Testosterone and mortality

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Summary

Epidemiological studies have found that men with low or low normal endogenous testosterone are at an increased risk of mortality than those with higher levels. Cardiovascular disease accounts for the greater proportion of deaths in those with low testosterone. Cancer and respiratory deaths in some of the studies are also significantly more prevalent. Disease-specific studies have identified that there are higher mortality rates in men with cardiovascular, respiratory and renal diseases, type 2 diabetes and cancer with low testosterone. Obesity, metabolic syndrome, type 2 diabetes, cardiovascular disease and inflammatory disorders are all associated with an increased prevalence of testosterone deficiency. Two major questions that arise from these findings are (1) is testosterone deficiency directly involved in the pathogenesis of these conditions and/or a contributory factor impairing the body's natural defences or is it merely a biomarker of ill health and the severity of underlying disease process? (2) Does testosterone replacement therapy retard disease progression and ultimately enhance the clinical prognosis and survival? This review will discuss the current state of knowledge and discuss whether or not there are any answers to either of these questions. There is convincing evidence that low testosterone is a biomarker for disease severity and mortality. Testosterone deficiency is associated with adverse effects on certain cardiovascular risk factors that when combined could potentially promote atherosclerosis. The issue of whether or not testosterone replacement therapy improves outcomes is controversial. Two retrospective studies in men with diagnosed hypogonadism with or without type 2 diabetes have reported significantly improved survival.

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Introduction

The prevalence of hypogonadism in male populations is not known with certainty, in part due to a lack of consensus on the threshold that should be used to define testosterone insufficiency. Hypogonadism is defined as a clinical syndrome which comprises both symptoms and biochemical evidence of testosterone deficiency.[1,2] Clinical guidelines have provided some direction for cut-off levels of testosterone, but these also differ.[1,2] Differences in the measurement of testosterone between assays and laboratories also lead to problems interpreting these thresholds.[3] The European Male Aging Study (EMAS), involving 3369 men, defined late-onset hypogonadism as the presence of at least 3 sexual symptoms (loss of morning erections, low sexual desire and erectile dysfunction), total testosterone (TT) <320 ng/dl (11 nmol/l) and free testosterone (fT) <64 pg/ml (220 pmol/l). Using this definition, the overall prevalence of hypogonadism in the EMAS study population was 2·1% and increased with age from 0·1% for men 40 to 49 years of age to 5·1% for those 70–79 years.[4] However, men already receiving testosterone replacement therapy (TRT) were excluded so this figure may represent an underestimate of the overall prevalence of hypogonadism. The Boston Area Community Health (BACH) study reported a prevalence of symptomatic hypogonadism of 4·2% in men aged 39–50 years and 8·4% between 50 and 79 years.[5]

Testosterone deficiency is associated with reduced insulin sensitivity, central obesity, dyslipidaemia, hypertension, osteoporosis, muscle weakness and frailty, cognitive impairment, lethargy and fatigue and sexual dysfunction.[6,7] Low testosterone is also an independent risk factor for the future development of obesity, the metabolic syndrome and type 2 diabetes.[7] Each of these conditions has a high prevalence in Klinefelter's syndrome.[8] Acute and/or chronic illness (including cardiovascular disease) can lead to suppression of the hypothalamic–pituitary–testicular axis. This raises the question as to whether testosterone deficiency is merely a biomarker for ill health or is bidirectional having an adverse effect on the underlying disease progression.

Mortality studies

The majority of longitudinal mainly community-based population studies (Table 1) have reported significant associations between all-cause mortality and low testosterone,[9–17] although

Table 1. Community-based population studies effect of baseline testosterone on all-cause mortality

Author, year (study name)	Country	N	Mean Follow-up years	All-cause Mortality HR/OR for TT unless indicated (95% CI)
Pye et al.[21] 2014 (EMAS)	Europe	2599	4·3	HR 5·5 (2·7,11·4) (with severe LOH) HR 2·3 (1·2,4·2) (TT <8 nmol/l) HR 3·2
Haring et al.[17] 2013 (Framingham Heart Study)	USA	254	At 5 and 10 years	HR (per quartile increment) NS
Hyde et al.[12] 2012 (Health in Men Study)	Australia	4249	5·1	HR 1·62 (1·20–2·19)
Haring et al.[8] 2010 (SHIP)	Germany	1954	7·2	HR 2·24 (1·41–3·57)
Menke et al.[11] 2010 (NHANES III)	USA	1114	At 9 and 18 years	HR – at 9 years FT: 1·43 (1·09, 1·87) TT; NS At 18 years: FT & TT NS
Vikan et al.[9] 2009 (Trosmø)	Norway,	1568	11·2	HR FT: 1·24 (1·01–1·54); TT: (NS)
Tiveston et al.[10] 2009 (MrOS)	Sweden	3014	4·5	HR 1·65 (1·29–2·12)
Lehtonen et al.[14] 2008 (Turku)	Finland	187	10	OR 0·93 (0·87–0·99)
Laughlin et al.[7] 2008 (Rancho–Bernardo Study)	USA	794	11·8	HR 1·44 (1·12, 1·84)
Araujo et al.[15] 2007 (MMAS)	USA	1686	15·3	RR TT: NS FT: NS
Khaw et al.[13] 2007 (EPIC-Norfolk)	UK	2314	7	OR (TT increasing quartiles compared to lowest) 0·75 (0·55–1·00);0·62 (0·45–0·84);0·59 (0·42–0·85)
Shores et al.[6] 2006 (Veterans)	USA	858	4·3	HR 1·88 (1·34–2·63)
Smith et al.[16] 2005 (Caerphilly)	UK	2512	16·5	HR: NS

EPIC-Norfolk, European Prospective Investigation into Cancer in Norfolk; MMAS, Massachusetts Male Aging Study; MrOS, Swedish Osteoporotic Fractures in Men; NHANES, Third National Health and Nutrition Examination Survey; Mortality StudySHIP, Study of Health in Pomerania; TT, total testosterone; BT, bioavailable testosterone; FT, free testosterone; HR, hazard ratio; OR, odds ratio; NS, not significant; NA, not applicable; CI, confidence interval.

some have not.[18–20] A recent systematic review and meta-analysis of 12 community-based studies concluded that low endogenous testosterone at baseline was associated with an increased risk of both all-cause and cardiovascular mortality.[21] A decrease of 2·18 nmol/l in testosterone was associated with a 35% increased risk of all-cause mortality and a 25% increased risk of cardiovascular mortality. Another meta-analysis found that low testosterone and high oestradiol independently predicted an increased risk of cardiovascular disease and mortality.[22] Meta-analyses in general have limitations in that there are differences between populations; for example, there may be a bias to a sicker cohort from clinic- and hospital-based studies than community-based studies. Evidence does suggest that testosterone status is linked to the general health of the male population and is a biomarker for the presence of occult diseases such as atherosclerosis and cancer and early death. Low testosterone has also been shown to be associated with increased all-cause mortality within disease-specific populations (Table 2).

Community- and population-based studies

As there are significant differences between the published studies, we have described each individual study. The Veterans study[69] followed men (>40 years) from the hospital database for a mean period of 4·3 years. All-cause mortality 34·9% in men with TT <8·7 nmol/l compared with 20·1% men with TT >12 nmol/l. Men with low and equivocal testosterone levels had higher mortality than men with normal testosterone levels after adjustment for age, comorbidities, body mass index (BMI), glucocorticoid and opiate treatment. After exclusion of those who died during the first year of follow-up, those with low testosterone had an increased hazard ratio (HR), after adjusting for covariants, of 1·88 for all-cause mortality.

The Rancho–Bernado study (California)[10], a prospective study of community-dwelling men (mean age 74 years) followed for a mean of 11·8 years, had a mortality rate of 57·5 per 1000 person-years. After adjusting for age, adiposity and lifestyle choices, the risk of death was 44% higher for men in the lowest quartile of TT

Table 2. Effect of baseline testosterone on all-cause mortality in disease-specific populations

Author, year	Country	Population studied	N	Follow-up	All-cause Mortality HR/OR for TT unless indicated (95% CI)
Muraleedharan et al.[45] 2013	UK	Type 2 DM	581	5·8 years	HR 2·02 (1·2–3·4)
Lerchbaum et al.[22] 2012	Austria	Coronary angiography	2069	7·7 years	HR 2·11 (1·60–2·79)
Haring et al.[24] 2011	Germany	CKD, albuminuria, kidney dysfunction	1822	9·9 years	HR 1·40 (1·02–1·92)
Kyriazis et al.[23] 2011	Greece	Haemodialysis	111	37 months (median)	HR 2·53 (1·22–5·25)
Malkin et al.[25] 2010	UK	CHD (+ve angiography)	930	6·9 years	HR BT: 2·2 (1·4–3·6) TT: NS
Carrero et al. 2011	Sweden	ESRD	260	3 years	HR 1·9 (1·0–3·9)
Militaru et al.[31] 2010	Romania	Acute MI	126	30 days	OR TT quartiles 2, 3, 4 vs 1: 0·82 (0·67–1·03); 0·67 (0·52–0·86);0·70 (0·56–0·89); (P-trend <0·01)
Corona et al.[26] 2010	Italy	Erectile Dysfunction	1687	4·3 years	HR NS
Ponikowska et al.[30] 2010	Poland	T2DM and stable CHD	153	19 months (median)	CVD Mortality, HR TT: 0·58 (0·39–0·87) eFT: 0·65 (0·52–0·81)
Carrero et al.[61] 2009	Sweden	Haemodialysis	126	41 months	HR 2·03 (1·24–3·31)

BT, bioavailable testosterone; CHD, coronary heart disease; CKD, chronic kidney disease; CHD, coronary heart disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; TT, total testosterone; eFT, estimated free testosterone; FT, free testosterone; HR, hazard ratio; OR, odds ratio; NS, not significant.

relative to the highest. The EPIC-Norfolk[14] study from the UK, a nested case–control community-based men aged 40–79 years. Testosterone was inversely related to all-cause, cardiovascular disease and cancer mortality after exclusion of each of these conditions at baseline. An increase of 6 nmol/l TT was associated with a 0·81 multivariate-adjusted mortality odds ratio for death.

The Study of Health In Pomerania (SHIP)[11] prospective community-based study (mean follow-up 7·2 year) also found men with low testosterone to have a significantly greater mortality risk from all causes which persisted after exclusion of deaths in the first year. After adjusting for age, BMI, waist–hip ratio, smoking, excess alcohol use and physical activity, low testosterone continued to be associated with increased mortality. The Tromsø study[12] analysed a cohort of randomly selected men followed for 10 years reporting men with FT in the lowest quartile had a 24% increased risk of all-cause mortality.

The Swedish MrOS (Osteoporotic fractures in men)[13] was a large prospective population-based cohort study involving 3014 men (mean age of 75 years) followed for a mean of 4·5 years. Testosterone levels were compared within lowest quartile to those in the 2nd to 4th quartile. They reported that the multivariate-adjusted hazard ratio for mortality was 1·65 for the men with low testosterone. The risk of death was increased (HR 1·96) in subjects with low levels of testosterone and oestradiol compared with those within quartiles 2–4 of both hormones.

The Third National Health and Nutrition Examination Survey (NHANESIII)[14] mortality analysis of men who had no history of cardiovascular disease or cancer at baseline demonstrated that low fT and bioT independently associated with an increased risk of all-cause and cardiovascular mortality, during follow-up between baseline and year 9, but these associations did not persist between years 9 and 18.

The Health in Men (HIM) study[15] from Western Australia reviewed a cohort of 3637 older community-dwelling men with average age 77 years with a mean follow-up of 5·1 years. This study found low free testosterone but not total testosterone, and higher SHBG and LH levels predicted death from all causes and low free testosterone and higher LH were associated with cardiovascular mortality. No associations were identified in regard to either cancer or respiratory disease, but a high free testosterone was associated with lung cancer mortality. Recently, further analysis of the HIM study has reported a U-shaped curve for endogenous total testosterone (measured by mass spectroscopy) with mid-range levels being optimal for a reduced risk of mortality from any cause.[21] There was a J-shaped curve for dihydrotestosterone (DHT) with a mid-range level having a reduced all-cause mortality whereas a higher normal range level which was associated with a lower mortality from ischaemic heart disease.[20]

Community-dwelling men between 71 and 72 years at recruitment, from Turku in Finland, were followed up for 10 years.[17] Men with diabetes mellitus, subjects unable to walk 500 m and those considered to be sick or very sick at recruitment were excluded. The mean TT was approximately 14% higher in those who were alive after 10 years compared with those deceased. The significant adjusted odds ratio and HR for testosterone to explain mortality were 0·93 and 0·95, respectively. The conclusion of the study was that it supported a favourable effect of endogenous testosterone on survival.

Three major studies have failed to show the relationship between testosterone and mortality. The Framingham Heart Study[18] prospectively evaluated elderly men (mean age 75 years) with up to four serial measurements of serum TT and, dehydroepiandrosterone sulphate (DHEAS). Using the multivariable-

adjusted Cox proportional hazard regression models, they assessed the relationship between baseline hormone concentrations and variation over time to the incidence of clinical cardiovascular disease and all-cause mortality at 5- and 10-year follow-up. The study failed to find any association between baseline concentrations of sex steroids, gonadotrophins and their trajectories with incident cardiovascular disease over the 5- and 10-year follow-up. The Massachusetts Male Aging Study (MMAS)[18] observed a younger cohort of men aged 40–70 with 15·3 years follow-up. In multivariate-adjusted models, higher fT and lower dihydrotestosterone levels were significantly associated with ischaemic heart disease mortality. The association between fT and ischaemic heart disease was not robust enough to show differences in model selection; however, fT was significantly associated with respiratory mortality ($P = 0.002$). The Caerphilly study[19], a prospective cohort study of men aged 45–59 (mean follow-up 16·5 years), found no association between TT and all-cause mortality.

Severe late-onset hypogonadism in men defined as a TT <8 nmol/l and the three sexual symptoms of testosterone deficiency had a greater than threefold (twofold without symptoms) risk of death from all-cause and cardiovascular disease than eugonadal men in the EMAS study over a median follow-up period of 4·3 years.[24] The fact that the MMAS and Caerphilly studies included younger men as well may possibly explain the difference between their findings and those studies which reported a negative correlation between testosterone and mortality.

Testosterone and cardiovascular mortality

Of the studies reported, the major cause of increased mortality was mostly attributable to cardiovascular disease

Table 3. Effect of baseline testosterone on cardiovascular disease mortality

Author, year (study name)	Country	Population studied	N	Follow-up	CVD Mortality HR/OR for TT unless indicated (95% CI)
Hyde et al.[12] 2012 (Health in Men Study)	Australia	Population based	4249	5·1 years	HR 1·71 (1·12–2·62)
Lerchbaum et al.[22] 2012	Austria	Coronary angiography referrals	2069	7·7 years	HR 1·77 (1·23–2·55)
Kyriazis et al.[23] 2011	Greece	Haemodialysis	111	37 months (median)	HR 2·92 (1·08–7·87)
Haring et al.[24] 2011	Germany	Men with CKD, albuminuria, kidney dysfunction	1822	9·9 years	HR 2·01 (1·21–3·34)
Malkin et al.[25] 2010	UK	CHD (−ve angiogram)	930	6·9 years	HR BT: 2·2 (1·2–3·9) TT: 2·5 (1·2–5·3)
Corona et al.[26] 2010	Italy	Erectile Dysfunction	1687	4·3 years	HR HR = 7·1 (1·8–28·6)
Menke et al.[11] 2010 (NHANES III)	USA	Population based	1114	18 years	HR: Baseline – year 9 FT: 1·53 (1·05, 2·23) TT: NS Year 9–18: NS
Haring et al.[8] 2010 (SHIP)	Germany	Population based	1954	7·2 years	HR 2·56 (1·15–6·52)
Vikan et al.[9] 2009 (Tromso)	Norway	Population based	1568	11·2 years	HR FT: 1·24 (1·01–1·54)
Carrero et al.[61] 2009	Sweden	Haemodialysis	126	41 months	HR 3·19 (1·49–6·83)
Laughlin et al.[7] 2008 (Rancho–Bernardo Study)	USA	Population based	794	11·8 years	HR 1·38 (1·02–1·85)
Araujo et al.[15] 2007 (MMAS)	USA	Population based	1686	15·3 years	RR FT: 0·80 (0·64–0·99), $P = 0.02$ for trend
Khaw et al.[13] 2007 (EPIC-Norfolk)	UK	Population based	2314	7 years	OR Quintile 2,3,4 *vs* 1 CVD 0·89 (0·60–1·32) 0·60 (0·39–0·92) 0·53 (0·32–0·86) CHD 0·71 (0·43–1·17) 0·59 (0·39–1·00) 0·52 (0·28–0·97)
Smith et al.[16] 2005	UK	Population based	2512	16·5 years	HR 0·94 (0·80–1·11) (NS) IHD

EPIC-Norfolk, European Prospective Investigation into Cancer in Norfolk; MMAS, Massachusetts Male Aging Study; NHANES, Third National Health and Nutrition Examination Survey Mortality Study; SHIP, Study of Health in Pomerania; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; TT, total testosterone, BT, bioavailable testosterone; FT, free testosterone; HR, hazard ratio; OR, Odds ratio; NS, not significant.

(Table 3).[10,11,15,16,25–30] There is supporting evidence from both clinical studies and those investigating surrogate markers that there is a link between low testosterone and cardiovascular disease.[30,31] Men with angiographically proven coronary artery disease have lower levels of testosterone compared with controls.[32]

In the Rancho–Bernardo study,[10] 264/529 deaths were attributable to cardiovascular disease (HR 1·38; 95% CI 1·02–1·85, which persisted after excluding deaths up to 5 years). Low TT was associated with central obesity, insulin resistance, hyperglycaemia, dyslipidaemia and blood pressure as well as emerging risk factors such as leptin, adiponectin, IL-6 and CRP. The EPIC-Norfolk study[16] reported 369/825 deaths were due to cardiovascular disease which persisted after age and covariate adjustment. Testosterone was inversely related to BMI, waist–hip ratio, triglycerides and prevalence of type 2 diabetes.[16]

A 7-year follow-up study of 930 men with angiographically proven coronary artery disease reported an excess mortality in the low-testosterone group compared to normal (21% vs 12% HR 2·27).[28] The presence of a low testosterone at baseline was only second to left ventricular dysfunction at baseline as a determinant of future mortality. Kaplan–Meier survival curves confirmed low bioT was significantly associated with all-cause ($P < 0·0001$) and cardiovascular mortality ($P = 0·007$). Interestingly, a cut-off of TT <15·1 nmol/l was associated with increase in all-cause and cardiovascular mortality. Low bioT was found to be a more sensitive marker than TT for increased cardiovascular mortality. A study of 153 patients (age 65 ± 9 years) with type 2 diabetes and stable coronary artery disease over a 19-month period demonstrated low TT, fT and DHEAS were independently associated with increased cardiovascular mortality.[33] A subsequent study in 2069 men who had had coronary angiography (80% had coronary artery disease) found that after 7·7-year mean follow-up, a combined deficiency of fT and 25,hydroxycholecalciferol was associated with all-cause and cardiovascular mortality.[25] A prospective cohort study evaluating a consecutive series of 1687 men attending an andrology clinic found that low testosterone was associated with a higher mortality from major adverse cardiovascular events.[29] The Caerphilly study did report a trend for increased ischaemic heart disease with lower serum testosterone and a significant association with increased cortisol/testosterone ratio.[19]

Testosterone levels in the acute setting may also predict clinical outcome after a coronary event as suggested in a study which included 126 consecutive male patients admitted with acute myocardial infarction. Low testosterone on admission was independently related to higher mortality after 30 days.[34]

The MrOs study[35] of 2416 men aged between 69 and 81 years reported that men in the highest quartile endogenous testosterone had a decreased 5-year risk of major cardiovascular events and mortality. High SHBG was predictive of lower frequency of cardiovascular events but not mortality. This study is particularly important as it measured testosterone by mass spectroscopy which removes several questions in relation to differences and problems with immunoassays and is more accurate. A Japanese study of 171 middle-aged men (30–69 years) with any coronary risk factor without evidence of prior cardiovascular disease followed for 77 months found that those in the lower tertile of

testosterone were associated with an increased risk of cardiovascular events.[36] Higher dihydrotestosterone was associated with a lower risk of coronary death in the HIM study although total and calculated testosterone had an optimal effect in the mid-range of the study.[22] A Chinese study found testosterone levels below the 10th centile increase risk of 5-year mortality in men with systolic chronic heart failure.[37]

In summary, the Rancho–Bernardo, Caerphilly, EPIC-Norfolk and SHIP prospective community-based studies found an association between low baseline testosterone with cardiovascular mortality, whereas the MMAS, NHANESIII and Tromso did not. Interestingly, however, the Caerphilly study did report a reduction in shaving frequency in men with cardiovascular disease with the authors suggesting that this may potentially be due to lower testosterone although it was not demonstrated statistically.[38]

Low testosterone is associated with an adverse effect on cardiovascular risk factors which include central obesity, dyslipidaemia, insulin resistance, hyperglycaemia, coagulation, endothelial dysfunction and inflammation.[30] The severity of coronary heart disease as assessed by greater than 75% stenosis of one, two and three vessels was associated with significantly higher serum interleukin-1β and lower interleukin-10 (an anti-atherogenic cytokine) and lower testosterone levels.[39] Testosterone replacement in men with coronary heart disease reduces tumour necrosis factor-α, interleukin-1β and increases interleukin-10.[40] Carotid intima media thickness (CIMT), a surrogate marker for the degree of *in vivo* atherosclerosis, correlates inversely with testosterone.[30] Furthermore, one study found that after a 4-year follow-up period, men who were in the lower tertile of testosterone had the greatest increase in CIMT.[41] The MrOs study reported a direct correlation between low testosterone and lower limb peripheral vascular disease by measuring the ankle–brachial index once again strongly suggesting a link between testosterone levels and vascular disease.[42] The Rotterdam study[43] found an independent inverse association between TT and bioT and the degree of aortic atherosclerosis. Some cross-sectional studies have found an association with low testosterone and the presence of coronary heart disease, whereas others have not.[30]

Morbidity and mortality in androgen deficiency state

Androgen deprivation therapy (ADT) for prostate cancer therapy induces profound hypogonadism and this has been linked to an increased risk of cardiovascular events and sudden death.[44] The largest study of 73196 men with loco-regional prostate cancer in which one-third received ADT and the rest were not treated and monitored for progression of their disease, were followed for up to 10 years.[45] ADT was associated with an increased risk of incident diabetes, coronary heart disease, myocardial infarction and sudden cardiac death. Another study involving 396 men with prostate cancer receiving androgen deprivation therapy showed increase in incidence of new onset of diabetes and worsening of glycaemic control in men with diabetes.[46] The major causes of death in men with hypopituitarism

followed for 8 years ($n = 1014$) were cardiovascular and respiratory disease.[47] The only hormonal deficiency was untreated gonadotrophin deficiency.

Testosterone and mortality in diabetes

A recently published study evaluated a population of the effect of baseline testosterone on mortality in men with type 2 diabetes over a mean follow-up period of 5·8 years.[48] Those men with either a low baseline TT (<10·4 nmol/l) or bioT had an increased risk of death compared to testosterone levels above these cut-off values. The multivariate-adjusted hazard ratios were 2·02 for TT <10·4 nmol/l (mortality 17·2% low testosterone *vs* 9% normal testosterone; $P = 0.009$) and 2·4 ($P = 0.006$) for bioT <2·5 nmol/l. There was a significant increased risk of cardiovascular mortality in those with a TT <8·4 nmol/l (below the normal range: HR 2·5; $P = 0.02$) with deaths within the first six months being excluded.

Testosterone and cancer

There is high prevalence of testosterone deficiency in men with cancer which can occur either before or after chemo/radiotherapy.[49,50] A study of 428 men with non-testosterone related cancers found that the prevalence of hypogonadism was 48% based on TT and 78% on fT measurement in men with non-testosterone related cancers.[49] Low testosterone occurred independently of cancer type, stage, weight loss and the use of chemotherapeutic or opioid drugs.[50] A meta-analysis of hypogonadism associated with advanced cancer did not, however, detect any correlation with the clinical and biological sequelae of cancer cachexia, such as higher inflammation, fatigue and body wasting.[51]

Some community-based population studies have reported an increased mortality due to cancer in men with low testosterone. Unlike cardiovascular disease, this association seems to be less clear-cut. In the Epic-Norfolk study [16]of the 304 cancer deaths identified, 55 were due to lung, 50 prostate, 37 colorectal, 15 oesophageal and 11 stomach cancer. The age-adjusted odds ratio for mortality due to cancer decreased significantly with the increasing quartile of testosterone. This finding persisted after adjustment for other hormones and covariates. The second commonest cause of death in Rancho–Bernardo study[10] was cancer, with an increased HR in men with low TT and bioT, but the changes were not significant when adjusted for age, adiposity and lifestyle. Men with Klinefelter's syndrome have high incidence of breast and mediastinal cancer.[8]

Testosterone and respiratory disease

Some epidemiological studies have shown an increased mortality from respiratory diseases.[10,18] In the Rancho–Bernardo study, cause-specific analyses found respiratory mortality was increased in patients with low testosterone persisting after adjustment for age, adiposity and lifestyle.[10] Importantly, this remained significant after excluding death in the first five years. In the MMAS study, fT was significantly associated with respiratory mortality.[18]

There is a high prevalence of primary and secondary hypogonadism in COPD patients.[52–54] Three mechanisms, which contribute to the hypogonadal state in COPD, are hypoxia, chronic low-grade inflammatory state with elevated inflammatory cytokines and chronic glucocorticoid use[55]. Testosterone in men with COPD correlates inversely with the severity of arterial hypoxia.[56] Muscle wasting including involvement of the intercostal muscles is common in men with COPD could contribute to morbidity and mortality through impaired respiratory effort. Testosterone replacement increases lean body mass in hypogonadal men with COPD[53] and improves bone mineral density in those receiving long-term glucocorticoid therapy for asthma.[57] The administration of a low-dose testosterone to men with COPD for 26 weeks was associated with improvement of body composition, erectile function and sexual quality of life without any clinical or biochemical side effects.[58] Klinefelter's syndrome men have more frequent episodes of pneumonia, chronic obstructive airway disease and asthma compared with the normal population.[8] However, the smoking status in this study population was unknown. It has also been recognized for several years prior to this particular study that Klinefelter's men have a higher mortality from pneumonia.

Testosterone and renal disease

Many studies have shown that testosterone deficiency is common in patients with renal disease[59–61] and contributes to sexual dysfunction, decreased bone mineralization, malnutrition, decreased muscle mass and anaemia.[62] It is present in 44% of men with end-stage renal disease, and a further 33% had borderline levels.[63] Testosterone was also strongly and inversely correlated to the inflammatory markers CRP, IL-6 and fibrinogen and was independently associated with cardiovascular comorbidity and death. The same group had earlier reported a prospective study of 126 patients from a renal unit undergoing haemodialysis, followed up for 40 months.[64] They found that men with testosterone values in the lowest tertile had increased all-cause and CVD mortality which persisted after adjustment for age, SHBG, previous CVD, diabetes, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) treatment, albumin and inflammatory markers.[64]

A large study ($n = 1822$) of up to 10 years of men with both renal dysfunction and low testosterone were identified as high-risk individuals showing a more than twofold increase in all-cause mortality (HR 2·52).[27] They also concluded that the effect of renal dysfunction and low testosterone are additive rather than synergistic mortality risk factors in this population. A Swedish study also found that men with end-stage renal failure and lower testosterone had a greater risk of dying.[31] Three studies have reported an increased risk of all-cause and one of cardiovascular death in men with low testosterone and renal failure being treated with haemodialysis.[26,64,65]

TRT and mortality

Two studies have now been published examining the effect of testosterone replacement therapy in men with hypogonadism. The Seattle study[66] retrospectively analysed 1031 male veterans greater than 40 years old who had attended clinics and found to have low testosterone ≤8·7 nmol/l (250 ng/dl). They compared survival rates in men who had received TRT with those who had not and found that TRT significantly reduced mortality over a mean follow-up period of 40·5 months. The mortality in testosterone-treated men was 10·3% compared with 20·7% in untreated men ($P < 0.0001$) with a mortality rate of 3·4 deaths per 100 person-years for testosterone-treated men and 5·7 deaths per 100 person-years for not treated. After multivariable adjustment including age, body mass index, testosterone level, medical morbidity, diabetes and coronary heart disease, testosterone treatment was associated with decreased risk of death (HR 0·61; 95% confidence interval 0·42–0·88; $P = 0.008$). In addition, this study showed no difference in the mortality rates from prostate cancer between testosterone-treated and testosterone-untreated groups.

The Barnsley type 2 diabetes study[48] examined retrospectively the effect of TRT for hypogonadism on all-cause mortality and has found significant survival benefits. The majority of patients 60/64 (93·75%) received testosterone gel, 3/64 (4·68%) buccal testosterone and one (1·56%) intramuscular testosterone undeconoate. TRT (mean duration 41·6 ± 20·7 months; $n = 64$) was associated with a reduced mortality of 8·4% compared to 19·2% ($P = 0.002$) in the untreated group ($n = 174$). The multivariate-adjusted hazard ratio for decreased survival in the untreated group was 2·3($P = 0.004$). The conclusion was that low testosterone levels predict an increase in all-cause mortality during long-term follow-up and that testosterone replacement may improve survival in hypogonadal men with type 2 diabetes.

These two studies from different populations and countries have shown very similar results of TRT on improving survival of hypogonadal men. It is accepted within the text of both manuscripts that there are limitations of the studies in regard to the lack of a prospective double-blind placebo-controlled approach and there may be a bias to those treated and those who were not. Firstly, although a prospective study would be ideal to assess scientifically the effect of TRT on mortality over prolonged period, probably five years, the question arises as to whether it would be ethical to treat a man with hypogonadism with placebo for such a long period. Secondly, the decision to treat certain patients was based on several factors which, for example, included individual clinicians criteria (as there were no clinical guidelines at the time), severity of symptoms (so there was a tendency to treat those with lower testosterone levels), contra-indications to TRT and the patient's decision to have the therapy or not. The mechanisms by which TRT may improve mortality could be related to benefits on cardiovascular risk factors such as reducing body fat content, cholesterol, systemic inflammation and improving insulin sensitivity and the immune response.

TRT and cardiovascular safety

Careful systematic meta-analyses[67–69] have not found any adverse effect of testosterone replacement being associated with an increase in cardiovascular events including mortality with the exception of one recent evaluation[70] which included the TOM trial.[71] The TOM trial reopened the debate as to whether or not TRT was safe in respect of the cardiovascular system.[71] However, there were some significant differences between this study and previous clinical trials of testosterone therapy. Firstly, the population comprised elderly men with multiple comorbidities with inclusion criteria of frailty. Secondly, the initiation dose of testosterone gel was 100 mg/day, twice the recommended dose used in normal clinical practise. Thirdly, the study was not adequately powered for assessment of cardiovascular events. The study primarily recorded a range of heterogeneous cardiovascular-related events which included self-reported syncope, oedema (which occurs in high-dose testosterone therapy) and exercise treadmill testing. This study is therefore an outlier in regard to the protocol and as it is not normal clinical practise should really not be included in meta-analysis where TRT is aimed at replacing testosterone to within the normal range. A similar clinical trial again examining the effect of TRT on frailty using conventional testosterone gel dosage of 50 mg/day did not find any difference in cardiovascular events between treatment and placebo study arms.[72] Apart from the TOM trial, no other major randomized double-blind placebo-controlled studies reported any adverse cardiovascular outcomes with testosterone therapy.

In this context, it is important to note that a recently published French study[73] of 3650 men aged >65 years found a J-shaped association between plasma total testosterone and ischaemic arterial disease (IAD – stroke and CHD) risk. The hazard ratios associated with the lowest and the highest total testosterone quintiles relative to the second quintile were 2·23 and 3·61, respectively. Additional analysis for coronary heart disease showed similar results, and they found a similar J-shaped association with bioavailable testosterone and risk of IAD. These findings are strongly supported by the results of the HIM study described above with mid-range and higher normal DHT being associated with the lowest risk of IHD.[23]

To be able to make any conclusions for normal day-to-day practice, included studies should be restricted to those that replace testosterone to within the normal healthy range. It may be that over-treatment may have an adverse effect on cardiovascular health, whereas normal replacement does not as is the case in thyroxine replacement. As described above, high normal levels of endogenous testosterone are not associated with an increased risk of cardiovascular events with one large study showing that these subjects are less likely to have such an event.

A retrospective cohort study of men in the Veterans Affairs system (USA)[74] with coronary heart disease evident at angiography and low testosterone (<10·4 nmol/l) compared the incidence of cardiovascular events (myocardial infarction, stroke and mortality) between subjects who received testosterone therapy and those who did not. This was a heavily flawed study for

several reasons. Firstly, once a subject was commenced on testosterone, it was assumed that treatment continued. In fact, 17·6% only had one prescription and the mean testosterone of patients who had testosterone level checked was 11·5 nmol/l, suggesting that many men were under-treated. Two-thirds received testosterone patches which are known to have a high discontinuation rate as a result of skin reactions. One-third received intramuscular testosterone ester injections which result in supra-physiological levels of testosterone. Secondly, no data on the diagnosis of hypogonadism which should include the presence of symptoms as well as low testosterone were presented. Thirdly, the raw data showed less events of each end-point in the testosterone-treated group. Statistical analysis using greater than 50 variables then suggested the opposite result. Fourthly, 1132 subjects with myocardial infarction or stroke which were given testosterone after these events were excluded from the analysis. If these had been included, then a beneficial effect of TRT would have been indicated. A safe conclusion cannot therefore be made without knowing the correct diagnosis; some patients not continuing therapy and those on testosterone having suboptimal testosterone levels on treatment even before the statistical methods are challenged.

A second study,[75] which collected data retrospectively from a health-care database following 55,593 prescriptions for testosterone in California, has reported an increased risk of nonfatal myocardial infarction in the 3 months after the prescriptions were issued compared to the prior 12 months in these patients and also with a cohort of men treated with phosphodiesterase type 5 inhibitors. There are several weaknesses in this study with no data on whether or not hypogonadism had been diagnosed or even if testosterone levels were measured, no evidence on compliance or monitoring of testosterone levels on treatment, haematocrit or PSA. The excess risk was only seen in men >65 years and who had pre-existing heart disease. Critically, there is no data on fatal MI and this could have led to confounding data as it could be argued that testosterone may have downgraded a fatal MI to a nonfatal MI. Furthermore, the PDE5 inhibitor group is likely to be a healthier group in relation to cardiovascular disease as those men with more severe heart disease would have been on nitrates for angina, a contra-indication for PDE-5 inhibitors.

Patients with known cardiovascular disease would logically be more expected to have an increased risk of events. However, several trials of TRT of between 3 and 12 months in men with either proven coronary artery disease[76] or moderate chronic heart failure[77,78] have not reported any more cardiovascular events than in the placebo groups. In summary, all of these studies found benefits. TRT increased time to 1-mm S-T depression (a measure of cardiac ischaemia) in men with chronic stable angina, an effect maintained at least up to 12 months of treatment.[76] Testosterone also improved functional exercise capacity and VO_2 max in men with chronic heart failure over studies up to 12-month duration.[77] It also has to be considered that if TRT reduced cardiovascular mortality that any benefit on reducing events such as myocardial infarction or stroke may be more difficult to detect as possibly there may be lesser severity of these episodes; that is,

cardiovascular death may be improved to a greater chance of surviving a myocardial infarction.

Conclusions

Longitudinal population studies have shown that especially in more elderly men in community-based studies and also men who have specific comorbidities which include cardiovascular, respiratory and renal diseases and those with cancer that a low testosterone is a biomarker for an increased risk of mortality. This is also true for men with Klinefelter's Syndrome, the commonest classical form of hypogonadism, who are known to be at increased risk of death from diabetes, cardiovascular disease, respiratory disease and cancer.[79] The main limitations of the different population studies are discrepancies between the cut-off values for low testosterone used, but some did analyse tertiles or quartiles of testosterone levels. Furthermore, differences between androgen receptor sensitivity as a result of the CAG repeat polymorphism and also symptom-specific thresholds suggest that there is more to the assessment of individual subject's androgen status than just a level below the normal range.[80]

The reason as to why testosterone is lower in these men at greater risk of earlier death may be that the degree of activation of pro-inflammatory cytokines reflects the severity of disease burden. There is clear evidence that testosterone levels are suppressed as a result of conditions which lead to the systemic production of inflammatory cytokines, be it as a result of low grade or more marked forms of chronic inflammation. Common clinical conditions which induce chronic inflammatory states are obesity, atherosclerosis, diabetes, chronic obstructive pulmonary disease and inflammatory arthritides. Acute illness as a result of infection, inflammation, infarction and trauma including surgery leads to severe suppression of the hypothalamic–pituitary–testicular axis resulting in levels of testosterone as low as 2 nmol/l. The majority of the studies described in this review especially in those which involve older men distinctly demonstrate that low testosterone is a biomarker disease severity and increased risk of mortality. It should, however, be recognized that mortality will and does depend on more factors in men than testosterone alone.

There is some evidence to support the notion that testosterone deficiency has an adverse effect on certain salient cardiovascular risk factors and also that promotes the progression of intimal media thickness albeit a surrogate marker of cardiovascular disease. There is little direct evidence apart from in animal studies that testosterone deficiency promotes the acceleration of atherogenesis in men. However, our knowledge of the effect of individual cardiovascular risk factors along with the data presented in this review and that men with higher endogenous testosterone levels have less cardiovascular events and that low testosterone increases the risk of cardiovascular death does suggest that a low-testosterone state over time has an adverse effect on the atherosclerotic process.

Apart from a potential direct effect on a particular disease process, testosterone deficiency may have an adverse effect on general health. Testosterone deficiency is associated with a poorer quality of life, reduced physical strength and muscle bulk,

fatigue, mood changes including lack of motivation, poor concentration and depression and that there may be an impairment of the immune system. These clinical parameters potentially would add to earlier mortality.

Evidence from two albeit mainly retrospective studies has reported near-identical results that testosterone replacement therapy improves survival of hypogonadal men compared to those untreated. The Barnsley study in addition found that testosterone replacement led to a realignment of survival prognosis with that expected in a testosterone replete man with type 2 diabetes. Although there are limitations associated with retrospective studies, the fact remains that a more than twofold improvement in the chances of survival is very significant. These exciting findings ideally will require verification by other studies and in longer-term placebo-controlled clinical trials. Recruitment and retention in such studies may prove difficult as well as ethical issues in conducting a placebo-controlled study in symptomatic men with hypogonadism.

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Declarations of interest

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