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INVITED REVIEW

Male Endocrinology

Endogenous testosterone and mortality risk

Emily J Meyer^{1,2}, Gary Wittert^{1,2,3}

In men, obesity and metabolic complications are associated with lower serum testosterone (T) and dihydrotestosterone (DHT) and an increased risk of, and mortality from, multiple chronic diseases in addition to cardiovascular disease (CVD). The causal interrelationships between these factors remain a matter of debate. In men with untreated congenital and lifelong forms of hypogonadotropic hypogonadism, there appears to be no increased risk. Men with Klinefelter's syndrome have an increased risk of various types of cancers, as well as CVD, which persist despite T therapy. In the absence of pathology of the hypothalamic–pituitary–gonadal axis, the effect of modest reductions in serum T in aging men is unclear. The prevalence of low serum T concentrations is high in men with cancer, renal disease, and respiratory disease and is likely to be an indicator of severity of systemic disease, not hypogonadism. Some population-based studies have found low serum T to be associated with a higher risk of deaths attributed to cancer, renal disease, and respiratory disease, while others have not. Although a meta-analysis of longitudinal studies has shown an association between low serum T and all-cause mortality, marked heterogeneity between studies limited a firm conclusion. Therefore, while a decrease in T particularly occurring later in life may be associated with an increase in all-cause and specific types of mortality in men, the differential effects, if any, of T and other sex steroids as compared to health and lifestyle factors are unknown at the current time.

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INTRODUCTION

This review aims to provide a perspective on the evolving evidence base relating to endogenous circulating testosterone (T) and its association with all-cause mortality and cause-specific mortality by examining data relating to long-standing treated and untreated forms of congenital hypogonadism, hypogonadism acquired late in life, and from longitudinal population-based cohort studies.

HYPOGONADISM INDUCED BY ANDROGEN DEPRIVATION THERAPY (ADT) IN MEN WITH PROSTATE CANCER (PCa)

Men with PCa who are treated with surgical or medical castration (resulting in extremely low or undetectable serum concentrations of T and its major metabolites, estradiol, and dihydrotestosterone) have a higher prevalence of all-cause mortality¹ as well as cardiovascular disease (CVD)-specific mortality.^{1–5} Men with a history of any form of cardiac or cerebrovascular disease or diabetes are at greatest risk of all-cause mortality independent of the level of risk from the PCa, even with short course of ADT.^{2–5} Furthermore, the combination of a low pretreatment serum T level and multiple preexisting comorbidities is associated with decreased overall survival following ADT for PCa.^{4,6–8} This suggests an interaction between T and other risk factors to increase all-cause mortality in these men.

CONGENITAL HYPOGONADOTROPIC HYPOGONADISM (HH)

Men with congenital forms of HH untreated to their late teens and early twenties have increased adiposity, endothelial dysfunction,

inflammation, insulin resistance,⁹ and carotid intima-media thickness (CIMT)¹⁰ compared to age-matched healthy controls. After 6 months of T-replacement therapy, cardiometabolic risk markers appear to worsen rather than improve,⁹ but after 9 months of treatment, improvements compared to baseline are seen.¹¹ There is limited mortality data on lifelong untreated HH, but there appears to be no increased risk of CVD.¹² After T treatment has been instituted, a short-term (2-week) withdrawal of T leads to an increase in fasting insulin.¹³

KLINFELTER'S SYNDROME

Klinefelter's syndrome is the most common sex chromosome disorder and cause of hypogonadism affecting 1 in 600 men.¹⁴ Men with Klinefelter's syndrome have a 40%–50% increased risk of early mortality, with a loss of between 2 and 5 years in lifespan compared to age- and sex-matched population controls.^{15,16} All-cause mortality risk appears to be similar across all ages.¹⁵ While mortality is increased for most causes (relative risk 1.63), specific causes of death include infectious causes, cancer, diabetes mellitus, vascular insufficiency of the intestine and cardiovascular (CV), neurological, urological, and pulmonary diseases.^{15,17} Significantly raised risk is seen for lung cancer, breast cancer, mediastinal tumors, and non-Hodgkin's lymphoma.^{16–19}

Men with Klinefelter's syndrome have an increased risk of CVD including nonischemic heart disease and cerebrovascular disease, but whether risk can be attributed to hypogonadism or the syndrome itself remains unclear and there is a lack of evidence

¹Endocrine, Diabetes and Metabolic Unit, Royal Adelaide Hospital, Port Road, SA 5000, Australia; ²Discipline of Medicine, University of Adelaide, Adelaide, SA 5000, Australia; ³Discipline of Medicine and Freemasons Foundation Centre for Men's Health, University of Adelaide, SA 5000, Australia.

Correspondence: Dr. EJ Meyer (emily.meyer@sa.gov.au)

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that T therapy abrogates CVD risk.^{17,20,21} Hypogonadism may be an important factor in determining metabolic syndrome, and men with Klinefelter's syndrome have a higher risk of type 2 diabetes mellitus and obesity.

At least in part, the increased risk may be conferred by the chromosomal abnormality.^{20–22} Androgen sensitivity is influenced by gene polymorphisms encoding the X-linked androgen receptor and by the number of CAG repeats in the receptor. Klinefelter's syndrome genotypes associated with polymorphisms of the androgen receptor and increased numbers of CAG repeats result in decreased androgen sensitivity.²² Studies of mice with intact testis showed that the variation in the number of X chromosomes contributed to sex differences in CVD, a finding that might explain the increased CVD risk in men with Klinefelter's syndrome.²³

ENDOGENOUS T AND ITS MAJOR SEX STEROID METABOLITES

Although T is the primary sex steroid in men, tissue-specific effects of T may be mediated or modulated by dihydrotestosterone (DHT) or estradiol (E2) depending on the presence of 5 α -reductase or aromatase. Serum E2 concentrations in adult men do not accurately reflect tissue activity as T is aromatized to E2 within many tissues and E2 is partly metabolized *in situ*. Differential associations of each of the endogenous sex steroids on markers of CV risk and CV outcomes have been observed, and further the effects might depend on the specific group of men studied. For example, in community-dwelling men, higher serum T is associated with favorable CIMT and lower prevalence of carotid plaque, while the opposite is shown with higher serum E2. In men with coronary artery disease, higher DHT or E2 levels are associated with less carotid plaque.²⁴ Furthermore, in elderly men, higher baseline serum T and DHT were associated with reduced risk of stroke, and higher DHT was associated with lower mortality from ischemic heart disease, but serum E2 was not associated with either.^{25,26}

ENDOGENOUS T AND ALL-CAUSE MORTALITY

A meta-analysis and systematic review of 12 observational studies, of which 11 examined all-cause mortality, found low endogenous T levels to be associated with an increased risk of all-cause mortality. However, there was a significant heterogeneity between studies, and the authors concluded that it is likely that low endogenous T levels are a marker of poor general health status.²⁷

More recent prospective longitudinal population studies in community-dwelling men have reported associations between low serum T and all-cause mortality; however, some have not (Table 1). A longitudinal study by Pye *et al.*²⁸ of 2599 men aged 40–79 years found mortality in men with late-onset hypogonadism (LOH), defined as a clinical and biochemical state of hypogonadism, had a higher mortality rate of 30.9% compared to that in the entire cohort of 5.7%. Nearly two-thirds of deaths in men with LOH were due to CVD and one-third from cancer, which was different than that observed from the total cohort with 38.1% of deaths caused by CVD and 40.8% from cancer. The association between LOH and all-cause mortality showed that over time, survival continued to decline. After adjustment for confounders, men with severe LOH had a 5-fold increased risk of all-cause mortality and an 8-fold increased risk of CVD mortality. Men with a serum T of <8.0 nmol L⁻¹, irrespective of sexual symptoms, had a 2-fold increased risk of all-cause mortality, compared to eugonadal men. This risk increased 3-fold in men with a serum T of <8.0 nmol L⁻¹ who also reported sexual symptoms.

Therefore again, the likely explanation is that LOH represents a prognostic marker of poor health in aging men.

A prospective study by Holmboe *et al.*³⁰ of 5350 men at different ages between 30 and 70 years were followed for a mean period of 18.5 years after baseline sex hormone levels. A positive association was observed between luteinizing hormone (LH) and the ratio of LH to T with all-cause and cancer mortality. While total and free T decreased with age, neither was associated with all-cause or cancer mortality, but low T was a predictor of CVD mortality. It was surmised that primary Leydig cell dysfunction, even when compensated by increased LH, is a risk factor for mortality in men. In contrast, secondary decreased Leydig cell function may be a marker of increased CVD mortality risk. It was concluded that the measurement of LH in addition to T in men with androgen insufficiency may inform poorer health and comorbidity risk that may otherwise be overlooked.

Dynamic changes in serum T in older men were found to be associated with all-cause mortality. Serum T was measured in men aged ≥ 70 years at baseline, with repeated levels taken at 2 and 5 years. Men with the lowest quartile of baseline serum T, E2, DHT, and calculated free testosterone (cFT) had the highest cumulative all-cause mortality risk. A progressive decline in serum T over time was associated with all-cause mortality (RR: 1.18, 95% CI: 1.05–1.32, $P = 0.004$) and cancer-specific mortality (RR: 1.32, 95% CI: 1.06–1.64, $P = 0.01$), which were significant even after adjusting for age, BMI, and smoking comorbidities. Serum T decline over time was also significant for CVD mortality, however after adjusting for confounders, this was no longer significant. A key finding was the association of progressively declining serum T and death from cancer within the 7-year period in which mortality data were collected.³¹

Not only low but also high serum T has been found to be associated with an increase in mortality in both community-dwelling men with and without type 2 diabetes.^{26,32} In older men aged 70–89 years, cumulative mortality was highest for men with total T within the lowest quartile of values, with the second highest rate seen in men with total T within the highest quartile.²⁶ This U-shaped association with total T- and all-cause mortality has also been demonstrated in men with type 2 diabetes with all-cause mortality greatest in those with a serum T in the lowest and highest quintile (serum T <8.6 and >16.9 nmol L⁻¹, respectively), and lowest risk in those within the middle quintile (serum T: 11.1–13.7 nmol L⁻¹).³² Men with low serum T are more likely to be obese and have metabolic syndrome. A longitudinal study of 581 men with type 2 diabetes mellitus by Muralledharan *et al.*³³ was the first to demonstrate that low baseline T of <10.4 nmol L⁻¹ is associated with an increased mortality risk. Men were followed for a mean period of 5.8 years, while some were receiving T therapy, mortality rates were increased within the group with T <10.4 nmol L⁻¹ of 17.2%, compared to 9% in men with T >10.4 nmol L⁻¹ ($P = 0.003$). Within the low T group, after separating those who received T therapy (mean duration: 41.6 months) from men who did not, there was a significant increase in mortality of 20.11% in the untreated group compared to 9.38% in the treated group ($P = 0.002$) and 9.12% in men with T >10.4 nmol L⁻¹. After excluding deaths within the first 6 months, the majority of deaths were from CVD.³³ A prospective cohort study of 1239 Chinese men with type 2 diabetes mellitus and median disease duration of 9 years were followed for 4.8 years. While men within the low T group with a mean serum T of 6.89 nmol L⁻¹ had a higher prevalence of CVD and metabolic syndrome, there was not an association between T and all-cause mortality.³⁴

Thus, epidemiological studies have found that men with low endogenous T have an increased risk of all-cause mortality compared

Table 1: Endogenous testosterone and all-cause mortality outcomes in men

Study	Design	Mortality outcomes	Precipitants	Number of subjects (n)	Number of deaths (n)	Mean duration (year)	Mean baseline T concentration	Conclusion
Pye <i>et al.</i> 2014 ²⁸	Prospective	All-cause, CVD and cancer mortality	Community-dwelling men. Mean age: 60 (range: 40–79) years	2599	147 (46 from CVD, 60 from cancer)	4.3	16.64 nmol l ⁻¹ (alive); 16.56 nmol l ⁻¹ (died)	Middle-aged and older men with severe late-onset hypogonadism had a 5-fold higher risk for all-cause mortality and 8-fold higher risk of CVD mortality
Yeap <i>et al.</i> 2014 ²⁶	Prospective	All-cause mortality	Community-dwelling men. Age range: 70–89 years	3690	974 (325 from IHD)	6.7	13.2 nmol l ⁻¹ (alive); 12.8 nmol l ⁻¹ (died)	Total T in the second and third quartiles had significantly lower all-cause mortality than those in the first, similar results seen with calculated free T. There were no significant associations with total or calculated free T with IHD mortality risk
Shores, <i>et al.</i> 2014 ²⁹	Prospective	All-cause mortality	Community-dwelling men. Age range: 66–97 years, mean age: 76 years	1032	777	10.8 (median)	3.89 ng ml ⁻¹	Total T and calculated free T was not associated with all-cause mortality
Holmboe, <i>et al.</i> 2015 ³⁰	Prospective	All-cause, CVD and cancer mortality	Community-dwelling men. Age range: 30–70 years	5350	1533 (428 from CVD, 480 from cancer)	18.5	Age (year): T (nmol l ⁻¹) (30:21.6; 40:19.7; 50:18.7; 60:19.1; 70:17.9)	LH and LH/T positively associated with all-cause mortality, suggesting that a compensated impaired Leydig cell function may predict death. Negative linear association between age-adjusted total T and CVD mortality. No association between total T and all-cause mortality
Hsu, <i>et al.</i> 2016 ³¹	Prospective	All-cause, CVD and cancer mortality	Community-dwelling men aged >70 years, mean age at baseline: 76.9 years	1705	510 (185 from CVD, 151 from cancer)	Follow-up: 5 years, mortality data collected for up to 7 years	4.3 ng ml ⁻¹	Dynamic change (decline) in total and calculated free T over time was associated with all-cause and cancer mortality, but not CVD mortality. LH/T was associated with all-cause, CVD and cancer mortality
Hamilton <i>et al.</i> 2016 ³²	Prospective	All-cause and CVD mortality	Community-dwelling men with T2D. Mean age: 65.8 years	788	102 (27 from CVD)	4	13.1 nmol l ⁻¹	U-shaped relationship between serum T quintiles and all-cause mortality in med with T2D. Serum T <8.5 and >16.9 nmol l ⁻¹ has reduced survival

CVD: cardiovascular disease; IHD: ischemic heart disease; LH: luteinizing hormone; T: testosterone; T2D: type 2 diabetes

to those with higher T levels, of which death from CVD remains the predominant cause. Men with low serum T are more likely to be obese and have metabolic syndrome, and men with type 2 diabetes mellitus and low endogenous T have an increase in all-cause mortality. It is not known if T deficiency is due to the disease and reflects the state of ill health or contributes to the underlying pathogenesis of these conditions.

ENDOGENOUS T CONCENTRATIONS AND DEATHS FROM NON-CV CAUSES

Cancer

The prevalence of T deficiency among men with cancer is high and is due to either the underlying disease or the treatment.³⁵ Men with metastatic disease have a high prevalence of androgen deficiency, and up to 90% of those receiving opioids for cancer pain are T deficient.^{36,37}

Men with advanced malignancies have lower T, and this was associated with higher LH levels, suggesting a testicular insufficiency within terminal stages of the disease.³⁷ Opioids inhibit the pituitary–gonadal axis;^{38,39} certain chemotherapy agents, including the alkylating and platinum-based therapies, impair testicular function; and high levels of inflammatory cytokines which are observed in advanced malignancy inhibit the pituitary–gonadal axis.³⁷ Androgen deficiency impacts on appetite and negatively affects metabolism, further aggravating cancer-related cachexia.

While some longitudinal studies have shown a relationship between low baseline serum T and cancer mortality,^{40,41} others have not.^{30,42,43} Men with progressively declining serum T had a greater mortality due to cancer.³¹ The EPIC-Norfolk study found an association with serum T and cancer mortality, however this was no longer significant after adjusting for covariates. Of the 304 cancer-related deaths, 55 were due to lung, 50 prostate, 37 colorectal, 15 esophageal and 11 stomach cancers.⁴¹ Men with Klinefelter's syndrome are also at an increased risk of cancer, but with a different at-risk cancer profile compared with breast, lung, and mediastinal cancer, and non-Hodgkin's lymphoma being more common.^{16–19,44}

Therefore, serum T is frequently low in men with cancer. The reasons for this are multifactorial and include the effects of the underlying malignancy and/or associated treatment. The extent to which androgen deficiency contributes to cancer morbidity and mortality and whether treatment with testosterone is beneficial remains to be determined.

Renal disease

Chronic kidney disease (CKD) leads to dysregulation of the hypothalamic–pituitary–gonadal (HPG) axis and subsequent androgen deficiency in men.⁴⁵ The estimated prevalence of androgen deficiency in men with CKD is approximately 48%–60%.⁴⁶ The degree of T deficiency is proportional to the severity of the underlying CKD however, whether this is a causal effect or an epiphenomenon remains in contention. It is not well established if androgens have a direct effect on the kidney, but it is postulated that low T might indirectly contribute to the pathogenesis of CKD through vascular and metabolic pathways. Longitudinal population studies showed CKD and low serum T to be additive risk factors for mortality.⁴⁷ A prospective cohort study of 143 males with CKD not receiving dialysis, receiving dialysis and post renal transplant, were followed up for a median of 5.8 years. Fifty-two (36%) patients died, of which 17 were with CKD, 28 were receiving dialysis, and 7 were post a renal transplant. Those who died during follow-up had a lower median T (9.9 nmol l^{-1}) compared to those who survived or received a kidney transplant (11.7 nmol l^{-1} , $P = 0.002$). Low serum T was an independent predictor of mortality ($P = 0.02$), and a decrease in serum T of 1 nmol l^{-1} was associated with a 9.8% increase in mortality. T was inversely associated with renal function, men on dialysis had a lower T compared to men with CKD and renal transplant recipients.⁴⁸

Respiratory disease

Low serum T has been reported in pulmonary disease, and some longitudinal studies have shown an increased mortality due to respiratory disease.^{42,43} A population-based study of 1686 men followed up for a mean of 15.3 years found that 9.6% of men died from respiratory diseases. Low calculated free serum T, but not total T, was associated with increased respiratory disease mortality. Men with the lowest free T quintile were five times more likely to die from respiratory disease compared to men with the highest quintile.⁴³ Another prospective population study of 794 men, with a median age of 73.6 years followed up to 20 years (mean follow-up period of 11.8 years), found that those

with a low baseline serum total and free T were associated with an elevated 20-year risk of death due to respiratory disease.⁴²

CONCLUSIONS

It remains unclear whether low serum T concentrations in men are an independent risk factor for CVD or a marker of the presence of CVD.⁴⁹ Genetic, lifestyle, behavioral and concomitant disease-related factors are likely more important in determining CVD risk than direct effects of sex steroids. What is clear, however, is that when low T is the consequence of obesity and lifestyle factors, substantial weight loss and exercise improve or normalize T concentrations^{7,50–53} improving CV risk. Older, overweight men with borderline low serum T concentrations can be expected to derive more CV benefit from a healthy diet and exercise regimen and statin and aspirin therapy, as appropriate, than they would from T therapy. There appears to be an association between low serum T and all-cause and CV mortality in older men; however, heterogeneity between studies limited a firm conclusion. Men with cancer, CKD, and respiratory disease have a higher prevalence of hypogonadism. Longitudinal population-based studies of community-dwelling men have found low serum T to be associated with a higher risk of death from cancer and renal and respiratory disease, while other studies have not found this association. Taken together, these data suggest that low serum T later in life may be associated with an increase in all-cause and specific types of mortality in men, this body of evidence is evolving and further research is required.

AUTHOR CONTRIBUTIONS

The planning for the manuscript was done by EJ and GW. The literature search and preparation of the manuscript was undertaken by EJ with review and editing by GW.

COMPETING INTEREST

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