Commentary

Testosterone and coronary heart disease: is there a link?

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Introduction

Despite a ten-fold difference in total coronary artery disease (CAD) mortality in 50 countries, the male-to-female ratio remains remarkably constant at around two. How is this excess risk in men explained? There is a higher prevalence of hypertension, smoking and hyperlipidaemia in men, and those males affected by these risk factors have higher mortality than similarly-affected women. However, when the risks associated with high systolic blood pressure, cigarette smoking, raised cholesterol, raised fasting plasma glucose, and obesity are controlled for by means of a multiple logistic analysis, a significant sex difference still remains.

In women, early menopause is associated with an increased risk of cardiovascular disease, and myocardial infarction is more common following bilateral oophorectomy. By comparison, exogenous oestrogen use is protective against CAD in post-menopausal women, and high levels of endogenous oestrogen may explain the extremely low prevalence of CAD in pre-menopausal women. Women with the polycystic ovary syndrome have a higher than normal level of testosterone which is associated with obesity, insulin resistance, low levels of high-density lipoprotein cholesterol (HDLC), and an increased risk of myocardial infarction. It seems therefore, in women, that physiological levels of endogenous oestrogen are protective, while abnormally high levels of testosterone are detrimental.

By contrast, in men, high levels of oestrogen and oestrone are associated with increased risks of myocardial infarction, angina and CAD at angiography. Giving oestrogens to men with prostatic carcinoma is associated with increased mortality from CAD, and oestrogens given to male survivors of myocardial infarction lead to an increased re-infarction rate. Not only do high levels of oestrogen appear detrimental in men, but there is evidence to suggest that low levels of testosterone are also associated with an increased risk of CAD. It may be the different balance of androgens and oestrogens in the two sexes which is important in determining the sex difference in mortality from CAD.

Testosterone and atherogenesis

The premature development and progression of atheroma is dependent upon the interaction of a number of risk factors which have been identified in recent years. These risk factors (hypertension, dyslipidaemia, diabetes, high fibrinogen, obesity and smoking), tend to cluster in individuals and in families. Although there are substantial data regarding the risks associated with these conditions, common causative links and the mechanisms by which they interact with each other are poorly understood. Abnormalities in the balance of sex hormones may be implicated.

Testosterone and lipids

Different lipoproteins are of varying importance in the development of atheroma. High levels of low-density lipoprotein cholesterol (LDLC) and lipoprotein a are strongly associated with the development of CAD, whereas high levels of HDLC are protective. Men have an atherogenic profile, with lower levels of HDLC and higher levels of LDLC compared with pre-menopausal women or pre-pubescent boys.

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These differences between men and women may reflect an interaction with the balance of sex hormones, and since these are derivatives of cholesterol, a close link may be expected. Studies in normal men have consistently shown a positive correlation between total or free testosterone level and HDLc, and a negative correlation with LDLC and triglycerides.¹¹⁻¹⁵ Serum lipoprotein a levels are decreased in normal men by the administration of exogenous testosterone.¹⁶⁻¹⁷ Thus, men with hypotestosteronemia have a pro-atherogenic lipid profile. However, intervention trials have produced conflicting results. Chemically-induced hypogonadism by gonadotrophin-releasing-hormone analogues induces a rise in HDLc, which is corrected with intramuscular testosterone enanthate therapy.¹⁸⁻²⁰ Results of these intervention studies should not be used to draw conclusions about the lipid abnormalities seen in naturally occurring hypogonadism.

**Testosterone and hypertension**

Both systolic and diastolic hypertension are established risk factors for CAD. The direct influence of sex hormones on blood pressure control has not been studied as a primary objective. A number of investigators have looked at the relationship between blood pressure and testosterone as part of case-control studies of many CAD risk factors. They have found a consistent relationship between hypotestosteronemia and raised systolic and diastolic blood pressure.¹¹ Low mean levels of testosterone have been found in populations of hypertensive men.²¹ Moreover, a high oestradiol:testosterone ratio is associated with a high renin-sodium profile in hypertensive men,²² suggesting a possible aetiological link.

**Testosterone and insulin resistance/obesity**

Hyperinsulinaemia is a risk factor for coronary artery disease.²³ Many studies have investigated the relationship between androgens and insulin level in women, but relatively few have studied the relationship in men. There is an association in men between low free and total testosterone and hyperinsulinaemia; this relationship being converse to that seen in women.¹¹,²⁴ Similarly, total testosterone has been shown to be lower in non-insulin-dependent diabetic men who have higher plasma insulin levels than in normoglycaemic men.¹² In centrally-obese middle-aged men, testosterone replacement reduces hyperinsulinaemia.²⁵

Obesity and increased waist:hip ratio are both predictors of hyperinsulinaemia. Free and total testosterone are decreased in proportion to the degree of obesity,²⁶ and a significant correlation has been found between decreased testosterone blood level and increased waist:hip ratio.¹¹,²⁴,⁴² This relationship may be explained by the fact that the oestrogen:testosterone ratio is determined, at least in part, by the peripheral conversion of androstenedione to oestrone by aromatase activity in adipose tissue and muscle. Thus, men with android obesity have lower testosterone levels, secondary to increased conversion of androgens to oestrogens in peripheral fat, and have a higher risk of CAD.

**Testosterone and smoking**

Estradiol levels are increased in otherwise healthy, young male smokers.²⁹ A recent study has demonstrated significant reductions in total testosterone levels in rats exposed to cigarette smoke for 60 days. This was associated with degeneration of Leydig cells on histological examination of the testis.²⁸ However, human studies have shown conflicting results, with some authors reporting low serum testosterone levels in smokers,²⁹ while others have found high levels.³⁰,³¹

**Testosterone and fibrinogen**

Fibrinogen is an independent risk factor for myocardial infarction and atheroma formation.³²⁻³³ Low levels of serum testosterone are associated with high fibrinogen levels,³⁴,³⁵,³⁷ and administration of exogenous testosterone causes fibrinogen levels to fall.³⁷ Low levels of testosterone may therefore predispose to accelerated atheroma formation through its effect on fibrinogen.

**Testosterone and age**

Increased age is one of the strongest predictors for coronary artery disease. The Telecom Study of 1400 males aged between 20 and 60 years demonstrated a significant stepwise decrease in testosterone concentration with each decade. This relationship was maintained after the exclusion of patients with chronic disease and statistical correction for body mass index, alcohol consumption and subscapular skin-fold thickness.³⁸

**Testosterone and atheroma at coronary angiography**

The summary of the evidence above shows clearly that a low level of serum testosterone is associated with all the common risk factors for CAD. If the association were of pathogenic significance, it should be reflected in a correlation between testosterone concentration and findings at coronary angiography. A significant negative correlation between testosterone level and the presence of CAD has been found in two studies using coronary angiography to detect
Testosterone and CHD

Testosterone and acute coronary thrombosis

Ninety percent of cases of myocardial infarction follow an acute thrombotic occlusion of an already damaged coronary artery. As already discussed, a low level of testosterone is associated with coronary atheroma. Is low testosterone also implicated in acute thrombotic episodes?

Testosterone and haemostasis/fibrinolysis

A number of studies have investigated the role of testosterone in the haemostatic/fibrinolytic pathways, with uniform results. Testosterone has been positively correlated with tissue plasminogen activator (the major stimulator of fibrinolysis) and negatively with the procoaguable factors, plasminogen activator inhibitor, fibrinogen, alpha-2 antiplasmin and factor VIlc. These results remain significant after control for other variables. Furthermore, exogenous testosterone administration causes a fall in plasma fibrinogen and plasminogen activator inhibitor. Hypotestosteronemia is therefore implicated in a pro-thrombotic tendency, and theoretically would be associated with an increased risk of acute myocardial infarction and thrombotic stroke, whereas a physiological level of testosterone should decrease thrombotic risk by reducing fibrinogen and increasing fibrinolytic activity.

Testosterone and myocardial infarction

Numerous studies have attempted to clarify the relationship between sex hormones and acute myocardial infarction. Many of these primarily studied oestrogen, oestradiol and oestrone, with testosterone being a secondary measurement. The period immediately prior to myocardial infarction is inevitably difficult to study, but a number of centres have demonstrated significantly low levels of testosterone immediately following myocardial infarction. This is, however, not a consistent finding, with the majority of studies showing no significant differences. Profiling of testosterone has demonstrated that the low levels seen post infarct may be due to an immediate fall in testosterone which subsequently returns to normal. This is mirrored by similar falls following surgery and trauma, suggesting it may be an acute response. A recent study in Denmark has examined the relationship between low testosterone and acute ischaemic stroke in 144 men. The authors found that total testosterone level was inversely associated with stroke severity, infarct size and six-month mortality. Again, these results may be due to an acute fall in testosterone levels following acute stroke. These studies do not show a causative link between a low level of testosterone and acute thrombotic events, but raise enough questions to warrant further studies.

Testosterone and coronary artery disease mortality

Work to date provides circumstantial evidence of a link between low testosterone levels, atherogenesis and acute arterial thrombosis. However, studies examining the association between low testosterone and CAD mortality have been inconclusive. A study of 1000 men aged between 40 and 79 years looked at the development of cardiovascular disease (heart attack, heart failure or stroke) over a 12-year period, and correlated this with total testosterone level taken at the beginning of the trial. The investigators found no significant association between total testosterone at baseline and the prevalence or development of cardiovascular disease. A further study of the sera of 163 men who died from a definite myocardial infarct or from coronary heart disease compared with 163 matched controls found no significant difference between free or total testosterone in cases or controls. The Caerphilly Heart Study again did not find testosterone level to be a primary risk factor for CAD mortality. All these studies have limitations: particularly, Barrett-Connor et al. did not examine free testosterone levels, and the population in the Caerphilly Heart Study was relatively young (aged 45–59 years) and followed for only 5 years. Stronger evidence might have been produced had the study been extended for a longer period. A further limitation in the study of the relationship between testosterone and CAD is that the measurement of testosterone has only been possible since the 1960s, and is still being developed. It can be subject to methodological problems, which arise from the fact that 98% of testosterone is bound to sex-hormone-binding globulin, and to a lesser extent, albumin. The assays for free testosterone are improving, but their sensitivity is not good enough to define borderline hypogonad-ism clearly. The measurement of testosterone is further complicated by its diurnal and circannual variation and wide intra-individual variability.

Conclusions

The protective value of sex hormones appears to be sex-specific, and the ratio of oestrogen to testosterone may be important. Oestrogens appear protective in women but detrimental in men, whereas it appears
that testosterone is protective in men, yet deleterious in women. A normal physiological level of testosterone in men may protect against the development of hyperlipidaemia, hyperinsulinism, hypertension, thrombophilic tendency, obesity and increased waist:hip ratio, all of which predispose to the development of CAD. Low or low normal testosterone may also be implicated in the pathogenesis of acute myocardial infarction and acute stroke. The decline of testosterone with age may partly explain the greater risk of CAD with advancing years. Moreover, there may be a population of younger men with relative hypogonadism who are at increased risk of premature CAD, complaining only of fatigue and depression, in whom the true diagnosis is unsuspected and undiagnosed.

Trials examining the association between CAD mortality and morbidity and sex hormone levels in men need to be large and over long time periods to identify trends associated with small differences in sex hormones. The importance of testosterone in the pathogenesis of CAD may be in part due its effect in the short or medium term on lipids or coagulation factors. Clearly, studies to determine the significance of these different effects in different time scales need to be sophisticated in design.

Now is the time to undertake the large prospective trials required to establish a cause and effect relationship between low testosterone levels and CAD.

References


