

Beneficial and Adverse Effects of Testosterone on the Cardiovascular System in Men

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Context: The widespread use of T therapy, particularly in aging males, necessitates knowledge of the relationship between T and the cardiovascular system.

Evidence Acquisition: The review is based on a 1970 to 2013 PubMed search with terms related to androgens in combination with cardiovascular disease, including T, dihydrotestosterone, trial, mortality, cardiovascular disease, myocardial infarction, blood pressure, endothelial function, dyslipidemia, thrombosis, ventricular function, and arrhythmia. Original articles, systematic reviews and meta-analyses, and relevant citations were screened.

Evidence Synthesis: Low T has been linked to increased blood pressure, dyslipidemia, atherosclerosis, arrhythmia, thrombosis, endothelial dysfunction, as well as to impaired left ventricular function. On the one hand, a modest association is suggested between low endogenous T and incident cardiovascular disease or cardiovascular mortality, implying unrecognized beneficial T effects, residual confounding, or a relationship with health status. On the other hand, treatments with T to restore “normal concentrations” have so far not been proven to be beneficial with respect to cardiovascular disease; neither have they definitely shown specific adverse cardiovascular effects. The cardiovascular risk-benefit profile of T therapy remains largely evasive in view of a lack of well-designed and adequately powered randomized clinical trials.

Conclusions: The important knowledge gap as to the exact relationship between T and cardiovascular disease would support a cautious, restrained approach to T therapy in aging men, pending clarification of benefits and risks by adequately powered clinical trials of sufficient duration. (*J Clin Endocrinol Metab* 98: 4300–4310, 2013)

Observational studies of associations between endogenous androgens and cardiovascular disease (CVD) are most often of cross-sectional design not allowing inference on causal relationships, whereas interpretation of available prospective cohort studies is hampered by insufficient possibilities to exclude residual confounding of risk for cardiovascular events. Clearly, use of T therapy that is beneficial, or at least safe, should be based both on a thorough understanding of the relationship between endogenous androgens and CVD in conditions of health and disease and on findings of controlled trials with relevant endpoints, with appropriate design, and of sufficient du-

ration. Unfortunately, experimental evidence for potential beneficial or adverse effects of T on the cardiovascular system is rather limited. First of all, there are no published reports on randomized clinical trials with the primary goal to evaluate T effects on incident cardiovascular events. Furthermore, many of the T trials were conducted in diseased men, such as men with alcoholic cirrhosis (1), chronic renal disease on dialysis (2), rheumatoid arthritis (3), cognitive decline (4), malnutrition (5), frailty (6, 7), coronary artery disease (8), heart failure (9), metabolic syndrome or type 2 diabetes (10, 11), thereby limiting interpretation and generalization of results. A small num-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

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Received April 14, 2013. Accepted August 20, 2013.

First Published Online September 24, 2013

Abbreviations: AR, androgen receptor; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.

ber of T trials have been performed in men who suffered solely from hypogonadism (12–16). However, in almost every study in diseased and/or hypogonadal men, characterization of the baseline cardiovascular risk profile and methodology to establish the incidence of cardiovascular events were generally poor.

The present narrative review aims to summarize present knowledge and to identify ways to increase the insight into potential beneficial and adverse effects of T on the cardiovascular system in men.

Physiological Action of T on the Cardiovascular System

The Leydig cells in the testes produce most of T in the circulation, with minor contribution from precursor androgens secreted by the adrenal cortices. Most T in the circulation (97–99%) is bound to plasma proteins, ie, tightly bound to SHBG and with lower affinity to albumin. Free T and at least part of the hormone loosely bound to albumin, together referred to as bioavailable T, are thought to freely diffuse into target cells and bind to the androgen receptor (AR) either directly or after 5α -reduction to dihydrotestosterone (17). SHBG-bound T may enter the cell by endocytosis (18). The contribution of free vs total T to final androgen effects is controversial. However, in a recent meta-analysis, the magnitude of effect size of free vs total T and CVD endpoints was robustly similar (19). Androgens display predominantly genomic effects, but there is also evidence for nongenomic effects, which contribute to considerable variation in duration of androgen actions (20).

Genomic effects involve binding of T or dihydrotestosterone to the AR and migration of the androgen-AR complex to the cell nucleus, where it induces transcription of specific segments of DNA. ARs are ubiquitously expressed in nearly all mammalian tissues, including cells from the cardiovascular system, like vascular smooth muscle and endothelial cells, myocardial fibers, macrophages, and platelets. The general mechanism of action and clinical implications of alterations in expression and degradation of the AR have been extensively reviewed by Lee and Chang (21). In addition to ligand binding, transcriptional activity of the AR is affected by coregulators that influence a number of functional properties of the AR, including ligand selectivity and DNA binding capacity, reviewed by Heinlein and Chang (22).

Furthermore, a functional polyglutamine tract polymorphism in the AR, encoded by a CAG triplet repeat in exon 1 of the AR gene, can influence the strength of the transcriptional response with a longer tract associated

with lower AR activity (23). Interestingly, one study reported that a low number of CAG repeats is associated with lower levels of high-density lipoprotein cholesterol and reduced endothelial response to ischemia, both known risk factors for coronary heart disease (CHD) (24).

The nongenomic effects of androgens are rapid as compared to the genomic effects and include the activation of kinase-signaling cascades and modulation of intracellular calcium levels, as reviewed extensively by Heinlein and Chang (25).

Finally and importantly, T is a prohormone because it is converted by the enzyme 5α -reductase to dihydrotestosterone, and T also exerts indirect effects through activation of estrogen receptors, after aromatization into estradiol by the aromatase (P450a) enzyme. Although both T and estradiol impact on the cardiovascular system (26, 27), the degree of conversion of T into estradiol might be important with respect to the balance between beneficial and adverse effects, as will be further discussed. The relationship between circulating androgens and clinical effects is further complicated by the potential for occurrence of 5α -reduction and/or aromatization locally in cardiovascular target tissues.

Androgens and Cardiovascular Risk Factors

Blood pressure

Epidemiological findings show that endogenous T and blood pressure are inversely correlated. Low T might be predictive of hypertension in aging males, but it is not established whether hypertension is the cause or consequence of low T (28). However, T treatment had no effect on blood pressure in hypogonadal males with type 2 diabetes or the metabolic syndrome (10) and resulted in a borderline significant increase in hypogonadal and older men (15). Dihydrotestosterone slightly decreased systolic blood pressure (borderline significantly) in healthy men (29). Studies in rat models provide a potential explanation for this complexity by showing that genetic background might determine prohypertensive effects of T. One study found that smooth muscle cells derived from rats with a genetic predisposition to arterial hypertension showed an increased responsiveness to T (30, 31). Another study showed that T supplements significantly increased mean arterial pressure in obese, but not in lean, Zucker rats (32), despite increased proteinuria and accelerated renal injury in the latter (32). The authors therefore suggested careful monitoring of blood pressure and renal integrity after treatment of obese men with chronic T supplements (32).

Endothelial progenitor cells and endothelial function

Cardiovascular health is dependent on angiogenesis, which might be stimulated by androgens in a sex-specific manner (33), and on proper endothelial healing after injury. The latter process is regulated by endothelial progenitor cells derived from bone-marrow cells (34). Some studies reported the endothelial progenitor cell number to be lower in hypogonadal men as compared to healthy control subjects (35), and that T and dihydrotestosterone could stimulate endothelial progenitor cells via the AR (36, 37). However, others found no direct effects of androgens on endothelial progenitor cell biology either in vitro or in vivo (38).

Reduction of endothelium-dependent, flow-mediated vasodilatation has been suggested to be an important predictor of atherosclerosis (39). Although some authors reported an adverse effect on flow-mediated vasodilatation by T therapy in hypogonadal men (40, 41), others suggested the opposite. Long-term oral supplemental administration of T was reported to improve brachial arterial vasoreactivity in men with coronary artery disease (42). Furthermore, a study on intracoronary T infusion showed coronary vasodilatation and increased coronary blood flow in men with low plasma T and CHD (43). Finally, an 8-week treatment with oral T undecanoate in men with CHD resulted in decreased basal arterial stiffness, possibly by a modest positive effect on myocardial perfusion (44). Possibly, discrepancies between studies might be explained by differences in the dose of T supplied, which was supraphysiological in the study on coronary vasodilatation (43).

Dyslipidemia

Obesity-associated alterations in circulating androgens and lipids are mutually involved in the pathogenesis of associated metabolic complications. Depending on the degree of aromatization, androgens directly and indirectly affect adipose tissue adaptation to the continuing exposure to energy excess (45–47). The specific relationship between sex steroids and lipid and lipoprotein metabolism has been extensively reviewed by Wang et al. (48). Intervention studies in hypogonadal men with type 2 diabetes and in elderly males show that exogenous T therapy has no effect on lipids (7, 10, 16) or is associated with a decrease in high-density lipoprotein cholesterol (15, 49). A recent metabolic study on lipid oxidation and very low-density lipoprotein-triglyceride production suggests that T is not a major determinant of resting very low-density lipoprotein-triglyceride kinetics in men (50).

Thrombosis

Abuse of anabolic-androgenic steroids by athletes has been associated with the development of myocardial infarction and stroke (51). T therapy may increase hemoglobin and hematocrit (49) and may regulate the expression of platelet thromboxane A2 receptors in humans (52). This may contribute to thrombogenicity. Furthermore, it was found that the risk for stroke might be ascribed not only to low T (53) but also to increased estradiol concentrations (54), especially in elderly males, who have higher rates of aromatization (55). A recent study reported a link between thrombotic events, like osteonecrosis of the hips, pulmonary embolism, and amaurosis fugax, and exogenous T therapy (56). The authors linked the events to positivity for factor V Leiden mutation and other familial and acquired thrombophilias. The report suggested that the events were likely caused by aromatization of exogenous T, an estradiol-induced thrombophilia, superimposed on familial thrombophilia (56, 57). Consequently, the degree of aromatization might be a factor to take into consideration if T treatment is considered.

Left ventricular function and myocardial infarction

In a cross-sectional observational population study of 1223 healthy middle-aged men, T appeared to associate inversely and estradiol positively with left ventricle systolic function (58). Also, rodent studies suggest opposite effects of T and estradiol on the heart, especially after ischemia (59–61). Mechanistically, it has been shown that both endogenous and exogenous T decrease the activity of the cardioprotective signal transducer and activator of transcription (STAT3)/suppressor of cytokine signaling (SOCS3) pathway in the myocardium after acute ischemia and reperfusion (62). Importantly, this decrease in myocardial STAT3 activation and SOCS3 expression is associated with a worse outcome (62). Accordingly, the transient decrease in T, observed after myocardial infarction in male patients (63), may therefore be considered as adaptive and limit damage to the postischemic myocardial function. Taken together, these findings suggest that changes in the degree of aromatization might be of significance for cardiac function and outcome after a myocardial infarction.

B-type natriuretic peptide

B-type natriuretic peptide is secreted by the brain and the heart atria and is stored mainly in cardiac ventricular myocardium. It can cause natriuresis, diuresis, and vasodilation, and it inhibits secretion of renin and aldosterone. It has favorable effects on the heart function.

Although T was inversely associated with circulating levels of B-type natriuretic peptide and the N-terminal

Table 1. Summary of Prospective Observational Studies on Endogenous T and Incident CVD in Healthy Men

First Author, Year (Ref.)	Age at Baseline, y	Duration, y	No. of Events/Progression of Disease	Outcome	Abstract Conclusions of Authors
Price, 1997 (72)	55–74	5	40	AS	No support for sex hormones in the development of peripheral arterial disease
Hak, 2002 (73)	>55	7	28	AS	An independent inverse association between T and aortic atherosclerosis
Muller, 2004 (74)	77.2	4	195	AS	Low free T was related to IMT of the common carotid artery
Eller, 2005 (75)	50	4	95	AS	T was borderline significantly associated (negatively) with progression in IMT
Hougaku, 2006 (76)	68	11.8	206	AS	Adverse influence of low T on the CV system in men may be mediated in part via effects of T on vascular structure and function
Tivesten, 2006 (77)	58	3	313	AS	No association between total or free T and change in IMT
Cauley, 1987 (79)	46	6–8	163	MI	No relationship between sex hormones and risk of a heart attack
Philips, 1988 (80)	52–74	7	96	MI	No association between sex hormones and MI
Vikan, 2009 (81)	59.6	11.2	144	MI	No significant changes in risk for first-ever MI across different total or free T levels
Yeap, 2009 (53)	78.4	3.5	119	S	Lower total T predicts increased incidence of S or transient ischemic attack
Yarnell, 1993 (82)	45–59	5	153	IHD	No support for T as primary risk factor for IHD
Araujo, 2007 (83)	40 to 70	15.3	101	IHD	Little support for the hypothesis that endogenous sex steroid levels are associated with risk of premature death but further investigation of the relationship between sex steroids and mortality from ischemic heart disease may be warranted
Hautanen, 1994 (84)	48	5	62	CVD	T no coronary risk factor
Arnlöv, 2006 (85)	56	10	386	CVD	Serum T was not statistically significantly associated with incident CVD
Khaw, 2007 (86)	40 to 79	7	293	CVD	T inversely related to mortality due to CVD
Akishita, 2010 (87)	48	6	20	CVD	Low T is associated with CV events
Ohlsson, 2011 (88)	69–81	5	485	CV events	High T predicted a reduced risk of CV events
Menke, 2010 (89)	40	9	42	CM	Low T has a higher risk of CV mortality
Hyde, 2012 (90)	70–88	5.1	207	CM	Low T predicts mortality from CVD

AS, atherosclerosis measurement; IHD, ischemic heart disease; CM, cardiovascular mortality; CV, cardiovascular; MI, myocardial infarction; S, stroke or transient ischemic attack; IMT, intima media-thickness.

fragment of pro-B-type natriuretic peptide (64), evaluation of the Framingham cohort suggested that T was not the primary mediator of circulating levels of these factors (65).

Arrhythmia

Both the long QT and the short QT syndrome are associated with atrial fibrillation and sudden cardiac death (66). Experimental models show that androgens can modulate a variety of ionic currents, with the net result that repolarization is shortened, as reviewed by James et al (67). Cross-sectional observational studies suggest that T levels may explain differences in QT-interval duration between men and women and could contribute to population variability in QT-interval duration among men (68). T therapy resulted in a direct effect of T to shorten QT intervals in older men. However, the observed mean decreases were small and, according to the authors, unlikely to affect risks of arrhythmic events in patients receiving QT-prolonging medications (69). Yet, a significant impact on the interval has been shown in androgen-abusing body builders (70). The question that remains to be addressed is how these findings fit into the complex genetic and environmental etiology of repolarization disturbances (71).

Androgens and Cardiovascular Events: Evidence From Prospective Observational Studies

A major limitation of cross-sectional studies is that they are essentially hypothesis-generating in nature, whereas

prospective studies could provide information on causality. As detailed in Table 1, a total of 19 studies have addressed the prospective relationship between endogenous T concentrations and cardiovascular events.

Atherosclerosis in observational studies

Six of the 19 studies evaluated the relationship between endogenous T and progression in atherosclerosis, as assessed by peripheral arterial disease (72), atherosclerosis of the abdominal aorta (73), progression of carotid atherosclerosis (74), progression of intima media thickness (75), arterial stiffness (76), and carotid artery intima media thickness (77). These studies reported either no association or a weak association between low T and progression of atherosclerosis. Accordingly, a meta-analysis of the data obtained for nearly 900 men with progression of atherosclerosis could not establish a statistically significant risk difference by endogenous T levels (1 SD) for atherosclerosis (19).

Incident cardiovascular events in observational studies

Two meta-analyses based on the findings of prospective studies on T and incident CVD (19) and mortality (78) identified an inverse association between T and incident CVD and mortality in elderly males. The conclusions of the meta-analyses and the earlier prospective studies (79–86) were supported by more recent prospective studies (87–90). Studies directed at the association between T and incident myocardial infarction did not reveal a relationship (79–81). Results from studies evaluating incident

CVD, ischemic heart disease, or cardiovascular death revealed more heterogeneous results (82–90). Nevertheless, all prospective studies taken together, which report on more than 2500 events, including incident CVD, ischemic heart disease, myocardial infarction, stroke, and cardiovascular death, are suggestive of a modest association between low endogenous T and incident cardiovascular events (Table 1).

Androgens and Cardiovascular Events: Evidence From Studies With T Treatment

A recent meta-analysis on exogenous T on cardiovascular-related events displayed a difference according to the source of funding, with an increase in risk in studies that were not funded by the pharmaceutical industry (91). However, randomized clinical trials with the primary endpoint to establish beneficial and adverse effects of T treatment vs placebo on incident cardiovascular events have not been published so far. Randomized clinical trials conducted in patients with hypogonadism reported small improvements in sexual function, bone mineral density, and muscle strength (7, 9), whereas randomized clinical trials

conducted in males with other underlying disorders (see introductory section), using a variety of dosages and treatment modalities, reported inconsistent results. Part of the difference in adverse events might already be explained by, eg, treatment modalities (92). These trials varied further with respect to duration from a few weeks to a maximum of 36 months, and handling of the cardiovascular risk profile at baseline and events at follow-up was generally limited.

To gain robust insight, we selected randomized, double-blind, placebo-controlled T trials that included more than 100 participants (1, 6, 7, 10–16) (Table 2). Five of the 10 identified trials reported T effects on lipids (7, 10, 13, 15, 16), and four trials reported blood pressure results (6, 10, 12, 15). Overall, no statistically significant difference between placebo and T treatment could be established, as shown by an estimated relative risk (RR) (95% confidence interval [CI]) of 1.64 (0.77–3.47) (all studies, Table 2, random-effects model), most likely due to a low number of events in all studies together ($n = 69$). The reported cardiovascular events in the T-treated participants included (in order of frequency) arrhythmia, hypertension, myocardial infarction, peripheral edema, coronary artery by-

Table 2. Summary of T Trials, Including More Than 100 Participants, and Reporting Cardiovascular Adverse Events

Author, Year (Ref.)	Age, y	Health Status/Low T (Y/N)	Duration, mo	T Dose	Randomization No., Placebo vs T	Lipids/BP After T	No. of Placebo vs T, CVD Events
Copenhagen Study Group, 1986 (1)	24–79	Alcoholic cirrhosis/N	28	Oral 600 mg/d	87:134		0:3, thrombosis
Snyder, 2001 (16)	>65	Y	36	Transdermal patch 6 mg/d	54:54	Lipids ↔	1:2, myocardial infarction; 2:2, CABG; 1:3, arrhythmia; 1:2, vascular events
Emmelot-Vonk, 2008 (15)	60–80	Y	6	Oral TU 160 mg/d	110:113	↓ HDL; ↑ BP ($P < .08$)	3:7, cardiovascular complaints
Legros, 2009 (14)	≥50	Y	12	Oral TU 80, 160, 240 mg/d	79:237		0:2, arrhythmia, cardiac arrest
Srinivas-Shankar, 2010 (7)	≥65	Frailty/Y	6	Transdermal gel 50 mg/d	132:130	Lipids ↔	1:0, myocardial infarction; 1:1, abdominal aneurysm; 0:2, pulmonary embolism, heart failure
Basaria, 2010 (6)	≥65	Limitations in mobility/Y	6	Transdermal gel 100 mg/d	103:106		1:2, syncope; 2:4, arrhythmia; 1:3, hypertension; 1:0, carotid-artery plaque; 0:5, coronary syndrome, chest pain, ischemia; 0:4, myocardial infarction, CABG, death due to myocardial infarction; 0:5, peripheral edema; 0:1, stroke; 0:1, heart failure
Kalinchenko, 2010 (11)	35–70	Metabolic syndrome/Y	7.5	Parenteral TU 1000 mg im at baseline, 6 and 18 wk	71:113	Lipids ↔	2:0, angina, myocardial infarction ^a
Jones, 2011 (10)	≥40	Type 2 diabetes or metabolic syndrome/Y	12	Transdermal gel 60 mg/d	112:108	Lipids ↔; BP ↔	12:5 ^b
Ho, 2011 (13)	≥40	Symptoms of T deficiency/Y	12	Parenteral TU 1000 mg im at baseline, 6, 18, 30, and 48 wk	60:60		1:1, died due to myocardial infarction; 1:1, chest pain
Kaufman, 2011 (12)	18–80	Y	6	Transdermal 1.62% gel 2.5 mg/d	40:234		0:11, vascular disorders

Abbreviations: TU, T undecanoate; HDL, high-density lipoprotein; BP, blood pressure; Y, yes; N, no.

^a According to report on discontinuation of intervention (Ref. 11, p 606).

^b According to safety report (phases 1 and 2) (Ref. 10, p 835).

pass graft (CABG), thrombosis, cardiovascular complaints, heart failure, chest pain, vascular events, syncope, stroke, pulmonary embolism, and abdominal aneurysm (Table 2). The most remarkable study was performed in 209 men 65 years of age or older who had limitations in mobility and low serum levels of total or free T (7). The trial was stopped before enrollment had been completed because of an incidence of adverse cardiovascular events that was higher in the T group than in the placebo group. Authors have argued that the generalizability of the data of this study about the safety of T therapy is limited by the fact that cardiovascular events were not a preplanned primary or secondary outcome, and therefore, a structured evaluation of cardiovascular events was not performed, a factor that may have influenced the ascertainment of events. Two studies evaluating specifically the effect of T on atherosclerosis and arterial stiffness are presently ongoing or recently completed (ClinicalTrials.gov, NCT00287586 and NCT00355537, respectively).

Androgens and Cardiovascular Subpopulations

Chronic heart failure

Chronic heart failure in men is associated with anabolic hormone depletion, and deficiency of circulating total and free T, dehydroepiandrosterone sulfate, and IGF-I has been suggested to be an independent marker of poor prognosis (93, 94). Trials with T therapy have been conducted in these patients with chronic heart failure, and a meta-analysis of 4 such trials indicates a treatment effect on improved functional capacity (95). An effect of T therapy on mortality has not been established, but a study on mortality (ClinicalTrials.gov, NCT01377103) is ongoing. Another study showed that physiological T replacement reduced QT dispersion in a heart failure cohort (96); T therapy had no effect on the rhythm in a cohort with stable coronary disease (96).

Coronary artery disease

Patients with stable angina have been shown to display reduced exercise-induced myocardial ischemia after low-dose supplemental T treatment (8, 97). These findings are supported by associations of altered androgen status with ST segment changes (98).

Obstacles and Limitations of Observational Studies

Assay, time of blood sampling, and the use of free, bioavailable, and total T

A source of variability in the interpretation of large epidemiological studies might be the quality of T assay as

well as the time of blood sample collection. T secretion displays a diurnal variation with highest serum concentrations early in the morning in younger men. Blood sample collection time was identified as a source of heterogeneity ($P < .03$) in a review on T and mortality (78). Studies that used morning samples (yes vs no) had an estimate RR (95% CI) of 1.15 (0.94–1.41), and studies that did not use morning samples had an increased estimate RR (95% CI) of 1.61 (1.28–2.03) for mortality. The same meta-regression analysis did not reveal differences according to the type of T assay (platform-based immunoassay vs gas chromatography/tandem mass spectrometry or RIA with extraction) with respect to mortality (78).

Presentation of the data according to total, free, or bioavailable concentrations may also cause confusion in interpretation of the data. First, there are issues as to the accuracy and comparability of different assay techniques and calculations used to estimate free and bioavailable T fractions (99). Second, there are also potential conceptual issues. For example, data presenting the relationship between total T and incident diabetes may differ from data presenting the relationship between free T and incident diabetes. Data with a statistically significant association between free T and incident type 2 diabetes suggest a direct sex steroid effect (100), whereas data with total T might reflect the relationship between SHBG and diabetes; low SHBG is a strong predictor of diabetes (101). SHBG levels correlate positively with insulin sensitivity (102), and a decrease in SHBG is correlated to a decrease in insulin sensitivity, which is a known feature preceding type 2 diabetes. A decrease in insulin sensitivity is also associated with low-grade systemic inflammation, which precedes CVD.

Aromatization

The rate of aromatization affects androgen concentrations through strong negative feedback inhibition of gonadotropin and T secretion exerted by estradiol (103). The rate of aromatization is higher in older men, partly related to higher percentage fat mass (55). Whether differences in circulating estradiol concentrations resulting from variation in aromatization per se affect CVD needs to be further investigated.

Genetic polymorphisms

Genetic polymorphisms in SHBG (104, 105), a polymorphism in locus FAM9B on the X-chromosome (104), and the CAG repeat polymorphism in the AR (106) have been described that impact on serum T concentrations. On the one hand, part of the genetically determined variation in serum T concentrations may reflect differences in androgen sensitivity and feedback set point (106). On the

other hand, some of these polymorphisms, as well as other genetic variants, may in turn contribute to the between-subject variation in T effects (107, 108). Thus, genetic contribution to the variability of T levels and T effects complicates the interpretation of observational studies.

Confounding

According to studies in legally castrated men and castrated male singers, who appear to have unaltered cardiovascular risk profiles and preserved life expectancy, endogenous T does not seem to have particular beneficial or adverse effects on the cardiovascular system (109, 110). Unfortunately, results of most observational studies of less healthy males of the general population might be affected by uncontrollable confounding. A variety of environmental influences may disturb clear insight into beneficial or adverse androgen effects on the cardiovascular system. Confounding may be considered a mixing of effects: the estimate of the effect of the exposure of interest, T, is distorted because it is mixed with the effect of an extraneous factor (111). Examples of relevant extraneous factors are smoking, medications, infectious diseases, alcohol, and physical activity. Examination of published prospective studies shows a wide variation in the way adjustment for confounding was performed (19). In fact, this item is probably one of the main obstacles to gaining unequivocal insight from observation studies, mainly because not all extraneous factors are confounders; some factors are in fact involved in the pathogenesis of androgen-related cardiovascular effects. For example, on the one hand, deterioration of body composition is associated with low T, and deterioration of body composition is related to the risk for metabolic syndrome, type 2 diabetes, and CVD. On the other hand, low T levels might deteriorate body composition (112). The question thus is whether a change in body composition precedes a change in sex steroid concentrations, or is the converse the case?

Two prospective studies revealed a role of low T for the development of the metabolic syndrome and type 2 diabetes (100, 113), and one study displayed risk of the presence of metabolic syndrome for low T (114). In the former two prospective studies, the baseline body mass index was already deteriorated (100, 113), suggesting that a change in body composition precedes a change in sex steroids. One may also argue that the main portion of an increase in body mass index will be caused by continuing energy excess, and that the contribution of sex steroids will probably be limited. Further arguments for the sequence of events are provided by normalization of T after weight loss by Roux-en-Y bypass surgery (115) and by the inverse relationship between Leydig cell T secretion and insulin resistance (116). Of course, a decrease in T and an increase

in estradiol due to weight gain may by itself accelerate metabolic dysfunction (46) and may affect the cardiovascular system (58, 117). The relevance of the degree of aromatization is further illustrated by rare cases of men with congenital aromatase deficiency. These male subjects, who present with high serum T and low estradiol display abdominal obesity, early-onset metabolic syndrome, dislipidemia, and nonalcoholic fatty liver disease, with concomitant increased cardiovascular risk (118). Experiments due to these findings suggested a protective role for estradiol with respect to metabolic disease (119).

Summary

In males of the general population, a growing number of prospective studies suggest a modest association between low endogenous T and both incident CVD and cardiovascular mortality. Low endogenous T might be related to specific events such as thrombosis or arrhythmia, or, because residual confounding cannot be definitely excluded, low T may reflect a status of poorer health. In general, studies do not provide substantial evidence for a relationship between low T and atherosclerosis. Results of prospective studies on atherosclerosis (72–77) and prospective studies on incident myocardial infarction (79–81) reveal no unequivocal relationship (19). Trials with exogenous T therapy report on the occurrence of thrombosis and arrhythmia, but they are inadequately powered for CVD events.

One may speculate that potential beneficial effects of androgens may depend on an “optimal window” of T concentration, depending on age, degree of aromatization, and genetic background, whereas adverse effects might be expected in concentrations below or above this optimal window. The hypothesis is supported by adverse effects in high-normal to supraphysiological androgen levels, as sometimes used by athletes (51, 56, 69), as well as by low androgen levels and its risk for osteoporosis (17), and extremely low or absent aromatization and risk for metabolic diseases (118, 119). Dose-response trials on cardiovascular outcomes such as arrhythmias, eg, along the same lines as has been performed for the study of T effects on body composition (120), may shed some light on this issue. So far, treatment with T to restore T concentrations to this optimal window have not been proven to be beneficial with respect to CVD. Nevertheless, males with low T and specific cardiovascular conditions, eg, heart failure or coronary artery disease, may benefit from substitution therapy. A cautious, restrained approach to T therapy in aging men is advisable, pending clarification of benefits

and risks by adequately powered clinical trials of sufficient duration.

Acknowledgments

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This work was supported in part by grant G.0867.11 from the Research Foundation - Flanders.

Disclosure Summary: The authors have no competing interests to declare.

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