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Review

Hormones and Cardiovascular Disease in Older Men

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Older men have lower circulating testosterone (T) and insulin-like growth factor-I (IGF-I) but higher levels of thyrotrophin (TSH) compared with younger men, and exhibit poorer health. Whether age-associated differences in hormone levels are causally related to cardiovascular disease, or are biomarkers reflecting accumulated ill-health remains under debate. Lower T levels are associated with aortic, peripheral vascular, and cardiovascular disease in middle-aged and older men. In some but not all studies, lower levels of T predict increased incidence of cardiovascular events and mortality. Recently, dihydrotestosterone (DHT) has also been identified as a predictor for peripheral vascular and ischemic heart disease. Small scale randomized clinical trials (RCTs) of T supplementation suggest a protective effect against myocardial ischemia in men with coronary artery disease. There have been no RCTs with the prespecified outcomes of cardiovascular events or mortality. One RCT of T in older men with mobility limitations was stopped due to an excess of cardiovascular adverse events in men receiving T, but other RCTs have not raised similar concerns. Observational studies of testosterone supplementation have reported contrasting results. Levels of IGF-I and its binding proteins 1 and 3 have been variably associated with mortality in some but not all studies, and RCTs of interventions to modulate IGF-I levels are either lacking or lacking in power to examine outcomes of cardiovascular events or mortality. Subclinical hyper- and hypothyroidism predict poorer outcomes, and emerging data implicate higher levels of free thyroxine with other outcomes such as dementia and mortality in older men. However, RCTs that manipulate free thyroxine levels within the normal range are lacking and would be challenging to perform. Further research is needed to clarify the role of these hormones as predictors of cardiovascular outcomes in aging men, and to test whether interventions that modulate levels of T, DHT, IGF-I or free thyroxine would reduce cardiovascular morbidity and mortality.

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Demographic change has increased the proportion of older persons in the community, and aging is accompanied by an increasing burden of ill-health.¹ In particular, cardiovascular disease (CVD) is a major contributor to both morbidity and mortality in aging men and women.² In parallel with the age-related attrition of health and well-being, characteristic endocrine changes occur. Aging men do not undergo the equivalent of the female menopause. Instead, a gradual decline in circulating levels of testosterone (T) is seen as men grow older.^{3–5} By contrast, levels of sex hormone-binding globulin (SHBG) are higher in older compared with younger men.^{6,7} T in the circulation is bound with high affinity to SHBG and lower affinity to albumin with a small fraction unbound or free.⁸ Therefore, the reduction in T and increase in SHBG levels results in a steeper rate of decline of free T compared with total T in aging men.^{4,5} The biological significance of

free T and its value as a reflection of androgen status have been debated. Recent studies have challenged the concept that the change in T levels during male aging is an age-associated phenomenon, associating low T or changes in T with the presence of obesity or disease.^{9–12} Therefore, the crucial question is whether lower T in older men is a biomarker reflecting poorer health including CVD, or a causal contributor to incident CVD. An additional layer of complexity and uncertainty exists, as T is converted by the enzyme 5 α -reductase to dihydrotestosterone (DHT), a more potent ligand for the androgen receptor, and by aromatase into estradiol (E2), which is a ligand for estrogen receptors α and β . Circulating DHT and E2 are largely the result of peripheral conversion in men. However, the trajectories of DHT and E2 during aging and the implications of lower circulating DHT and E2 levels for health in aging men are not well defined.

As men grow older, changes occur in the growth hormone (GH)-insulin-like growth factor-I (IGF-I) axis and the hypothalamo-pituitary-thyroid axis. Older men exhibit reduced GH secretion, and this is reflected in lower levels of IGF-I.^{13,14} Clarifying the influence of reduced circulating IGF-I on health outcomes during male aging and

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Table 1

Observational Cohort Studies Examining Associations Between Sex Steroid Levels and Cardiovascular Events in Middle-Aged and Older Men

Study Author and Year	Size (n of Men)	Follow-Up (y)	Age (y)	Results
Smith GD 2005 ³⁹	2512	16.5	45–59	482 deaths, 192 fatal and 128 nonfatal IHD events. Higher cortisol: T ratio associated with IHD deaths and IHD events in age- but not multivariable adjusted analyses.
Arnlöv J 2006 ⁴⁰	2084	10	56	386 had first cardiovascular event. Higher total E2 at baseline associated with lower incidence of CVD events. T not associated.
Abbott RD 2007 ⁴¹	2197	≤7	71–93	124 had first stroke. Baseline E2 in top quintile (≥125 pmol/L) associated with higher risk, total T not associated.
Vikan T 2009 ⁴²	1318	9.1	59.6	146 men had first ever MI. No association of total or free T or total E2 with incident MI.
Yeap BB 2009 ⁴³	3443	3.5	≥70	First stroke or TIA occurred in 119 men. Total and free T in the lowest quartiles (<11.7 nmol/L and <222 pmol/L) predicted increased incidence of stroke or TIA (HR 1.99 and 1.69).
Hyde Z 2011 ⁴⁴	3637	5.1	70–88	618 men experienced IHD event. Higher LH associated with incident IHD.
Ohlsson C 2011 ⁴⁵	2416	5	69–81	485 CVD events. Men with total T* in highest quartile (≥19 mol/L) had lower risk of CVD event (HR 0.77).
Haring R 2013 ⁴⁶	254	5, 10	75.5	No associations of baseline total T or total E2 with incident CVD events.

CVD, cardiovascular disease; E2, estradiol; GC-MS, gas chromatography-mass spectrometry; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; T, testosterone; TIA, transient ischemic attack.

Unless otherwise specified, total T and total E2 were measured by immunoassay; free or bioavailable T and free E2 were calculated.

*Total T measured using GC-MS. Mortality outcomes from the studies by Vikan et al⁴² and Haring et al⁴⁶ are shown in Table 2.

the role of its binding proteins IGF-binding protein 1 (IGFBP1) and protein 3 (IGFBP3) would be a helpful prerequisite before interventional studies of GH are considered. Changes are also seen in the thyroid axis during aging. The prevalence of subclinical thyroid disease is higher in older adults.¹⁵ Subclinical hyperthyroidism manifests with thyrotrophin (TSH) levels below the reference range despite normal free thyroxine (T4) and triiodothyronine (T3) concentrations, whereas subclinical hypothyroidism is present when TSH levels are raised despite normal thyroid hormone levels.^{15,16} A more subtle age-related phenomenon is seen in the upward shift of TSH distributions in older compared with younger populations.^{17–19} These changes have necessitated a closer examination of the putative role of these components of the thyroid axis as biomarkers or causal determinants of health outcomes during aging.

Testosterone, Dihydrotestosterone, Estradiol, and Markers of Vascular Disease

Carotid intima-media thickness (CIMT) is a marker of preclinical atherosclerosis and a predictor of future CVD events.²⁰ Several observational studies have associated lower T levels with increased CIMT^{21–25} or with the presence of atheromatous plaque in the carotid artery.²⁶ However, lower T levels do not consistently predict longitudinal increases in CIMT.^{27–29} In 1 study, higher E2 levels were associated with progression of CIMT.²⁸ Lower T levels are associated with abdominal aortic calcification³⁰ and with increased likelihood of abdominal aortic aneurysm³¹ both markers of poorer vascular outcomes. Lower T levels have also been associated with the presence of peripheral vascular disease, defined by measurement of the ankle brachial index or the presence of intermittent claudication or both.^{32–35} Several of these studies used immunoassay for measurement of T and immunoassays for T (or DHT and E2) suffer from nonspecificity and method-dependent bias.^{36,37} Thus, liquid chromatography-tandem mass spectrometry (LC-MS) is the preferred methodology for sex hormone assays.³⁸ In 1 study of 2703 men aged 70–89 years where sex hormones were measured using LC-MS, lower levels of T or DHT, but not E2, were associated with the presence of intermittent claudication independently of age, smoking, obesity, and other cardiovascular risk factors.³⁵ However, cross-sectional observational studies are limited by inability to define the direction of causality.

Testosterone, Estradiol, and Incident Cardiovascular Events

Recent longitudinal studies exploring the association of baseline sex hormone levels with incident CVD events are summarized in

Table 1. Several of these have not shown an association of lower T with the incidence of CVD events such as myocardial infarction (MI) or stroke.^{39–42,46} Two of our longitudinal analyses from the Western Australian Health In Men Study (HIMS) are relevant.^{43,44} In the first, there were 3443 men aged 70–89 years followed for a median of 3.5 years with a first ever stroke or transient ischemic attack occurring in 119 of these men. Having total T in the lowest quartile of values was associated with an almost 2-fold increase in risk of stroke or transient ischemic attack after adjusting for other risk factors.⁴³ In the second analysis of 3637 men followed for 5.1 years, of whom 618 experienced an ischemic heart disease (IHD) event, lower T or higher luteinizing hormone levels were associated with incident IHD but only the association with LH persisted after adjustment.⁴⁴ Ohlsson et al reported a study of 2416 men aged 69–81 years followed for 5 years with 485 incident CVD events. Men with total T in the highest quartile of values had a lower risk of experiencing a CVD event [hazard ratio (HR) = 0.77].⁴⁵ Therefore, some of these large observational cohort studies support an independent association of lower baseline T levels with increased incidence of CVD events. E2 was variably and inconsistently associated with CVD events. E2 measured by immunoassay was negatively associated with incident CVD in 1 study,⁴⁰ positively associated with stroke in a different study,⁴¹ and not associated with CVD events in 2 other studies.^{42,46} Interpretation of these studies is further hampered by the use of immunoassay for E2, which is sub-optimal at the low levels found in men.^{38,47}

Testosterone and Mortality

Longitudinal studies examining the association of baseline sex hormone levels with all-cause and CVD-related mortality are shown in Table 2. Lower levels of total T have been associated with all-cause mortality^{42,46,48,49,52,53,56} and with CVD-related deaths.^{49,52,56} Lower levels of calculated free T have also been associated with all-cause^{42,55,57} and CVD-related mortality.^{55,57} However, there have been equivocal or inconsistent results, with 1 study suggesting a positive association of free T with IHD mortality⁵⁰ and another finding higher mortality only in men with the combination of low T, IGF-I, and dehydroepiandrosterone sulphate.⁵¹ Furthermore, there are issues to be considered in interpreting these results. These studies include separate analyses from the same cohort. Few of these studies used LC-MS rather than immunoassay for total T, and free T was calculated rather than assessed by equilibrium dialysis.^{59–62} Considerable heterogeneity was noted between the different studies limiting the usage of meta-analysis.⁶³ Therefore, larger and more comprehensive studies are required including the T metabolites DHT and E2.

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