Hormones and the heart
**Aim and Scope**

*Heart and Metabolism* is a quarterly journal focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications. Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

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The effect of hormones on the heart usually relates to tachycardias such as thyroid overactivity, bradycardias such as thyroid underactivity, and arrhythmias such as adrenaline excess. In this edition of Heart and Metabolism, we focus on the hormone “of the moment”—testosterone. We know that in chronic conditions testosterone depletion is quite common, eg, affecting nearly 50% of type 2 diabetics. The question has always surrounded the safety of replacing testosterone in those who are hypogonadal. Recently, the replacement of testosterone has been thought to increase cardiovascular risk. This has caused considerable consternation as the bulk of preceding trials suggested the opposite. So, it was particularly interesting to read a systemic review and meta-analysis of cardiovascular risk associated with testosterone replacement therapy (TRT).1

This report from a well-recognised unit does not support a causal link between TRT and adverse cardiovascular risk events.1 Similarly, the European Medicines Agency (EMA) could find no evidence that TRT in hypogonadal men increased cardiovascular risk.2 In an editorial, Wu reviewed the position of TRT and the absence of cardiovascular risk, but more information was needed with regard to benefit.3

Wu’s reassurance that there is no obvious disadvantage in using TRT is alluded to by Professor Hugh Jones in his paper featuring in this edition of Heart and Metabolism, and even raises the possibility that TRT reduces mortality. The body of evidence, as discussed in this issue, is very much in favour of TRT improving quality and possibly quantity of life. This is further reinforced by the Vlachopoulos et al paper, where they found that a low plasma testosterone in hypertensive patients was associated with an increased risk of major cardiac events.4

My personal approach is, if the patient is hypogondal and there are no contraindications, to replace testosterone to normal levels (>12 nmol/L). Furthermore, there is increasing evidence that testosterone may be important with regard to reducing abdominal obesity, which in turn should therefore decrease cardiovascular risk further.5

Therefore, whilst there is a degree of confusion, we hope that this issue of Heart and Metabolism will help to clarify the position of TRT as a hormone that benefits the heart.

REFERENCES
Endocrine function is a cornerstone in both cardiovascular physiology and cardiovascular disease. As expected, endocrine disorders, either in the form of overt hypofunction/hyperfunction or even in their subclinical form, have essential effects on the cardiovascular system. Two endocrine glands associated mostly with cardiovascular physiology are the thyroid and the adrenal gland. There is a large number of clinical studies that have explored the effect of these two glands and their secreted hormones on cardiovascular health. The scope of this review is to investigate the main cardiovascular alterations that are related to the thyroid hormones and aldosterone in cases of endocrine dysfunction. Additionally, we comment on the cardiovascular therapeutic opportunities offered by these hormones for improvement of cardiovascular health and prognosis.

Thyroid and cardiovascular disease

Thyroid hormones, triiodothyronine (T₃) and thyroxine (T₄), are produced in the thyroid gland in a molar ratio of approximately 1 to 7. Every enzymatic step in the synthesis and secretion of T₄ and T₃ is regulated by thyrotropin, also known as thyroid-stimulating hormone (TSH). The TSH test is the appropriate initial screening for thyroid dysfunction in several cardiovascular clinical entities and risk factors known to be affected by thyroid disease such as hypertension, atrial fibrillation, and dyslipidemia.²

Keywords: aldosterone; cardiovascular disease; heart failure; hormone; thyroid

Abstract

The endocrine and cardiovascular systems have essential pathophysiological links. As expected, dysfunction of one leads to harmful consequences to the other. Thyroid hormones and aldosterone are two examples of this close association. Dysfunction of the thyroid gland is usually suspected due to cardiovascular symptoms, such as those related to increased blood pressure and rhythm disturbances. Thyrotropin, also known as thyroid-stimulating hormone, is the initial screening test used. Importantly, even subclinical forms of thyroid dysfunction can affect cardiovascular prognosis. Similarly, increased levels of aldosterone are implicated in several cardiovascular disorders, such as hypertension and heart failure. Blockade of aldosterone in these conditions leads to improved prognosis. Contrary to some other chronic diseases, endocrine dysfunction can be reversed or at least adequately managed in order to improve cardiovascular health and reduce cardiovascular events. For these reasons, it is of paramount importance for the cardiologist to work hand in hand with the endocrinologist in such patients. Heart Metab. 2015;66:3-6

Keywords: aldosterone; cardiovascular disease; heart failure; hormone; thyroid

Endocrine function is a cornerstone in both cardiovascular physiology and cardiovascular disease.¹ As expected, endocrine disorders, either in the form of overt hypofunction/hyperfunction or even in their subclinical form, have essential effects on the cardiovascular system. Two endocrine glands associated mostly with cardiovascular physiology are the thyroid and the adrenal gland. There is a large number of clinical studies that have explored the effect of these two glands and their secreted hormones on cardiovascular health. The scope of this review is to investigate the main cardiovascular alterations that are related to the thyroid hormones and aldosterone in cases of endocrine dysfunction. Additionally, we comment on the cardiovascular therapeutic opportunities offered by these hormones for improvement of cardiovascular health and prognosis.

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The effects of thyroid hormones on cardiovascular system are the most clinically useful and sensitive signs of thyroid dysfunction. Regarding pathophysiology, thyroid dysfunction has essential cardiovascular consequences in myocardial contractility, peripheral hemodynamics, and heart rate (Figure 1). Thyroid hormones, in addition to their direct effects on cardiovascular function, also have indirect effects mediated through the autonomic nervous system, renin-angiotensin-aldosterone system (RAAS), and renal function, and resultant changes in vasoreactivity, arterial stiffness, and atherosclerosis. The importance of vascular function and especially aortic stiffness as assessed by pulse wave velocity is high, as arterial stiffness is an independent and strong predictor of cardiovascular prognosis and all-cause mortality.

**Hyperthyroidism**

Cardiovascular symptoms are often the principal clinical elements of patients with hyperthyroidism. Palpitations are common in most patients, resulting from increases in cardiac contractility. Heart rate increase is caused by an increase in sympathetic tone and a decrease in parasympathetic stimulation. Heart rate increase during exercise is exaggerated. Many patients with hyperthyroidism experience exercise intolerance and exertional dyspnea.

Systolic hypertension is common in hyperthyroid patients. This elevation in systolic pressure may result from the combined effect of increased preload and cardiac output, as well as of increased arterial stiffness. Consequently, left ventricular hypertrophy has been associated with the hyperthyroid state. Furthermore, in the long term, hyperthyroidism is also associated with diastolic dysfunction. In severe, untreated cases, it may even lead to heart failure. Increased rates of pulmonary hypertension have been observed in hyperthyroidism.

Sinus tachycardia is the most common rhythm alteration in patients with hyperthyroidism. However, atrial fibrillation is the most clinically important arrhythmia of hyperthyroidism. The prevalence of atrial fibrillation ranges from 2% to 20% and increases progressively with age. Symptomatic treatment of atrial fibrillation includes β-blockers that can rapidly alleviate symptoms of hyperthyroidism in contrast to the mainstay treatment for hyperthyroidism that requires a longer period of time to restore the euthyroid state. Anticoagulation in patients with hyperthyroidism and atrial fibrillation is controversial. A small percentage of hyperthyroid patients can present with angina-like chest pain that could imply myocardial ischemia due to increase in cardiac work or even a form of vasospastic angina. Even in its subclinical form, hyperthyroidism is associated with an increased risk of coronary heart disease events and mortality, especially when levels of TSH are below 0.10 mIU/L.

**Hypothyroidism**

The cardiovascular features of hypothyroidism are more subtle and less conspicuous. Bradycardia, diastolic hypertension, and narrow pulse pressure are all typical. Changes in cardiovascular function and hemodynamics caused by hypothyroidism are entirely opposite to those of hyperthyroidism (Table I). Furthermore, hypothyroidism also produces increases in total cholesterol and low-density lipoprotein cholesterol analogous to the rise in TSH level. The serum creatine kinase level is substantially elevated in up to 1 out of 3 patients with hypothyroidism. Pericardial effusion may also be a consequence of hypo-

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**Abbreviations**

ARR: aldosterone-to-renin ratio; RAAS: renin-angiotensin-aldosterone system; T₃: triiodothyronine; T₄: thyroxine; TSH: thyrotropin/thyroid-stimulating hormone.
thyroidism. Plausible mechanisms are a decrease in lymphatic clearance function and an increase in the volume of distribution of albumin. Prolongation of QT interval can also be observed.

As expected, exacerbation of cardiovascular risk factors, such as hypertension, hypercholesterolemia, and increased homocysteine, with hypothyroidism can lead to atherosclerosis and eventually overt cardiovascular disease. Hypothyroidism, even in the form of a subclinical condition, is associated with coronary heart disease events and mortality, particularly in those patients with a TSH concentration of 10 mIU/L or greater.8 Hormone replacement treatment with levothyroxine in patients older than 50 years with known or suspected coronary artery disease should be cautiously initiated following the combined assessment by both a cardiologist and an endocrinologist.

Aldosterone and cardiovascular disease

Aldosterone is a mineralocorticoid hormone that is produced from cholesterol in the zona glomerulosa of the adrenal cortex by a series of enzymatic reactions.9 The RAAS regulates aldosterone synthesis mainly by angiotensin II, which binds to the angiotensin II type I receptor on cells of the zona glomerulosa. Other regulatory factors include serum sodium and potassium levels and adrenocorticotropic hormone. Mineralocorticoid hormones work to maintain normal sodium and potassium concentrations, and to maintain normal volume status. Renin secretion responds principally to changes in intravascular volume.

**Hyperaldosteronism**

Primary hyperaldosteronism is a group of clinical entities in which aldosterone production is disproportionately high, resulting in inhibition of the RAAS.9 Hypertension is the hallmark clinical characteristic of hyperaldosteronism.10 The prevalence of hyperaldosteronism is reported as up to 1% to 5% of patients with hypertension, and 5% to 20% of patients with resistant hypertension.1 Potassium depletion is also a hallmark of hyperaldosteronism. Screening for hyperaldosteronism is made by measuring plasma aldosterone and plasma renin activity, and calculating an aldosterone-to-renin ratio (ARR). Patients with a positive ARR (ARR >20 with aldosterone >15 ng/dL) should be further evaluated.

Hyperaldosteronism causes pathologic cardiac remodeling and has been implicated in left ventricular hypertrophy, diastolic dysfunction, and cardiac fibrosis. Increased aldosterone levels have been shown to cause endothelial dysfunction and promote inflammation, while aldosterone-mediated vascular fibrosis leads to increased arterial stiffness. Finally, hyperaldosteronism has been associated with impaired glucose tolerance and decreased insulin sensitivity. These deleterious effects could partly explain the detrimental effect of primary aldosteronism on cardiovascular mortality, even in treated patients.11

In myocardial infarction and heart failure, aldosterone levels are elevated and contribute to maladaptive cardiovascular remodeling via direct effects on collagen deposition and consequent cardiovascu-

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*Table I* Cardiovascular symptoms, signs, and hemodynamics in different thyroid states.

Abbreviations: ms, milliseconds; bpm, beats per minute.

Thyroid, aldosterone, and cardiovascular disease

lar fibrosis. Many studies have shown that aldosterone blockade ameliorates these deleterious effects. Two large randomized clinical studies, the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), confirmed the beneficial effect of aldosterone blockade and introduced aldosterone antagonists in the treatment of heart failure. However, the beneficial effects of aldosterone blockade in diastolic dysfunction and heart failure are controversial and probably minimal. Finally, despite the fact that studies have shown a beneficial effect of mineralocorticoid receptor blockade when added to standard therapy on proteinuria in patients with diabetic nephropathy, hyperkalemia still remains an important issue.

Conclusion

Both thyroid hormones and aldosterone have essential effects on the cardiovascular system. Imbalance of their levels leads to disturbance in the homeostasis of the cardiovascular system. Importantly, most of these deleterious hormone-mediated cardiovascular effects can be reversed or managed with the proper regulation or blockade of these hormones. Therefore, it is important for both endocrinologists and cardiologists to apply a global approach in the assessment of such patients.

REFERENCES

Testosterone and cardiovascular disease

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Abstract
Low levels of endogenous circulating testosterone in men in community-based epidemiological studies are associated with an increased risk of mortality from all causes, with some studies identifying a link with cardiovascular (CV) disease. Testosterone deficiency is associated with several CV risk factors including central obesity, dyslipidemia, hypertension, and insulin resistance. Testosterone replacement therapy (TRT) in men with hypogonadism, when carefully replaced to the normal range, has been shown to improve some risk parameters including waist circumference, total and low-density lipoprotein cholesterol, lipoprotein(a), insulin resistance, and hyperglycemia. TRT does slightly lower high-density lipoprotein cholesterol in some trials; the clinical significance of this effect is not known. Beneficial effects of TRT have demonstrated reduced exercise-induced cardiac ischemia in men with chronic stable angina and improved functional exercise capacity, and $V_{O2\text{max}}$ in men with moderate chronic cardiac failure. Evidence from well-conducted trials where TRT achieves normal testosterone values and meta-analysis of the studies have not identified any increased risk of major CV events. Some recent studies have shown increased CV risk, but have major flaws in design and either over- or under-treated patients. Clearly only a large, long-term, placebo-controlled randomized clinical trial may provide the definitive answer. The benefits of TRT on quality of life and sexual function are very important to the majority of men with hypogonadism. Furthermore, two retrospective studies have reported that TRT can reduce mortality in hypogonadal men with and without type 2 diabetes. Careful diagnosis, titration of testosterone dose to maintain levels within the mid-normal range, and long-term safety monitoring are key to the reduction in complications. ■ Heart Metab. 2015;66:7-12

Keywords: cardiovascular; diabetes; heart; testosterone

Sexual dysfunction has been identified as a biomarker for the presence of cardiovascular (CV) disease, which may predate the onset of a future CV event. Erectile dysfunction (ED) may be the first symptom of CV disease.\(^1\) It is well recognized that CV risk reduction by improvement in lifestyle (diet, exercise, and cessation of smoking) and control of hypertension, cholesterol, and diabetes can reduce CV events. ED is one of a triad of sexual symptoms found in male hypogonadism with reduced, or loss of, libido and morning erections accounting for the other two.\(^2,3\) Between 20% to 30% of men with ED have
hypogonadism. There is good evidence that low levels of circulating testosterone have a high prevalence in men with CV disease, metabolic syndrome, and type 2 diabetes.\textsuperscript{4,5} Low testosterone may merely be a biomarker of illness secondary to the chronic inflammatory state of atherosclerosis. Accumulating evidence has demonstrated that low testosterone levels are associated with an increased risk of death and that higher endogenous testosterone may protect against major CV events.\textsuperscript{6-10} There is evidence, mainly from animal studies, that testosterone deficiency may promote atherogenesis, whereas replacement can ameliorate the disease.\textsuperscript{11} Testosterone replacement therapy (TRT) has been shown to improve exercise-induced cardiac ischemia, cardiac failure, and may improve mortality. However, some recent retrospective studies have raised concerns over testosterone therapy increasing CV events, although these are heavily flawed, whereas the majority of studies and meta-analyses have not supported this. This short review will discuss current clinical aspects of testosterone deficiency and replacement therapy.

**Epidemiology**

The majority of community-based population studies have reported that low testosterone levels (in particular <12 nmol/L) are associated with an increased all-cause mortality risk.\textsuperscript{6} Several of these studies have shown that the most common cause of mortality is CV disease.\textsuperscript{6} In disease-specific populations, which include men with proven CV disease by coronary angiography (Figure 1), and in type 2 diabetes, low testosterone increases mortality risk two-fold.\textsuperscript{12,13} Two studies support an effect of low testosterone on an increased risk of CV events. The MrOS study from Sweden has demonstrated that men in the upper quartile of testosterone levels have lower CV events than those in the lower three quartiles combined.\textsuperscript{9} Another study found that there was a “J-shaped” curve with a reduced frequency of CV events in the mid-normal range.\textsuperscript{10} The Health in Men (HIM) study from Australia reported that there was a reduced risk of all-cause mortality in the mid-to-higher normal range compared with low and high levels representing a “U” shaped curve.\textsuperscript{6} Additionally, this study found that CV mortality was decreased in men with dihydrotestosterone levels in the high-normal range. This knowledge that testosterone deficiency is associated with an increased risk of CV mortality is supported by the findings that men receiving androgen deprivation therapy (ADT) for prostate cancer have increased frequency of CV events and death.\textsuperscript{14}

The reasons as to why testosterone deficiency is associated with CV disease and mortality have not been fully established. Low testosterone may be a biomarker as a consequence of ill health. Chronic inflammatory disorders, which include atherosclerosis, may suppress the hypothalamic-pituitary-testicular axis, thus lowering testosterone levels. However, there is evidence that testosterone deficiency is associated with major CV risk factors.\textsuperscript{5} These include central adiposity, dyslipidemia, insulin resistance, hyperglycemia, and a proatherogenic cytokine profile. Hypogonadism has an increased prevalence in men with type 2 diabetes and hypertension as well as CV disease.\textsuperscript{5,5}

**Abbreviations**

ADT: androgen deprivation therapy; BMI: body mass index; CHF: chronic heart failure; CV: cardiovascular; ED: erectile dysfunction; FDA: Food and Drug Administration; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LP(a): lipoprotein(a); MACE: major adverse cardiovascular events; PDE5: phosphodiesterase type 5; TRT: testosterone replacement therapy.
Carotid intima-media thickness (CIMT) is increased in men with low testosterone. One study showed that after a 4-year follow-up, progression of CIMT was greatest in men with testosterone levels in the lower tertile. Animal studies have demonstrated that testosterone deficiency leads to an increased risk of lipid streak formation within aortic and coronary arteries. Testosterone supplementation ameliorates the deposition of lipid. This raises the question as to whether or not TRT may have an atheroprotective effect.

Pathogenesis

The European Male Aging Study (EMAS) has demonstrated that obesity and comorbidities are the major promoters for the suppression of testosterone deficiency, with aging accounting for a lesser effect. Evidence supports a bidirectional mechanism between obesity and testosterone status. Hypogonadism is well known to increase body fat and reduce muscle mass. This is evident in men with Klinefelter’s syndrome who may present with a female distribution of body fat (eunuchoid habitus). Furthermore, men with low testosterone in epidemiological studies have an increased risk of developing the metabolic syndrome and type 2 diabetes, independent of obesity at baseline.

Obesity is considered to be a proinflammatory state as adipocytes secrete adipocytokines, which include tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), interleukin-6 (IL-6), and leptin. These adipocytokines act upon the hypothalamus to inhibit pulsatile gonadotropin-releasing hormone (GnRH) release leading to the suppression of luteinizing hormone and then testosterone secretion from the testes. In addition, the aromatase activity correlates positively with the degree of visceral fat, leading to more rapid breakdown of testosterone to estradiol, lowering circulating testosterone levels further. The testosterone-deficient state enhances the uptake of triglycerides into adipocytes and promotes the relative increase in fat cells derived from stem cells compared with muscle cells. This bidirectional relationship between fat and testosterone metabolism is known as the hypogonadal-obesity-adipocytokine hypothesis (Figure 2). The greater the fat deposition, the greater the breakdown of testosterone. Adipocyte aromatase activity increases further, eventually leading to a hypogonadal state. Weight reduction and exercise may break the cycle, but hypogonadism can be associated with lack of motivation and therefore a poor response to lifestyle changes.

Angina

Testosterone therapy was first shown to relieve symptoms of angina in 1939 with several case report studies finding that the majority of men and also women responded. More recently, these observations have been confirmed in placebo-controlled studies over periods between 1 and 12 months. Testosterone therapy improves time to 1 mm ST depression on exercise testing in men with chronic stable angina, either when administered acutely or over several months. Importantly, the lower the baseline testosterone level the greater the reduction in ischemia. Evidence strongly supports a role of testosterone as a rapid-acting arterial vasodilator in the coronary arteries as well as in other systemic vessels, including mesenteric and pulmonary vascular beds. In particular, one study in which testosterone was given directly into coronary arteries in men undergoing routine angiography showed testosterone significantly increased coronary artery diameter and coronary blood flow within a period of 2 to 5 minutes. In vitro experi-

![Fig 2: Hypogonadal-obesity-adipocytokine hypothesis.](image)
ments have shown that testosterone may promote vessel dilation by blocking L-calcium channels at the nifedipine binding site. Other sites of action include inhibiting potassium channels and intracellular, store-operated calcium release, increasing the expression of \( \beta_1 \)-adrenergic receptors as well as upregulating the response to noradrenaline and acetylcholine. Conversion of testosterone to estradiol may also lead to a vasodilatory response, but there is a direct effect of testosterone and its metabolite dihydrotestosterone (DHT) that is endothelium independent.

**Chronic heart failure**

Chronic heart failure (CHF) is commonly caused by coronary artery disease. CHF significantly impacts quality of life, causes cachexia, and has a high mortality rate that is worse than several forms of cancer. Low testosterone is common in men with CHF and is likely to occur as a consequence of chronic inflammation resulting from atherosclerosis, heart failure, and/or the cachectic state. Supraphysiological levels of testosterone promote the retention of extracellular water and if patients with hypogonadism are overtreated, then this can lead to an exacerbation of cardiac failure. Unlike older formulations, transdermal administration of testosterone replacement can be carefully titrated and replace testosterone to within the mid-normal range.

There have been a small number of trials of up to 12 months that have reported a beneficial effect of TRT in men with moderate CHF. Testosterone improved functional exercise capacity, \( V_{O_{2max}} \), and, in one-third of men, improvement in New York Heart Association class in the 12-month study. Furthermore, in the 12-month study blood pressure and left ventricular length did not deteriorate, whereas there was worsening of these parameters in the placebo population. This suggests that testosterone may possibly retard progression of left ventricular dysfunction.

**Testosterone replacement therapy and cardiovascular risk factors**

The major clinical indication for TRT is to improve the symptoms of hypogonadism, which primarily include sexual dysfunction. However, there have been several studies that have reported beneficial effects on certain CV risk factors, which include central adiposity, total and low-density lipoprotein (LDL) cholesterol, lipoprotein(a) (Lp[a]), and insulin resistance, as well as suppressing serum levels of proinflammatory cytokines.

Visceral adiposity, as assessed by waist circumference, waist-hip ratio, and computed tomography (CT)/magnetic resonance imaging (MRI) scanning, in hypogonadal men is significantly decreased by TRT. Furthermore, several trials have reported a reduction in fat mass and an increase in lean mass supported by a fall in serum leptin when this has been measured. The corresponding rise in muscle bulk may explain why most studies have not shown changes in body mass index (BMI). A longer-term observational study has shown a gradual improvement in waist circumference and BMI over a period of 3 years.

TRT consistently lowers total cholesterol by 0.25 to 0.5 mmol/L. Some studies have demonstrated falls in LDL cholesterol and/or triglycerides, whereas some have not. The effect of TRT on high-density lipoprotein (HDL) cholesterol is less clear, with small decreases, no change, or increases. The explanation for these alterations in HDL are not clear, however commentators have suggested that as a result of reverse cholesterol transport, increased shuttling of cholesterol from lipid laden tissues back to the liver may lead to the fall in concentration. Further work needs to examine and exactly determine the biological and indeed clinical relevance, if any, of these phenomena. Lp(a) correlates positively with CV risk and research has shown that TRT significantly lowers levels of this lipoprotein. No studies, however, have been performed to determine if suppression of Lp(a) improves CV outcomes.

TRT does decrease insulin resistance in hypogonadal men with metabolic syndrome and/or type 2 diabetes. Insulin resistance is considered to be an intermediate CV risk factor as it does lead to hyperglycemia, hypertension, dyslipidemia, as well as endothelial dysfunction and a proinflammatory serum cytokine profile. TRT suppresses TNF\( \alpha \), IL-1\( \beta \), and IL-6, and raises IL-10, an antiatherogenic cytokine.

Whether or not there is an overall benefit of TRT on CV risk in men when replaced to the normal physiological range is unknown.

**Testosterone replacement therapy and cardiovascular safety**

There has been some recent controversy over whether or not TRT increases the risk of adverse CV events
as a result of two retrospective studies and one trial that used high doses of testosterone in elderly men. Many clinical trials (including several randomized controlled trials), clinical use of TRT over more than 70 years, and other meta-analyses have not unmasked any increased risk. Indeed a meta-analysis of studies in men with metabolic syndrome and type 2 diabetes has shown reduced risk.

Both retrospective trials have received heavy criticism due to flawed study design and analysis. The Vigen et al study compared two groups; those receiving TRT and those who did not. There was a complicated statistical analysis using over 50 variables, which changed a positive effect of TRT with lower CV events to an adverse result. Furthermore, there was no evidence that all patients were carefully diagnosed with hypogonadism and, once on treatment, 17.6% received only one prescription. The mean testosterone level on treatment in those who continued was subtherapeutic. Later, the authors also admitted that they had included a significant number of females in their analysis. Comments and responses to the Vigen et al paper are discussed in the Journal of the American Medical Association.

The Finkle et al study using data on 55,000 testosterone prescriptions in California compared reporting of myocardial infarction in the first 3 months with either the same patients in the 12 months prior to the prescription or a cohort of men receiving phosphodiesterase type 5 (PDE5) inhibitors. They reported an increased risk of myocardial infarction on TRT compared with the other group. No data were given on whether hypogonadism was diagnosed before initiation of therapy or if testosterone levels had been performed, nor testosterone levels on treatment. The comparator groups were not appropriate. Use of nitrates associated with more severe CV disease are contraindicated with PDE5 inhibitors, so the latter group would potentially have been a healthier cohort in respect to preexisting disease.

A recent systematic review and meta-analysis of randomized placebo-controlled clinical trials (testosterone treated, n=3016; placebo, n=2747) did not detect any increased risk of major adverse CV events (MACE) in those men on TRT. Other meta-analyses have been limited by not having a defined end point of MACE and have used a wide definition of CV-related episodes. The US Food and Drug Administration (FDA) have stated that “these studies do not provide conclusive evidence of increased risk associated with the use of testosterone therapy.” Recently a large study of 6355 testosterone treated men did not show an increased risk of myocardial infarction. Many experts in the field have called for a large, well-powered clinical trial to determine whether or not TRT has adverse or beneficial effects on CV outcomes. This has now been recognized by the FDA.

Conclusion

Erectile dysfunction and testosterone deficiency are independent biomarkers for the presence and severity of CV disease, metabolic syndrome, and type 2 diabetes. Each biomarker could potentially raise awareness as an early marker of atherosclerosis. Hypogonadism requires careful diagnosis preferably by an experienced clinician in this area. Quality of life is very important to many people and TRT may achieve an improvement. The decision to treat with TRT should be discussed with patients with regards to benefit and risks. Only a longer-term trial will provide answers to whether or not there is an effect, positive or negative, on patients.

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Ischemic heart disease (IHD) is the leading cause of death and disability worldwide, one major manifestation of which is an acute ST-segment elevation myocardial infarction (STEMI). For these patients, the treatment of choice is timely myocardial reperfusion using primary percutaneous coronary intervention (PPCI). However, the process of reperfusion can in itself independently induce myocardial injury and cardiomyocyte death—a phenomenon that has been termed “myocardial reperfusion injury” and that contributes to up to 50% of the final myocardial infarction (MI) size. Therefore, novel cardioprotective therapies are required to protect the heart against myocardial reperfusion injury in order to reduce MI size, preserve myocardial function, and prevent the onset of heart failure. In this regard, a number of hormones have been reported in preclinical animal studies and early clinical trials to reduce MI size when administered at the time of reperfusion. Assessing the cardioprotective efficacy of a novel therapy requires the measurement of the area at risk (AAR) of MI and MI size, as this allows the calculation of myocardial salvage, which is a more sensitive measure of cardioprotection than absolute MI size reduction as it takes into account the AAR. Cardiac magnetic resonance imaging (MRI) is an important imaging modality for assessing myocardial salvage in reperfused STEMI patients. The recent availability of hybrid simultaneous positron emission tomography (PET)/MRI will allow one to investigate the effects of novel cardioprotective therapies in the reperfused heart on cardiac metabolism, fibrosis, angiogenesis, apoptosis, and inflammation, providing new insights into the pathophysiology of acute MI and the post-MI remodeled heart. In this article, we review the emerging role of cardiac MRI to assess myocardial salvage of novel cardioprotective therapies such as hormones.

Keywords: acute myocardial infarction; cardiac MRI; cardioprotection; myocardial reperfusion injury; myocardial salvage; PET/MRI
patients going on to develop heart failure is actually increasing. Therefore, novel therapies are required to prevent myocardial reperfusion injury, reduce myocardial infarction (MI) size, and preserve cardiac function, thereby preventing the onset of heart failure. In this respect, experimental animal and early clinical studies have reported beneficial effects in terms of myocardial salvage with several different hormones administered at the time of myocardial reperfusion. The ability to assess the cardioprotective efficacy of novel therapies requires the in vivo measurement of the area of myocardium at risk of MI (the area at risk or AAR) and MI size. In this regard, T2-weighted cardiac magnetic resonance imaging (MRI) can quantify the size of the AAR by detecting areas of myocardial edema, an approach that has been used to measure myocardial salvage in clinical cardioprotection studies. In this article, we highlight myocardial reperfusion injury as a neglected therapeutic target, review the therapeutic potential of hormones as a novel cardioprotective therapy for preventing reperfusion injury, and explore the role of cardiac MRI for measuring myocardial salvage.

**Myocardial reperfusion injury: a neglected therapeutic target**

“Myocardial reperfusion injury” describes the myocardial injury and cardiomyocyte death that occurs on reperfusing ischemic myocardium. In STEMI patients reperfused by PPCI, the presence of myocardial reperfusion injury mitigates the benefits of reperfusion in terms of myocardial salvage, contributing to up to 50% of the final MI size (Figure 1). There are four types of myocardial reperfusion injury, the first two of which are reversible and include reperfusion arrhythmias and myocardial stunning. The second two, which are irreversible and induce cardiomyocyte death, are microvascular obstruction and lethal reperfusion injury. The existence of lethal reperfusion injury as an independent mediator of cell death had been fiercely contested in the past. This was due to an inability to directly demonstrate reperfusion inducing the death of cardiomyocytes that were viable at the end of ischemia. However, the fact that therapeutic interventions have been reported in both animal and clinical studies to reduce MI size when administered solely at the time of reperfusion has been accepted as indirect evidence for the existence of myocardial reperfusion injury. Examples of therapies that have been reported to reduce MI size when given at reperfusion include a variety of different hormones.

**Hormones as novel cardioprotective therapies**

A large number of hormones have been found in animal MI studies to prevent myocardial reperfusion injury and reduce MI size when exogenously administered at the time of myocardial reperfusion (Figure 2). These hormones mediate their cardioprotective effect via a number of different cell-surface receptors (including serine threonine, tyrosine kinase, G-protein coupled, natriuretic, and cytokine receptors), which activate a wide variety of intracellular cardioprotective signaling cascades (including the cyclic guanosine monophosphate–protein kinase G [cGMP-PKG], the reperfusion injury salvage kinase [RISK], and the survivor activating factor enhancement [SAFE] pathways), many of which terminate on mitochondria.
an important target of cardioprotection (Figure 2).\textsuperscript{7} Only an overview of hormone cardioprotection can be provided in this section; for a more comprehensive account the reader is directed to extensive reviews of this topic.\textsuperscript{5-7,12,13,15} A selected number of these cardio-protective hormones including atrial natriuretic peptide (ANP), insulin (glucose-insulin-potassium [GIK] therapy), and exenatide (a glucagon-like peptide 1 [GLP-1] analogue) have been translated into the clinical setting and have been reported to reduce MI size when administered at the time of reperfusion in STEMI patients receiving PPCI (Table I).\textsuperscript{16-21} Ongoing clinical cardioprotection STEMI studies are currently investigating the hormone melatonin and a number of hormones (including erythropoietin\textsuperscript{16}) that have failed to have any beneficial effects in the clinical setting despite reduced MI size in animal studies (Table I).\textsuperscript{16-21} The reason for the failed translation of cardioprotective therapies from bench to bedside has been extensively reviewed.\textsuperscript{4,22}

The ability to assess the cardioprotective efficacy of novel therapies administered at the time of myocardial reperfusion to prevent reperfusion injury requires the assessment of myocardial salvage, as this is a more sensitive measure of cardioprotection than absolute MI size reduction. Cardiac MRI has recently been shown to quantify myocardial salvage in clinical cardioprotection studies.

**Assessing myocardial salvage using cardiac MRI**

Following an acute coronary artery occlusion, the amount of myocardium at risk of infarction (or AAR) is a major determinant of MI size. Therefore, it is essential to take this into account when assessing the ability of a novel cardioprotective therapy to limit MI size reduction.

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**Fig. 2** Signaling pathways underlying hormone cardioprotection at reperfusion. Simplified scheme illustrating the intracellular signaling pathways underlying the cardioprotection elicited by hormones investigated in animal studies and translated into the clinical setting (*). Exogenously administered hormones will bind to their respective receptor on the cardiomyocyte cell surface, activating a variety of signaling cascades, including the reperfusion injury salvage kinase (RISK; Raf-Mek1/2-Erk1/2 and PI3K-Akt), survivor activating factor enhancement (SAFE; JAK-STAT), and cyclic guanosine monophosphate–protein kinase G (cGMP-PKG) pathways, which then terminate on either mitochondria (where mitochondrial permeability transition pore [mPTP] opening is inhibited) and the sarcoplasmic reticulum (where sarco/endoplasmic reticulum Ca\textsuperscript{2+}-ATPase [SERCA] is inhibited), thereby inducing cardioprotection.

**Abbreviations:** Akt, protein kinase B; ANP, atrial natriuretic peptide; BAD, Bcl-2-associated death promoter; eNOS, endothelial nitric oxide synthase; GF, growth factor; GIK, glucose-insulin-potassium therapy; GLP-1, glucagon-like peptide 1; GSK, glycogen synthase kinase; JAK, Janus kinase; K\textsubscript{ATP}, adenosine triphosphate–sensitive potassium channel; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase; STAT, signal transducer and activator of transcription. Modified from reference 7: Hausenloy DJ, Yellon DM. Cardiovasc Res. 2009;83(2):179-194. © 2014, Oxford University Press.
size. This is especially important in patients presenting with an acute STEMI, in whom the size of the AAR can vary from 5% to 40% of the left ventricular (LV) volume from patient to patient depending on the site of the acute coronary artery occlusion. Myocardial salvage, which takes into account the AAR, is a more sensitive measure of cardioprotective efficacy than absolute reduction in MI size, meaning that a smaller number of patients is required in clinical trials investigating novel cardioprotective therapies. Myocardial salvage, which is calculated by subtracting MI size from the AAR, represents the amount of myocardium salvaged by the novel cardioprotective therapy (Figure 3). When normalized to the AAR, the myocardial salvage index is the proportion of the AAR that has been salvaged by the novel cardioprotective therapy (Figure 3).

The ability to assess myocardial salvage in the clinical setting requires a reliable and robust in vivo measure of the AAR. In this regard, cardiac MRI has emerged as a potential approach for achieving this. Cardiac MRI has recently been reported to be beneficial in patients presenting with an acute coronary syndrome, as it can measure LV volumes and function, detect regional wall motion abnormalities, and exclude LV thrombus. Furthermore, a unique characteristic of cardiac MRI is its ability to tissue characterize the different components of the infarct. For reperfused STEMI patients, cardiac MRI can be safely performed in the first week to quantify both the AAR and the MI size, thereby enabling the calculation of myocardial salvage. Cardiac MRI performed in the first week of hospital admission has been shown to retrospectively quantify the AAR in STEMI patients. This relies on the ability of T2-weighted cardiac MRI to detect myocardial edema, a marker of reversible myocardial ischemic reperfusion injury within the AAR (Figure 3). There have, however, been several issues with using T2-weighted cardiac MRI to measure the AAR in reperfused STEMI patients including imaging artifacts, low signal-to-noise ratio, and the cardioprotective therapy reducing the circumferen-

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<td>Insulin (GIK therapy)</td>
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<td>Atrial natriuretic peptide (ANP)</td>
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**Table 1** Hormone cardioprotection at reperfusion in ST-segment elevation myocardial infarction (STEMI) patients.

Abbreviations: AUC, area under the curve; CK, creatine kinase; GIK, glucose-insulin-potassium; IU, international units; IV, intravenous; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRI, magnetic resonance imaging; MSI, myocardial salvage index; MVO, microvascular obstruction; n, number; PPCI, primary percutaneous coronary intervention. Data from references 16-21.
Measuring myocardial salvage: hormone cardioprotection

The very recent availability of hybrid simultaneous PET/MRI provides the opportunity to simultaneously relate changes in cardiac metabolism (myocardial 18F-fluorodeoxyglucose [18FDG] uptake) to constituents of the reperfused myocardial infarction. It allows the PET and MRI images to be acquired simultaneously with the patient in the same position on the scanner table, facilitating accurate coregistration of fused images, and precise voxel-by-voxel comparison images of cardiac anatomy and metabolism.\textsuperscript{29-32} Using this technique, we have recently demonstrated impaired glucose metabolism as evidenced by reduced myocardial 18FDG uptake within the AAR that corresponds to that delineated by T2-mapping cardiac MRI imaging (unpublished data, \textit{Figures 4 and 5}). The relationship between the colocalized areas of myocardium with impaired glucose metabolism (imaged by PET) and edema (imaged by T2 mapping) in reversibly injured myocardium within the AAR is unclear and needs further investigation. With the availability of novel tracers for detecting hypoxia, apoptosis, fibrosis, inflammation, and angiogenesis, hybrid PET/MRI of the heart should provide unique insights into the pathophysiology of acute MI and subsequent post-MI LV remodelling. This should result in the identification of novel cellular and molecular targets for treating MI and heart failure.

\textbf{Summary and conclusion}

Despite optimal therapy, the morbidity and mortality in patients presenting with a STEMI remains significant. One neglected therapeutic target for which there is currently no effective therapy is “myocardial reperfusion injury,” which refers to the cardiomyocyte death that occurs on reperfusing acutely ischemic myocardium and that has been reported to reduce MI size by 50%. As such, novel cardioprotective therapies are required to target myocardial reperfusion injury to limit MI size, preserve cardiac function, and prevent the onset of heart failure. In this regard, certain hormones have been reported in animal studies and initial clinical trials to reduce MI size when administered at the onset of reperfusion through the activation of established intracellular cardioprotective signaling pathways. Cardiac MRI has emerged as a potential noninvasive imaging tool.

\textit{Fig. 4} Hybrid simultaneous positron emission tomography/magnetic resonance imaging (PET/MRI) of left anterior descending (LAD) coronary artery myocardial infarction (MI). This figure shows representative long-axis fused 18F-fluorodeoxyglucose (18FDG)-PET/MRI images (left-sided panels) and late gadolinium enhancement (LGE; right-sided panels; white arrows) cardiac MRI images of a patient presenting with a transmural MI (containing microvascular obstruction; yellow arrows) within the LAD coronary artery territory. There is an area of markedly reduced myocardial uptake of glucose, which spatially matches the distribution of LGE (left-sided panels; red arrows).

\textit{Fig. 5} Positron emission tomography/magnetic resonance imaging (PET/MRI) of transmural and subendocardial myocardial infarction (MI). This figure shows representative short-axis images of late gadolinium enhancement (LGE) cardiac MRI (showing MI), 18F-fluorodeoxyglucose (18FDG)-PET (showing reduced myocardial FDG uptake in areas of MI and the area at risk [AAR]), T2-mapping MRI (increased T2 values within the AAR), and fused FDG-PET:LGE MRI in two patients with subendocardial MI ([1] and [2], with significant myocardial salvage) and two with transmural MI ([3] and [4], with minimal myocardial salvage).
Measuring myocardial salvage: hormone cardioprotection

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Testosterone levels in men have been shown to decrease gradually with age. This decline is about 2% per year, but in healthier men, the decline is attenuated. The exact prevalence of testosterone deficiency is controversial. In a study involving more than 10,000 men, 80% were found to have symptoms of testosterone deficiency. In another study done in the primary care setting, where a total of 2,162 men >45 years old were sampled, the prevalence of testosterone levels of less than 300 ng/dL (8.4 nmol/L) was 38.7%. In the US, less than 10% of men with low testosterone received testosterone replacement therapy (TRT). A total of 50% of older men with type 2 diabetes mellitus have testosterone deficiency. As a consequence, in the US where the prevalence of type 2 diabetes mellitus is expected to increase over the next 20 years, the health impact of testosterone deficiency syndrome will cost the US economy up to 500 billion US dollars.

The rise in the usage of TRT has generated a lot of interests and controversies. Many studies have been done and the role of testosterone and its effect on the cardiovascular system is a hot issue at the moment. This review aims to address some of these issues.

Testosterone level and its association with the heart

There are some epidemiological studies that have shown the correlation between testosterone and cardiovascular disease. In over 40 epidemiological studies conducted so far, no one has found any association between high testosterone levels and cardiovascular disease. In contrast, many found an association between low testosterone levels and cardiovascular disease. These include studies on carotid artery atheroma and peripheral arterial disease.

Seventeen prospective cohort or nested case-controlled studies have also examined the relationship between testosterone levels and cardiovascular disease.
morbidity and mortality. In ten of these studies, there was no correlation between baseline testosterone levels and subsequent development of fatal or non-fatal coronary heart disease, cerebrovascular disease, or heart failure after adjustment for confounders, during observation periods of 5 to 31 years. Weak correlations of high androgen levels with cardiovascular mortality were observed in two studies. Conversely, two studies reported significant correlations between low baseline testosterone levels and cardiovascular deaths, and two others between low baseline testosterone and progression of carotid artery intima-media thickness, or between low testosterone and an increased incidence of stroke or transient ischemic events. However, two other prospective studies were unable to confirm the correlations with intima-media thickness progression, and with an increased risk of stroke. Lastly, the Caerphilly study found a positive association of the cortisol/testosterone ratio with chronic heart disease incidence and mortality.

Recent evidence has proven that men with lower levels of testosterone are more prone to developing coronary artery disease. This was shown after only taking into account bioavailable testosterone levels, as compared with older studies that did not do this. Bioavailable testosterone includes both free testosterone and testosterone bound loosely to albumin. Testosterone, which is bound to sex hormone–binding globulin (SHBG), is biologically inactive. There is also evidence that the lower the levels of testosterone, the more severe the degree of coronary artery disease. This could be due to its effect on the carotid intima-media thickness. Various studies have shown the inverse relationship between endogenous testosterone levels and intima-media thickness of the carotid arteries, abdominal aorta, and thoracic aorta. This suggests that those with low testosterone levels are more prone to developing atherosclerosis.

Besides coronary artery disease, testosterone levels have also been studied in congestive heart failure. Studies have shown that men with congestive heart failure have significantly reduced total and free testosterone levels. As the severity of congestive heart failure worsens, the levels of both total testosterone and estimated free testosterone lower correspondingly. In fact, it was shown that reduced levels of total and estimated free testosterone were both predictors of increased mortality in men with congestive heart failure.

Metabolic syndrome, which is comprised of insulin resistance, hypertension, dyslipidemia, and visceral obesity, is associated with an increased risk of cardiovascular disease (relative risk, 2.35). Testosterone levels are also known to affect metabolic syndrome. Low testosterone levels have been shown to correlate with worsening type 2 diabetes and obesity. In fact, not only are the total testosterone levels lower in diabetics, the free testosterone and the testosterone bound to SHBG are also lower. This means that total testosterone in diabetics is not entirely caused by the reduction in levels.

At the moment, the evidence for testosterone levels and dyslipidemia is poor. Most of the studies done were cross-sectional studies based on small sample size. Therefore, the results are inconclusive. However, the relationship between testosterone levels and obesity is quite established. It has been shown that the odds ratio for having hypogonadism was significantly higher in obese men, and there was a statistically significant negative correlation between total testosterone level and body mass index (BMI). In terms of mortality, studies have consistently shown that lower levels of endogenous bioavailable testosterone are associated with higher rates of all-cause and cardiovascular mortality.

Testosterone replacement therapy: a new approach for the heart

TRT may be beneficial to the heart. There are a few ways that testosterone, through its effect on other parameters (components of metabolic syndrome), may improve cardiovascular health.

Testosterone replacement therapy in obesity

As discussed earlier, low testosterone levels are associated with obesity. This could be because adipose tissue is rich with the aromatase enzyme, which converts testosterone to estrogen. Studies have shown

Abbreviations
BMI: body mass index; HDL: high-density lipoprotein; SHBG: sex hormone–binding globulin; TRT: testosterone replacement therapy
that TRT decreases fat mass and BMI.\textsuperscript{13} Testosterone is believed to cause a reduction in abdominal adiposity by inducing lipolysis. Besides that, testosterone also activates the enzyme 11-hydroxysteroid dehydrogenase in adipose tissue, which transforms glucocorticoids into their inactive form.\textsuperscript{17}

Long-term testosterone therapy for up to 6 years has been shown to result in significant and sustained improvements in weight. In a study by Haider et al, TRT caused a decrease of waist circumference by 11.56 cm and weight decline by 17.49 kg (15.04%).\textsuperscript{18} What is more interesting to note is that the reduction in waist circumference with testosterone undecanoate in more than 500 hypogonadal men appears to be superior when compared with data published for other drugs, in combination with lifestyle and behavioral interventions.\textsuperscript{19}

**Testosterone replacement therapy in diabetes mellitus and glycemic control**

There is also strong evidence that TRT in diabetic men improves the homeostatic model of insulin resistance, hemoglobin A\textsubscript{1c}, and fasting plasma glucose.\textsuperscript{20} How it does this is still controversial, although it is believed to be mediated partly by its effect on visceral fat. Besides that, testosterone is also believed to be involved in promoting glucose utilization by stimulating glucose uptake, glycolysis, and mitochondrial oxidative phosphorylation. Testosterone also increases Glut4 in cultured skeletal muscle cells. Glut4, in turn, facilitates glucose transportation into the cell.\textsuperscript{21}

The effects of TRT on diabetic men with hypogonadism go beyond glycemic control. In a study by Muraleedharan et al,\textsuperscript{22} mortality was increased in the low testosterone group (17.2%) compared with the normal testosterone group (9%; P=0.003). TRT (mean duration 41.6±20.7 months; n=64) was associated with an 8.4% reduced mortality compared with 19.2% (P=0.002) in the untreated group (n=174).

**Testosterone replacement therapy and hyperlipidemia**

TRT has beneficial effects on lipids as well. In a 5-year study on the effects of TRT, an improvement in lipid profile (total/high-density lipoprotein (HDL) cholesterol ratio, -2.9±1.5; P<0.0001) was shown.\textsuperscript{23} However, a meta-analysis and systematic review on randomized controlled trials showed that triglyceride values improved in those given TRT, but no specific difference was found in cholesterol levels between the TRT and control groups.\textsuperscript{24}

**Testosterone replacement therapy and hypertension**

The positive effect of TRT on blood pressure has also been documented. A study by Francomano et al showed an improvement in both systolic and diastolic blood pressure (-23±10 and -16±8 mm Hg; P<0.0001) over 5 years.\textsuperscript{23} However, a meta-analysis of randomized controlled trials did not show any significant difference in the blood pressure between TRT and the control.\textsuperscript{24}

**Testosterone replacement therapy and lifestyle**

It is widely known that lifestyle modifications, along with diet, exercise, and weight loss, are able to reduce insulin resistance, and therefore, prevent the progression to overt diabetes. However, the addition of TRT to lifestyle interventions has been shown to improve the glycemic control better and, in fact, is able to reverse the metabolic syndrome in 52 weeks.\textsuperscript{20} The combination of TRT and lifestyle modifications is also able to increase insulin sensitivity, reduce fatty liver, and improve muscle mass, compared with placebo and lifestyle modifications alone.\textsuperscript{13,25}

**Testosterone replacement therapy and myocardium**

Besides its effects on metabolic syndrome, TRT has a direct effect on the heart as well. It has been found to improve myocardial ischemia in men with coronary artery disease. In fact, TRT has been shown to increase time to angina in stress tests.\textsuperscript{26} Both acute and chronic testosterone therapy improved myocardial ischemia independent of the method of administration. It is hypothesized that testosterone promotes coronary vasodilation by its action on the calcium and potassium channels on the surface of vascular smooth muscle cells.

TRT has also been demonstrated to shorten the corrected QT (QTc) interval by augmenting the activity of slowly activating delayed rectifier potassium channels, while simultaneously slowing the activity of L-type calcium channels.\textsuperscript{27} This stabilizes the heart.
Testosterone replacement therapy and mortality

TRT was associated with decreased risk of death (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.42-0.88; \( P=0.008 \)). In fact, TRT is able to reduce mortality by 50% in men with low testosterone (testosterone <300 ng/dL) as compared with those not receiving TRT.\(^\text{28} \) The key is to achieve optimal testosterone levels with TRT and not to go overboard with supra-normal testosterone levels. Yeap et al have also shown that the greatest benefits are seen with testosterone levels in the third quartile.\(^\text{29} \) They concluded that optimal androgen levels are a biomarker for survival because older men with mid-range levels of testosterone and dihydrotestosterone had the lowest death rates from any cause.

Conclusion

Testosterone levels have been shown to be associated positively with metabolic syndrome and cardiovascular diseases (Figure 1). TRT, on the other hand, has also shown positive outcomes in terms of metabolic parameters and cardiovascular outcomes, but the long-term effects are not known. So far, all the studies published were small and short-term. The two controversial papers, which raised the alarm on TRT, showed that more needs to be done to allay our fears on TRT.\(^\text{30,31} \)

Despite the obvious benefits of TRT on the heart, caution needs to be heeded, especially in men with severe heart problems and those above 75 years of age. In frail elderly men, it is not advisable to use high-dose TRT. The administration of TRT requires close monitoring. Lifestyle changes are also needed to complement the benefit of TRT. When men are appropriately diagnosed, treated, and monitored, TRT is relatively safe and beneficial. Indeed, the ongoing Testosterone Trial in Older Men (NCT00799617) will provide important guidance to older men who meet current recommendations for TRT.

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Effects of trimetazidine on hormones and the heart

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Abstract
Trimetazidine is a well-known, clinically effective antianginal agent recommended by guidelines for the treatment of stable angina pectoris. There is also substantial evidence for its benefit in patients with heart failure. Natriuretic peptides are markers of myocardial load and findings from recent studies suggest that trimetazidine treatment has a positive effect on this neurohormonal pathway in patients with ischemic heart disease or heart failure. \textit{Heart Metab.} 2015;66:24-26

Keywords: angina pectoris; cardiac metabolism; coronary artery disease; heart failure; natriuretic peptides

Coronary artery disease (CAD) and congestive heart failure (CHF) represent two major public health problems that impair quality of life and reduce longevity. The impairment of cardiac function in chronic CAD and CHF is related to left ventricular remodeling, a pathologic process by hemodynamic overload and neurohormonal activation. The heart exerts an endocrine function where both atria and ventricles are able to produce cardiac natriuretic hormones. The activation or deactivation of the cardiac natriuretic hormone system is almost always the result of one or more physiological or pathological changes. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are secreted from the heart as a result of direct wall stress, to protect the human body from volume overload and also to inhibit the renin-angiotensin system, endothelin secretion, and sympathetic activity. Measurement of plasma concentrations of natriuretic peptide is now increasingly being used as a tool for clinical diagnosis and prognosis in patients with CHF and CAD.

Trimetazidine’s mechanism of action

In the heart, adenosine-5’-triphosphate (ATP) is produced primarily by the metabolism of free fatty acids (FFAs) and carbohydrates. FFA oxidation provides more energy, but it is associated with increased oxygen consumption. Trimetazidine is a partial inhibitor of the β-oxidation enzyme long-chain 3-ketoacyl coenzyme A thiolase (3-KAT) activity, the final enzyme in the FFA β-oxidation pathway (Figure 1). It increases pyruvate dehydrogenase.

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activity and the metabolic rate of glucose. This results in decreased oxygen consumption, hydrogen ion production, intracellular acidosis, and reduced calcium ion accumulation. Trimetazidine reduces myocardial injury caused by free radicals, therefore modulates the inflammatory response. In this way, trimetazidine protects the whole myocardium against necrotic and apoptotic cell death and reduces the remodeling process.

**Trimetazidine in coronary artery disease**

Existing data support the use of drugs that optimize cardiac energy metabolism such as trimetazidine for the treatment of patients with CAD. The VASCO study is the largest randomized controlled study conducted with trimetazidine. Patients with stable angina receiving 50 mg of atenolol were randomized to the addition of trimetazidine MR 70 mg or 140 mg, or placebo for a 12-week period. In the cohort of all chronic stable angina patients, trimetazidine significantly improved total exercise duration compared with baseline and placebo. Recent European Society of Guidelines on stable angina pectoris recommended that trimetazidine may be used as an add-on drug after β-blockers.

Major metabolic changes occur during the early hours of myocardial infarction and during ischemia/reperfusion. FFA concentrations are greatly increased, and exert a toxic effect on the myocardium. This effect determines increased membrane damage, endothelial dysfunction, tissue inflammation, and decreased cardiac function. Trimetazidine reduces ischemia/reperfusion damage following ischemia and preserves myocardial contractile function. Decreasing plasma FFA concentrations and cardiac fatty acid oxidation, together with the stimulation of glucose and lactate uptake, might reduce these detrimental effects. Demirelli et al assessed the impact of treatment with trimetazidine in patients with non-ST segment elevation myocardial infarction undergoing percutaneous coronary intervention. Forty-five patients were randomly assigned to receive either placebo or trimetazidine. In patients on trimetazidine at 1-month follow-up, a considerable improvement in left ventricular end-diastolic volume was reported and BNP levels decreased compared with patients on placebo. The authors concluded that the beneficial effects of percutaneous coronary intervention (PCI) may be reinforced with a combination of PCI and trimetazidine treatment.

**Trimetazidine in heart failure**

Natriuretic peptide is used in the diagnosis, monitoring, and prognosis of patients with congestive heart failure. Its concentration falls in patients with decompenated heart failure after treatment, suggesting that measurement of plasma natriuretic peptide may be helpful in titrating therapy. The plasma measurement of natriuretic peptide is also used in the diagnosis and prognosis of patients with CAD. Increased natriuretic peptide was found to be related to ischemia.

Trimetazidine has documented effects on improving the left ventricular function, exercise tolerance, and New York Heart Association (NYHA) class. A recent study demonstrated that short-term trimetazidine treatment in patients with ischemic cardiomyopathy improves exercise tolerance and reduces plasma level of BNP. The study involved 50 patients with ischemic cardiomyopathy; 25 patients were assigned to receive conventional treatment plus trimetazidine, while the remaining 25 patients constituted the control group. After a 6-month follow-up, both groups achieved an insignificant reduction in NYHA class. The group receiving trimetazidine demonstrated a considerable reduction in BNP levels and cardiac troponin T, while the control group showed increased plasma BNP levels, with no significant changes in cardiac troponin T levels. Trimetazidine administration also resulted in a significant improvement in exercise tolerance assessed with a 6-minute walk test, however, it was not associated with a significant improvement in left ventricular systolic function, at baseline, and after 1 month and 6 months, respectively. Fragaasso et al obtained similar results in 55 patients with heart failure and left ventricular dysfunction of various etiologies. Zhang et al presented a meta-analysis on the use of trimetazidine in CHF patients. Sixteen randomized...
studies were evaluated, with 884 patients in the study group. This meta-analysis demonstrated that the use of trimetazidine was associated with improved left ventricular ejection fraction, increased exercise tolerance, reduced NYHA class, decreased left ventricle volume and plasma BNP levels, and a reduced rate of cardiovascular hospitalizations.

ANP, another biomarker of heart failure, appears to be noninferior to BNP for diagnosis of acute heart failure and also has prognostic value in patients with CHF. The rise in ANP secretion can be reversed by successful treatment of heart failure. Morgan et al., using an experimental heart failure model, also demonstrated that treatment with trimetazidine over a 12-week period reduced the levels of ANP.

Conclusion

In conclusion, trimetazidine is a well-known, clinically effective drug for the treatment of stable angina pectoris. Evidence for its benefit in patients with heart failure is also substantial. Considering natriuretic peptides to be a marker of myocardial load, findings from recent studies suggest that trimetazidine treatment has a positive effect on this neurohormonal pathway in patients with ischemic heart disease or heart failure.

REFERENCES

Erectile dysfunction and lower urinary tract symptoms should trigger a metabolic screen and cardiovascular risk estimation

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Abstract
The UK has made great strides in reducing death from cardiovascular disease (CVD), but there is still room for improvement compared with other Western European Countries. CVD accounts for approximately one-third of all deaths in men and women in the UK. Half of these deaths are related to coronary heart disease (CHD), which is the most common cause of premature death in those under the age of 75 years. Atherosclerotic changes in the coronary arteries eventually lead to CHD, and nine key risk factors have been well recognized. Erectile dysfunction (ED) is an independent risk factor and provides a window of opportunity to identify early CVD. ED and lower urinary tract symptoms (LUTS) share underlying pathophysiological etiological mechanisms and will often drive men to consult. This provides the opportunity to consider what burden of CVD risk factors the patient carries, and to perform an appropriate metabolic screen. ■ Heart Metab. 2015;66:27-31

Keywords: cardiovascular disease; erectile dysfunction; lower urinary tract symptoms; metabolic syndrome; lifestyle

The UK has made great strides in reducing death from cardiovascular disease (CVD), but there is still room for improvement compared with other Western European Countries. CVD accounts for approximately one-third of all deaths in men and women in the UK. Half of these deaths are related to coronary heart disease (CHD), which is the most common cause of premature death in those under the age of 75 years. Atherosclerotic changes in the coronary arteries eventually lead to CHD, and nine key risk factors have been well recognised. In 2001, we raised the question “Is erectile dysfunction a marker for cardiovascular disease?” and recently highlighted the importance of the co-diagnosis of erectile dysfunction (ED) and lower urinary tract symptoms (LUTS).

The link between ED and LUTS was brought home by the multinational survey of the aging male (MSAM)
Many large epidemiological studies using well-powered multivariate analyses consistently provide overwhelming evidence of a link between ED and LUTS. The pathogenic mechanisms underlying the relationships between ED and LUTS have been the subject of several recent reviews. The underlying mechanisms include the alteration of the nitric oxide–cyclic guanosine monophosphate pathway; enhancement of the Rho-kinase (ROCK) signalling; autonomic hyperactivity; and pelvic atherosclerosis, secondary to endothelial dysfunction. Additional contributing factors may include chronic inflammation and sex steroid ratio imbalance.

Two meta-analyses have clearly shown that ED predicts CVD events and all-cause mortality. Because ED and LUTS are very common worldwide clinical problems, enquiring about these symptoms in middle-aged men who have no cardiac symptoms provides a window of opportunity to identify those with underlying CVD. This is important, as it has been well demonstrated in two significant studies that ED can precede a cardiac event by an average of 2 to 5 years. Therefore, a multidisciplinary collaborative approach is encouraged and the screening net should be cast as widely as possible.

It is important to recognise that ED is an independent marker of increased CVD, over and above the conventional risk factors. It has been well demonstrated in a systematic review and meta-analysis that lifestyle intervention together with cardiovascular risk factor reduction improves erectile function. In addition to this, factors associated with decreased risk of LUTS include increased physical activity, moderate alcohol intake, and increased vegetable consumption, and LUTS can also be improved by means of lifestyle changes.

**Case history**

**Initial visit**

A 60-year-old scientist and company director attended with some concern regarding perineal discomfort that had been present for two weeks. There had been a past history of prostatitis 15 years previously, but he had been prescribed no treatment for this. He had undertaken a company medical 14 years previously, when it was noted that he had an elevated cholesterol of 6 mmol/L and triglycerides (TG) of 2.61 mmol/L. He was advised to deal with this by means of diet and exercise. He gave a history of ED for the previous 5 years, which had been treated with on-demand Cialis and Viagra, neither of which he had found particularly helpful. His urinary symptoms included frequency, some morning urgency, getting up once at night, and a rather poor flow rate.

On direct questioning, his general health appeared to be good. He had a history of some acid reflux, but no cardiac symptoms. His exercise level was low to moderate, in terms of playing tennis once per week with occasional walks. He was a nonsmoker and consumed 15 to 20 units of alcohol per week. He was not taking any medication. There was a family history of type 2 diabetes in his father and brother. In his personal history, he had experienced pericarditis at the age of 24 and a Bell’s palsy in 2009.
Initial clinical examination and investigations

Clinical examination revealed height 181 cm, weight 91 kg, waist circumference 98 cm, and blood pressure 150/92 mm Hg. His heart was normal and all peripheral pulses were present. There were no abdominal bruits and the chest was clear. There were no abnormal swellings in the abdomen. Digital rectal examination revealed a nontender and nodular prostate, which felt to be about 30 g. This was subsequently confirmed to be 31 g on the transrectal ultrasound report (Table I). The abdominal ultrasound showed some features suggesting fatty liver infiltration. His urinary investigation findings are summarized in Table II.

The electrocardiogram (ECG), renal function, and liver function were normal. His cholesterol profile was: cholesterol 6.6 mmol/L, high-density lipoprotein (HDL) 1.3 mmol/L, low-density lipoprotein (LDL) 4.6 mmol/L, TG 1.5 mmol/L. HbA1c 43 mmol/mol (6.1%) and fasting plasma glucose 5.8 mmol/L. Fibrinogen was 4.5 g/L (normal range 1.5 to 4). Testosterone was 17.8 nmol/L, prostate-specific antigen (PSA) 3.09 mcg/L, free PSA 0.52 mcg/L, and free,total PSA ratio 17.8. Occult blood tests were negative.

This patient had the features of metabolic syndrome (Table III), with an increased waist circumference, raised blood pressure and blood glucose, and dyslipidemia.

Using the Joint British Societies recommendations on the prevention of Cardiovascular Disease (JBS3) risk calculator, his heart age was 74 years. He had a 17% 10-year risk of a cardiovascular event, with a life expectancy of 83 years. The calculator predicted that he would gain 3 extra years of life and his 10-year risk would reduce to 5.3% if his risk factors were suitably adjusted, giving him a life expectancy of 86 years.

At the time the patient was seen, the threshold for intervention with statins was a 20% 10-year risk, but having ED in addition to his current risk factors put this man at high risk of having underlying and future CVD. He was, however, reluctant to take statins due to adverse reports of side effects that he had read in the media.

It was decided that, to further evaluate his potential CVD risk, he would undertake a computed tomography coronary calcium scan, which was duly performed. This showed a total calcium score of 585 (left marginal artery, 0; left anterior descending artery, 319; left circumflex artery, 0; and right coronary artery, 266), putting him in the 80th-centile range for age and gender. There was no abnormality identified in the lungs.

This man therefore had a high burden of coronary artery calcification for his age and an exercise stress echo was performed. On standard Bruce protocol, the patient achieved 89% maximum predicted heart rate (MPHR) and 13.4 metabolic equivalents (METs).

Table I Transrectal ultrasound results.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voided volume</td>
<td>441 mL</td>
</tr>
<tr>
<td>Maximum flow rate</td>
<td>14.7 mL/sec</td>
</tr>
<tr>
<td>Average flow rate</td>
<td>7.7 mL/sec</td>
</tr>
<tr>
<td>Residual urine</td>
<td>190 mL</td>
</tr>
<tr>
<td>IPSS</td>
<td>22 (severe symptoms)</td>
</tr>
<tr>
<td>IIEF</td>
<td>14 (moderate to severe erectile dysfunction)</td>
</tr>
</tbody>
</table>

Table II Results of urinary investigations and IPSS/IIEF scores after initial visit.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate volume</td>
<td>31 mL</td>
</tr>
<tr>
<td>Perineural calcification</td>
<td></td>
</tr>
<tr>
<td>Echogenic areas in central gland</td>
<td></td>
</tr>
<tr>
<td>Vascular pattern in peripheral zone</td>
<td></td>
</tr>
<tr>
<td>Gland vascularity</td>
<td>within normal limits</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>symmetrical and normal in appearance</td>
</tr>
</tbody>
</table>

Conclusion: There are some areas of prostate that would suggest previous episodes of prostatitis, but no definite current active inflammatory changes seen. The bladder and upper tracts appear normal.

Table III International Diabetes Federation (IDF) definition of the metabolic syndrome.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>≥94 cm for Europid men; ≥80 cm for Europid women; with ethnicity specific values for other groups*</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>Systolic ≥130 or diastolic ≥85 mm Hg, or taking medication for previously diagnosed hypertension</td>
</tr>
<tr>
<td>Raised triglyceride level</td>
<td>≥150 mg/dL (1.7 mmol/L) or taking medication for this specific lipid abnormality</td>
</tr>
<tr>
<td>Reduced high-density lipoprotein cholesterol</td>
<td>&lt;40 mg/dL (1.03 mmol/L) in men, &lt;50 mg/dL (1.29 mmol/L) in women, or taking medication for this specific lipid abnormality</td>
</tr>
<tr>
<td>Raised fasting plasma glucose</td>
<td>≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If ≥5.6 mmol/L or 100 mg/dL, oral glucose tolerance test is strongly recommended, but is not necessary to define presence of the syndrome</td>
</tr>
</tbody>
</table>

*If body mass index is ≥30 kg/m², central obesity can be assumed and waist circumference need not be measured.

of workload. He did not have any chest pain and no ischemic ECG changes. Left ventricular wall motion was normal both before and after exercise. He therefore had a negative exercise stress echocardiogram.

Management

He agreed to take statin therapy and was started on atorvastatin 40 mg. He was also recommended a Mediterranean-style diet and provided with a twice-daily exercise programme. Regarding the ED and LUTS, he was started on daily Tadalafil (phosphodiesterase type 5 [PDE5] inhibitor) at a dose of 5 mg.

In summary, this man presented with LUTS, ED, and some perineal discomfort, possibly related to previous prostatitis. Clinical examination and subsequent investigations confirmed that he had the metabolic syndrome and this, combined with a history of ED, gave him a significant risk of having underlying CVD. This was subsequently confirmed on a coronary calcium scan and he was started on statin therapy (atorvastatin 40mg daily), aiming for a reduction of 50% in the lipid profile. He was provided with a diet and exercise programme. He was asked to check his own blood pressure at home.

In addition to the statin therapy, he was prescribed daily Tadalafil 5 mg, which has the benefit of providing daily Tadalafil 5 mg, which has the benefit of a pedometer. He had gained 3.1 life years.

Three-month review

Repeat clinical examination, investigation, and score results at 3-month review are summarized in Table IV.

At this 3-month review, he reported feeling very well, and was eating a Mediterranean-style diet and walking twice daily. Pelvic/perineal discomfort was no longer a problem. He reported walking 10 000 steps per day using a pedometer. He had gained 3.1 life years.

This is a good response to daily PDE5 inhibitor therapy relating to ED and LUTS, with a significantly reduced risk of future CVD as the result of lifestyle changes and statin therapy.

REFERENCES


<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-month review</th>
<th>Initial visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>85 kg</td>
<td>91 kg</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>97 cm</td>
<td>98 cm</td>
</tr>
<tr>
<td>PSA</td>
<td>2.33 mcg/L</td>
<td>3.09 mcg/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.1% (43 mmol/mol)</td>
<td>No change</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>3.1 mmol/L</td>
<td>6.6 mmol/L</td>
</tr>
<tr>
<td>LDL</td>
<td>1.4 mmol/L</td>
<td>1.3 mmol/L</td>
</tr>
<tr>
<td>BP</td>
<td>132/84 mm Hg</td>
<td>150/92 mm Hg</td>
</tr>
<tr>
<td>IIEF</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>IPSS</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>JBS3 heart age</td>
<td>61 years</td>
<td>74 years</td>
</tr>
</tbody>
</table>

Table IV Examination and investigation results at 3-month review compared with initial visit.

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; JBS3, Joint British Societies recommendations on the prevention of Cardiovascular Disease; LDL, low-density lipoprotein; PSA, prostate-specific antigen.


Cardiovascular disease (CVD) is a leading cause of death in men worldwide. Erectile dysfunction (ED) is a common disorder in men as they age that often leads them to engage in medical care in the absence of underlying and unknown cardiovascular disease or risk equivalents. Several risk factors overlap for the development of both cardiovascular disease and erectile dysfunction. The evaluation and management of cardiovascular risk in men with vasculogenic erectile dysfunction, but no known underlying cardiovascular disease, can include exercise stress testing, determining the coronary artery calcium score, and measuring carotid intima-media thickness. Knowledge of potential underlying increased cardiometabolic risks can alert the clinician toward appropriate risk stratification and evaluation to minimize future coronary events. 

**Abstract**

Cardiovascular disease and erectile dysfunction are commonly encountered disorders in men of advancing age that share a common pathophysiologic pathway with endothelial dysfunction. Metabolic syndrome and its various components play pivotal roles in the development of both cardiovascular disease and erectile dysfunction. The evaluation and management of cardiovascular risk in men with vasculogenic erectile dysfunction, but no known underlying cardiovascular disease, can include exercise stress testing, determining the coronary artery calcium score, and measuring carotid intima-media thickness. Knowledge of potential underlying increased cardiometabolic risks can alert the clinician toward appropriate risk stratification and evaluation to minimize future coronary events. 

**Keywords:** cardiometabolic risk; erectile dysfunction; male sexual dysfunction; metabolic syndrome

Heart Metab. 2015;66:32-36
The metabolic syndrome

MetS is commonly defined by a cluster of overlapping factors including dyslipidemia (eg, elevated triglycerides and apolipoprotein B [apoB]–containing lipoproteins, low levels of high-density lipoprotein [HDL] cholesterol), hypertension, and deregulated glucose homeostasis) that directly increase the risk of coronary heart disease and other forms of cardiovascular atherosclerotic disease. In addition to the many clinical implications of MetS, there are still no universally accepted pathogenic mechanism(s) or consensus diagnostic criteria. The most current definition of MetS incorporates the International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definitions and requires a patient to have any three of the following five conditions:\(^13\): (i) waist circumference >40 inches in men and >35 inches in women; (ii) triglycerides >150 mg/dL; (iii) HDL <40 mg/dL; (iv) blood pressure >135/85 mm Hg; and (v) fasting glucose >100 mg/dL.

ED has been causally linked to multiple aspects of the MetS including overall CVD risk, type 2 diabetes mellitus, hypertension, and visceral adiposity.\(^14-19\) Several interrelated mechanisms have been proposed to explain the observed relationship between the MetS and ED. The most commonly suggested mechanism is a low serum testosterone level, which has been shown to be associated with both moderate and severe degrees of ED via diminished nitric oxide (NO) synthesis.\(^20\) Increasing α-adrenergic activity has been linked to several established aspects of the MetS and could explain the link between the MetS and ED.\(^21\)

Cardiovascular evaluation of erectile dysfunction

Evaluation of subclinical CVD in men at low to intermediate risk via noninvasive testing for underlying cardiovascular disease provides a useful strategy in identifying CAD in men with ED, MetS, and type 2 diabetes mellitus.\(^22,23\) ED and CVD, specifically CAD, have the common denominator of endothelial dysfunction. Several studies have determined that ED may precede a clinically significant CAD event by a period estimated between 2 and 5 years and at an average of 3 years.\(^24,25\) Reported symptoms of ED also have the ability to predict the likelihood of an acute coronary syndrome as well as increased mortality, suggesting the rupture of an asymptomatic coronary plaque. Figure 1 provides an algorithm for the evaluation and management of cardiovascular risk in men with vasculogenic erectile dysfunction, but no known cardiovascular disease recommended for the primary care physician.\(^26\)

Exercise stress testing

A prospective trial of 65 men with physical ED and no symptoms of CAD were screened for CVD via exercise stress testing (EST) and multidetector computed tomography, which aims to detect subclinical plaque formation that may be at risk of rupture and that does

<table>
<thead>
<tr>
<th>Risk factor management</th>
<th>Risk factor management; consider emerging prognostic markers (eg, testosterone)</th>
</tr>
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<tbody>
<tr>
<td>Abnormal</td>
<td>Referral to cardiologist</td>
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<tr>
<td>Abnormal</td>
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</tr>
</tbody>
</table>

Abbreviations

- **CAD:** coronary artery disease
- **CIMT:** carotid intima-media thickness
- **CVD:** cardiovascular disease
- **ED:** erectile dysfunction
- **EST:** exercise stress testing
- **HDL:** high-density lipoprotein
- **MetS:** metabolic syndrome
- **NO:** nitric oxide

not have a significant luminal stenosis to negatively influence the EST. In three men, the exercise electrocardiogram was borderline abnormal and in 62 men it was normal. CT calcium was present in 53 men (score range 5 to 1671) and noncalcified plaque was present in seven men. Thus, the estimated window of 2 to 5 years between ED and a clinically significant CAD event offers an opportunity for aggressive risk factor reduction, and should, thus, be a routine component in any cardiovascular risk calculator.

**Carotid intima-media thickness**

Carotid intima-media thickness (CIMT) has been proposed as a possible measurement of determination of risk for ED. The American College of Cardiology Foundation (ACCF)/AHA, and, more emphatically, the Society for Heart Attack Prevention and Eradication Task Force, support assessment during evaluation of patients at intermediate risk for underlying CVD. One trial found that 50% of 136 asymptomatic subjects (mean age, 57±11 years) with no history of vascular events and a Framingham Risk Score less than 10% had CIMT ≥75th percentile. The challenge with interpreting this data is the assumed extrapolation to ED as a risk factor for CVD. Another study of 32 men with MetS compared with 29 healthy controls yielded a higher prevalence and severity of ED in men with MetS, as scores on the International Index of Erectile Dysfunction (IIEF-5) correlated inversely with CIMT.

**Coronary artery calcium scoring**

Coronary artery calcium (CAC) scoring has been validated prospectively in several trials as a predictor of CVD. A recent review of four major trials concluded that CAC is the strongest marker for clinical risk prediction and is the most likely to positively predict future clinical cardiovascular outcomes. CAC scores are considered more accurately predictive of CVD outcomes compared with CIMT measurements and have been shown to be independently predictive of mortality in men less than 45 years of age and in the elderly via a cohort study of over 44,000 subjects. One trial, which consisted of EST and CAC scoring in 20 men aged 39 to 69 years with ED and no cardiac symptoms or known underlying CVD, yielded CAC scores of >50 in 11 men, all of whom were found to have angiographic evidence of CAD on coronary CT angiography, nine of whom had normal ESTs. The authors concluded that ED is a bona fide predictor of subclinical, non–flow-limiting CAD that was not detectable via EST, and that CAC coupled with coronary CT angiography may help detect subclinical CAD in men with normal ESTs.

**Testosterone and the metabolic syndrome**

Increasing evidence supports the notion that testosterone supplementation can have a positive effect in men with MetS and ED. The Princeton III Consensus Recommendations from 2012 posit that testosterone levels should be measured in all men with physical ED. This statement is in contrast with the American College of Physicians guideline from 2009 that neither recommend for or against hormonal testing and/or treatment in men with ED. The TIMES2 study (Testosterone replacement in hypogonadal Men with Either metabolic Syndrome or type 2 diabetes), a large randomized trial, demonstrated that 6 to 12 months of transdermal testosterone replacement therapy significantly improved insulin resistance and glycemic control in hypogonadal men with diabetes. A meta-analysis of five randomized controlled trials determined that men who received testosterone replacement therapy for an average of 58 weeks demonstrated significant benefit in the reduction of fasting serum glucose, insulin, and triglyceride levels as well as waist circumference. It was noted, however, that testosterone replacement therapy, in this meta-analysis, was not found to have an appreciable improvement in HDL, blood pressure, or body mass index.

**Conclusion**

Growing evidence supports the relationship between MetS and ED. Additional research will further investigate biomarkers relative to visceral adiposity, testosterone, dyslipidemia, and other inflammatory and endocrine factors that place men at increased risk of a hopefully reversible metabolic disease. Clinicians in both primary and specialty care require the inquisitiveness to investigate each male patient’s risks and offer appropriate evidence-based risk stratification. We recommend the following metabolic investigation in men with ED, in conjunction with the 2013 atherosclerotic cardiovascular disease (ASCVD) Risk Esti-
mator\textsuperscript{27} (in conjunction with the AHA and AAC) to determine 10-year and lifetime ASCVD risk (myocardial infarction and cardiovascular accident) for men aged 40 to 59 years:

- Abdominal waist circumference.
- Blood pressure and heart rate.
- Fasting serum insulin and glucose levels.
- Baseline renal function (serum blood urea nitrogen and creatinine).
- Fasting serum lipid profile.
- Morning serum total testosterone level.
- Serum high-sensitivity C-reactive protein.
- Serum 25-hydroxyvitamin D.

Men’s health specialists are uniquely poised to educate their male patients on both cardiometabolic risk factors as well as lifestyle strategies to reduce risk. Engaging men to understand the link between MetS and ED can serve as a powerful motivating factor in promoting such changes.

**REFERENCES**


Recent guidelines suggest that a level of total testosterone less than 8 nmol/L or free testosterone less than 180 pmol/L in conjunction with bothersome symptoms requires testosterone replacement therapy (TRT), whereas total testosterone greater than 12 nmol/L or free testosterone greater than 225 pmol/L does not. Between these levels, a trial therapy for a minimum of 6 months should be considered based on symptoms without defining what constitutes a satisfactory response.\(^1\,\,^2\)

### Low testosterone and increased mortality

There is increasing evidence from multiple long-term studies that testosterone deficiency syndrome (TDS) is associated with increased cardiovascular and all-cause mortality, especially in populations with established cardiovascular disease and type 2 diabetes. Haring et al\(^3\) looked at the data in terms of several models and found that, even after strict adjustment for comorbidities, there was a consistent link between mortality risk and testosterone level throughout the studies, but that this did not prove causation (Table I).\(^4\,\,^9\)

The EMAS group (European Male Aging Study)\(^10\) recently reported 4.3-year follow-up data on 2599 men aged 40 to 79 years and concluded that men with a baseline total testosterone ≤8 nmol/L and sexual symptoms had a 3-fold increased mortality and a 5-fold increased risk of cancer death. The authors concluded that there are a small number of men with low testosterone at considerable risk of early death.

### Effect of low testosterone on surrogate markers for cardiovascular risk

Several of the above studies have shown reductions in waist circumference, visceral fat, and body mass index (BMI). There is a high level of evidence that TRT improves insulin resistance and reduces HbA\(_{1c}\) by approximately 0.89% by 18 months in men with poorly controlled diabetes.\(^11\) There is also a high level of evidence for reductions in total cholesterol, weight, BMI, visceral fat, and improvement in lean muscle mass.\(^12\)

### The effects of testosterone replacement therapy on cardiovascular mortality

A prospective recent study of 587 men with type 2 diabetes involved a 6.8-year follow-up. Low testosterone was defined as total testosterone <10.4 nmol/L. The mortality rate was 20% in the untreated group, 9.1% in the normal group independent of comorbidity, and 8.6% in the treated group.\(^13\)

A retrospective US study involved 1031 men with 372 undergoing TRT. The cumulative mortality was 21% in the untreated group vs 10% in the treated group (\(P=0.001\)) with the greatest effect in younger men and those with type 2 diabetes.\(^14\)

A recent retrospective US study was conducted on 8709 men with baseline total testosterone of 10.4 nmol undergoing coronary angiography. In the cohort of 7486 patients not receiving testosterone therapy, 681 died, 420 had myocardial infarctions, and 486 had strokes. Among the 1223 patients receiving testosterone therapy, 67 died, 23 had myo-
cardiac infarctions, and 33 had strokes. At first sight, these results would suggest benefit, but a complex statistical analysis reversed the trend and concluded that there was a greater risk in the TRT group. There were concerns that 1132 patients experiencing events were excluded because they were prescribed TRT after the event, when surely these patients should have been included in the untreated group. The authors later conceded that this number should have been 128 and conceded that 104 women had been wrongly entered into the study.

The baseline total testosterone was 1 nmol/L lower in the treated group and symptoms were not considered. Men were likely to be treated if they suffered from erectile dysfunction (ED), an independent marker for cardiac events. Only 60% had any record of a follow-up testosterone level, and in the men with a follow-up, the mean treatment level was 10.2 nmol/L, suggesting suboptimal therapy. The level of criticism of this paper led to widespread demands for retraction.

Another recent US publication looked at prescribing data in men treated with TRT, but with no data on blood results or symptoms. Coronary events were assessed in the 12 months before and 3 months after therapy, even though benefits would take much longer. Curiously, a cohort of men taking phosphodiesterase type 5 inhibitors (PDE5 inhibitors) were considered to be the “control” group even though these drugs have been shown to increase testosterone. Although widely quoted in public media, the several design flaws and statistical analyses have discredited this paper.

The TOM study (Testosterone in Older Men with mobility limitations) involved frail elderly men with multiple comorbidities treated with 100 mg of testosterone gel, which was increased to 150 mg after 2 weeks. The treatment group had significantly greater risk factors at baseline. The study was stopped prematurely due to 23 vs 5 adverse events for active vs placebo (one death). Strangely, peripheral edema and a rise in blood pressure were classified as cardiovascular events along with self-reported syncope.

Anderson et al analyzed data from 5695 men (mean age 62) on TRT over a 5-year period on the basis of levels of total testosterone achieved by therapy (Figure 1). They showed a significant reduction in all-cause mortality where therapeutic levels were achieved and no evidence of harm with levels in the upper range. There was no reduction in the number of myocardial infarctions or stroke. This suggests that the major impact of TRT is on survival from events rather than absolute numbers.

### Table 1

<table>
<thead>
<tr>
<th>Cut-off for the definition of low TT</th>
<th>MMAS; TT &lt;6.94 nmol/L (200 ng/dL)</th>
<th>Wang study; TT &gt;8.0 nmol/L (230 ng/dL)</th>
<th>Rancho Bernardo study; TT &lt;8.36 nmol/L (241 ng/dL)</th>
<th>Male Veterans Study; TT &lt;8.7 nmol/L (250 ng/dL)</th>
<th>HIM; TT &lt;10.41 nmol/L (300 ng/dL)</th>
<th>EPIc; TT &lt;12.5 nmol/L (360 ng/dL)</th>
<th>Age-specific cut-off &lt;10th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low TT (n)</td>
<td>34</td>
<td>69</td>
<td>82</td>
<td>98</td>
<td>241</td>
<td>474</td>
<td></td>
</tr>
<tr>
<td>Model 1, HR (95% CI)</td>
<td>1.59 (0.83; 4.02)</td>
<td>1.96 (0.93; 3.63)</td>
<td>2.21 (1.26; 3.89)**</td>
<td>2.24 (1.41; 3.57)**</td>
<td>1.33 (0.93; 1.90)</td>
<td>1.28 (0.95; 1.72)</td>
<td>2.21 (1.40; 3.49)**</td>
</tr>
<tr>
<td>Model 2, HR (95% CI)</td>
<td>2.12 (1.01; 4.46)*</td>
<td>2.08 (1.12; 3.86)*</td>
<td>2.33 (1.33; 4.12)**</td>
<td>2.10 (1.34; 3.29)**</td>
<td>1.28 (0.89; 1.84)</td>
<td>1.20 (0.88; 1.62)</td>
<td>2.26 (1.43; 3.59)**</td>
</tr>
<tr>
<td>Model 3, HR (95% CI)</td>
<td>2.50 (1.18; 5.27)*</td>
<td>2.24 (1.21; 4.17)*</td>
<td>2.53 (1.43; 4.47)**</td>
<td>2.32 (1.38; 3.89)**</td>
<td>1.37 (0.95; 1.99)</td>
<td>1.28 (1.03; 1.75)</td>
<td>2.35 (1.47; 3.74)**</td>
</tr>
<tr>
<td>Model 4, HR (95% CI)</td>
<td>2.68 (1.19; 6.04)*</td>
<td>2.13 (1.06; 4.26)*</td>
<td>2.56 (1.38; 4.76)**</td>
<td>2.56 (1.38; 4.76)**</td>
<td>1.92 (1.18; 3.14)**</td>
<td>1.11 (0.72; 1.69)</td>
<td>1.10 (0.70; 1.56)</td>
</tr>
</tbody>
</table>

**Abbreviation:** CI, 95% confidence interval; DHEAS, dehydroepiandrosterone sulfate; EPIC, European Prospective Investigation into Cancer; HIM, Hypogonadism In Men study; HR, hazard ratio; MMAS, Massachusetts Male Aging Study; WC, waist circumference. *P<0.05, **P<0.01, ***P<0.001.

**Modified from reference 3:** Harring R et al. Eur Heart J. 2010;31:1494-1501. © 2010, the author.
Testosterone and erectile dysfunction

ED is an established marker for future cardiovascular risk and the major presenting symptom leading to a diagnosis of low testosterone. Current guidelines suggest that all patients presenting with ED, irrespective of age, should be screened for low testosterone, as it is a potentially curable cause of ED, especially in men without other comorbidities. National Institute for Health and Care Excellence (NICE) guidelines and the UK general practice contract have suggested that all men with type 2 diabetes be assessed for ED annually; increased demand for testosterone supplementation will be a natural consequence of this correction of previous underdiagnosis and undertreatment.

**Fig. 1** Testosterone replacement therapy reduces major adverse cardiovascular events and death, but not absolute rate of myocardial infarction and cerebrovascular accident. Cardiovascular impact of testosterone therapy in 5695 men with low testosterone levels. (A) Event rates of major adverse cardiovascular events and death. (B) Event rates of major adverse cardiovascular events and death. (B) Event rates of major adverse cardiovascular events and death.

**Abbreviations:** fu, follow-up; T, testosterone.


Conclusions

Low levels of testosterone are manifested by ED, reduced sexual desire, and loss of morning erections. Increasing numbers of men are being diagnosed with ED that requires treatment according to published guidelines. Increasing evidence shows that testosterone deficiency is associated with increased cardiovascular and all-cause mortality. Recent data suggest that testosterone replacement therapy may reduce cardiovascular mortality as well as improving multiple surrogate markers for cardiovascular events. Specific clinical trials of testosterone replacement therapy are needed in selected populations, but in the meantime, we must treat patients based on the best current evidence.

**REFERENCES**


Drugs affecting testosterone
Drugs affecting testosterone are any medication/agent that influences circulating testosterone levels and includes antihypertensives, and agents such as statins (ie, atorvastatin and simvastatin) and spironolactone, which decrease testosterone levels, whereas the ovulation inducer clomiphene increases testosterone levels.

Erectile dysfunction
Erectile dysfunction is a form of sexual dysfunction that involves an inability of the penis to maintain an erection during sexual activity. Erectile dysfunction is commonly treated with phosphodiesterase type 5 inhibitors such as sildenafil (Viagra), which prevent the breakdown of cyclic guanosine monophosphate and relaxes smooth muscle cells in the blood vessels supplying the corpus cavernosum of the penis.

Follicle-stimulating hormone
Follicle-stimulating hormone (FSH) is a heterodimeric glycoprotein consisting of α and β subunits, and has a molecular weight of 28-29 kDa. FSH is synthesized and released by gonadotrophs in the anterior pituitary in response to stimulation by gonadotropin-releasing hormone, itself released from hypothalamic neurons into the capillary networks of the hypothalamic median eminence and lower infundibular trunk. In males, FSH stimulates Sertoli cells in the testis, which are critical to germ-cell development. In females, it acts on the ovaries to stimulate follicle development and is the main hormone controlling estrogen secretion.

Hormones
Hormones are chemical substances classically released from ductless cells into the circulation (can also be released into the interstitial fluid), and elicit effects at target cells. These effects may occur at distant target cells, nearby cells (paracrine), or the same cell (autocrine). Hormones regulate and coordinate biological functions via cell-to-cell communication and thus contribute to the maintenance of homeostasis.

Luteinizing hormone
Luteinizing hormone (LH) is a heterodimeric glycoprotein consisting of α and β subunits, and has a molecular weight of 28-29 kDa. LH is synthesized and released by gonadotrophs in the anterior pituitary in response to stimulation by gonadotropin releasing hormone, itself released from hypothalamic neurons into the capillary networks of the hypothalamic median eminence and lower infundibular trunk. In males, LH stimulates Leydig cells in the testis to produce testosterone. In females, LH causes ovulation, the formation of the corpus luteum, and stimulation of the ovaries to produce estrogen and progesterone.

Pituitary gland
The pituitary gland is a pea-sized endocrine gland consisting of three lobes (anterior, intermediate, and posterior) that protrudes from the bottom of the hypothalamus of the brain, and synthesizes and secretes a number of hormones that control/regulate growth (human growth hormone), blood pressure (vasopressin), sexual reproduction (FSH and LH), and pregnancy (oxytocin).

Prostate-specific antigen
Prostate-specific antigen (PSA) is a member of the kallikrein (KLK)-related peptidase family, and is also known as KLK3. PSA is a serine protease synthesized in prostate cells as 261 amino acid preproprotein, which is subsequently processed to a 244 amino acid pro-PSA. Pro-PSA is processed via cleavage of a seven amino acid peptide to yield mature/active PSA, which circulates as an 80-90 kDa complex with α1-antichymotrypsin. PSA is widely used as a tumour marker, as cancerous prostate tissue releases up to 10-fold greater amounts when compared with normal and benign hyperplastic prostate tissue, despite similar levels of overall expression.

Testosterone
Testosterone is an anabolic steroid hormone (derived from cholesterol). In males, testosterone is required for the development of secondary sexual characteristics and spermatogenesis. In the bloodstream, the majority of testosterone is tightly bound to sex hormone-binding globulin (SHBG), weakly bound to albumin (and other proteins), or freely circulating. Only a minor fraction of testosterone in the circulation is free/nonprotein bound. Testosterone that is not bound to SHBG (ie, albumin bound and free testosterone) is considered to be bioavailable. Several algorithms have been developed to calculate free testosterone concentration. If the circulating concentration of SHBG (nmol/L) and total testosterone (nmol/L) is measured, an estimate of circulating free testosterone concentration (nmol/L) can be calculated as follows:

\[
\text{[Free testosterone]} = \frac{\text{[Total Testosterone]}}{6.11 - 2.38 \log_{10} \text{[SHBG]}}
\]
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