underlying disease state also may be critical. As detailed below, androgens (not specifically testosterone) may trigger deleterious vasomotor symptoms in healthy individuals quite opposite from those observed in individuals with disease- or trauma-damaged vascular endothelium. Supplemental androgens impair endothelium-dependent arterial relaxation in postmenopausal women (Penotti and others 2001), women on high-dose androgens for nonvascular concerns (McCredie and others 1998), male bodybuilders (Herman and others 1997), and orchidectomized men (Ebenbichler and others 2001). For example, flow-mediated dilation (FMD) is modestly diminished in male bodybuilders taking anabolic-androgenic steroids to enhance athletic performance (Ebenbichler and others 2001). Testosterone depletion in otherwise healthy men improves FMD in the brachial artery but leaves endothelium-independent dilation unaltered (Herman and others 1997).

Last, there is some evidence that women with vascular disease may not respond identically to androgens (not necessarily testosterone) as do their male counterparts. Several studies in women suggest an association between androgens and potential enhancement of cardiovascular disease. Recent retrospective analysis of the Women Health Initiative Study established a strong positive association between low SHBG, high free androgen index, and cardiovascular disease development in postmenopausal women (Rexrode and others 2003). It must be noted, however, that body mass index or other cardiovascular risk factors may have confounded these findings. Elevated testosterone is present in women with hypertension of differing etiologies (Phillips and others 1997a; Jirecek and others 2003), although this is not necessarily a causal relationship. Higher testosterone levels have been correlated with a reduction of both the coronary artery diameter (Phillips and others 1997b) and the carotid artery cross-sectional area (Bernini and others 1999). Last, the hyperandrogenism of polycystic ovary syndrome (PCOS) and the higher incidence of coronary disease in women with PCOS provide indirect evidence to support an association between testosterone and CAD. Although women with PCOS demonstrate higher peripheral 5-α-reductase activity (Fassnacht and others 2003) and increased carotid wall thickness (Talbott and others 2000), long-term risk for cardiovascular events has not been demonstrated (Legro 2003). Unlike studies in men with existing CAD, in whom administration of exogenous testosterone is associated with improved vascular and cardiac function, the bulk of studies in women suggests a positive correlation between androgens and vascular pathology. Available data certainly emphasize that androgen supplementation in women should be undertaken with caution.

Summary

The vascular effects of the principal mammalian androgen, testosterone, are complex and linked to dose, duration of exposure, presence of underlying vascular disease, and, possibly, biological sex differences. Data from isolated vessels and animal models suggest that pharmacological doses of testosterone or its potent intracellular metabolite, DHT, produce vasodilation. Testosterone's major effect on vascular beds at physiologic concentrations remains unclear, with documentation of both vasodilatory and vasoconstrictive actions. Testosterone can alter vascular tone both by endothelium-dependent and endothelium-independent mechanisms in a variety of vascular beds and vessel types. Testosterone's endothelium-dependent effects are likely mediated at least in part though NO elaboration, whereas mechanisms of endothelium-dependent effects involve 1 or more types of VSM ion channels. Data from clinical studies indicate that, in men, androgen replacement may provide beneficial effects when CAD is present. Conversely, in women, testosterone may augment existing hypertension, increase risk for cardiovascular events, or promote atherogenesis. However, it should be emphasized that most of these observations are anecdotal or come from small-scale clinical studies, and limited information is available in women. Therefore, more information is essential before large-scale clinical trials can be carried out. These are important issues that affect nursing given the controversy surrounding the safety and efficacy of androgen supplementation in heath and disease.

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