Maturitas 67 (2010) 15–19

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Testosterone and coronary artery disease in men

Carolyn M. Webb[a,b,*], Peter Collins[a,b,c]

[a] Cardiovascular Sciences, National Heart & Lung Institute, Imperial College London, London, UK
[b] Department of Cardiology, Royal Brompton & Harefield NHS Foundation Trust, London, UK
[c] IRCCS San Raffaele, Rome, Italy

ARTICLE INFO

Article history:
Received 16 March 2010
Received in revised form 29 March 2010
Accepted 31 March 2010

Keywords:
Coronary artery disease
Testosterone
Men
Risk factors
Vascular effects
Atherosclerosis

ABSTRACT

Coronary artery disease (CAD) is the leading cardiovascular cause of death, and in men, endogenous testosterone concentrations are inversely related to the extent and severity of CAD. Testosterone is known to affect a number of risk factors for CAD and has effects on vascular tone, vasoreactivity and blood flow of blood vessels beyond the reproductive system, indicating that testosterone may be involved in the pathogenesis of CAD. In this review we will present and discuss the actions of endogenous testosterone and testosterone treatment on risk factors for CAD, on the blood vessel wall and blood flow, and on atheroma development and progression, and discuss the potential for testosterone use in men with CAD.

Contents

1. Introduction

Cardiovascular disease is the most prevalent non-communicable cause of death worldwide (World Health Statistics 2009, World Health Organization) and within this coronary artery disease (CAD) is the leading cause of death [1]. Although mortality from CAD is decreasing, morbidity is increasing, particularly in older age groups (BHF statistics database, www.heartstats.org). The health and economic implications of caring for a growing aging population with CAD is enormous. Maintaining a 'healthy' elderly population that is mobile and independent with a good quality of life is vital, and any intervention that can potentially help to achieve that is worth investigation and consideration.

Sex hormones are known to have cardiovascular effects, and concentrations of oestrogens and androgens tend to decrease with age. Epidemiological studies have identified an inverse association between testosterone and CAD in men, with reduced testosterone concentrations being linked to premature CAD [2] and with increased risk of cardiovascular mortality independent of age [3]. In addition, a similar relationship exists between decreased testosterone concentrations and extent and severity of coronary atheroma in men undergoing coronary angiography [4]. This evidence indicates that testosterone may be involved in the

* Corresponding author at: Cardiovascular Sciences, NHLI, Imperial College London, Dovehouse Street, London SW3 6LY, UK. Tel.: +44 20 7351 8860; fax: +44 20 7351 8771.
E-mail address: c.webb@imperial.ac.uk (C.M. Webb).

0378-5122/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2010.03.029

pathogenesis of CAD. In this review we will present and discuss the effects of endogenous testosterone and testosterone treatment on risk factors for CAD, on the blood vessel wall and blood flow, and on atheroma development and progression in men. Testosterone has effects on blood vessels in a number of vascular beds however the following discussion will focus mainly on the peripheral and coronary circulations. It is also important to consider the differences between endogenous testosterone concentrations, and effects induced by exogenous testosterone or testosterone replacement treatment as well as the differing effects induced by the different available preparations of testosterone and other androgen treatments.

2. Testosterone and CAD risk

Modifiable risk factors for CAD that are influenced by testosterone concentrations in men include plasma lipids, type-II diabetes, central adiposity, insulin concentrations, the metabolic syndrome and blood pressure. The evidence relating to the effects of testosterone on lipid profile are conflicting, and have been comprehensively reviewed elsewhere [5,6]. Although not consistent in their findings, epidemiological and observational studies have generally shown that low endogenous testosterone concentrations in men are independently associated with dyslipidaemia and an atherogenic lipid profile, specifically decreased high-density lipoprotein (HDL)-cholesterol and elevated total cholesterol, triglyceride, low-density lipoprotein (LDL)-cholesterol levels [7–9]. The effect of testosterone treatment on lipid profile depends on route of administration and resultant plasma concentrations of testosterone. Oral and transdermal testosterone replacement in men with low testosterone concentrations results in a small detrimental (lowering HDL-cholesterol) effect or a null effect on plasma cholesterol and lipoprotein levels [10–12]. A meta-analysis of the effects of intramuscular testosterone replacement in hypogonadal men showed a small, dose-dependent decrease in total cholesterol and LDL-and HDL-cholesterol [13], and a more recent study showed that intramuscular testosterone replacement in hypogonadal men with type-II diabetes decreases total cholesterol levels but had no effects on lipoproteins [14]. In contrast, high doses of testosterone or anabolic steroids dramatically derange lipid profile [15].

Central adiposity, a 'male' fat deposition pattern, is associated with insulin resistance, hyperinsulinaemia, type-II diabetes, and the metabolic syndrome, and these are all linked to reduced testosterone concentrations in men [16,17]. Testosterone levels are inversely related to degree of obesity; that is, men with low testosterone levels have increased abdominal adipose deposition, possibly secondary to increased aromatisation of testosterone to oestradiol in white fat [16]. Testosterone substitution therapy reduces abdominal fat [18]. Central obesity and low testosterone levels are both linked to insulin resistance and type-II diabetes, and men with diabetes have lower endogenous testosterone levels than non-diabetic men [16]. Kapoor et al. showed that intramuscular testosterone replacement in hypogonadal men with diabetes reduced insulin resistance, waist circumference and waist/hip ratio, and improved glycaemic control [14].

From puberty, blood pressure is higher in men than women of a similar age [19], and in men, low endogenous testosterone concentrations are associated with elevated blood pressure independent of age and BMI [20,21]. Testosterone treatment in hypogonadal men, or in men with low testosterone concentrations and CAD, has no effect on blood pressure [12,22,23], however we could find no evidence describing the treatment effects of testosterone in hypertensive men. Studies in animals suggest detrimental effects. In spontaneously hypertensive rats, testosterone treatment in castrated females exacerbated hypertension by reducing pressure naturesis, and in male salt-sensitive rats fed a high salt diet, testosterone contributed to the development of hypertension and renal injury, proposed to be via up-regulation of the intra-renal rennin–angiotensin system [24,25]. Future studies investigating whether there is an association between low testosterone levels and hypertension in men similar to that shown in men with CAD would be of interest, and might clarify whether testosterone treatment might be worthy of investigation in hypertensive men.

The National Cholesterol Education Program (NCEP) definition of the metabolic syndrome is the presence of at least three of the following criteria: central obesity, elevated triglycerides (or receiving treatment), elevated HDL-cholesterol (or receiving treatment), arterial blood pressure $\geq$130/85mmHg (or receiving treatment), fasting plasma glucose $\geq$6.1 mmol/l or type-II diabetes [26]. The metabolic syndrome is associated with increased risk of developing type-II diabetes, and suffering a myocardial infarction or stroke [27]. Large studies have revealed an inverse association between testosterone concentrations and the prevalence of metabolic syndrome [28,29]. The Massachusetts Male Aging study showed a marked association between lower testosterone concentrations and the metabolic syndrome but only in men with a body mass index <25 kg/m^2, indicating that central adiposity rather than overall adiposity together with decreased testosterone concentrations are associated with increased risk of developing the metabolic syndrome [29]. Although there have been no studies investigating the effects of testosterone replacement therapy in men with the metabolic syndrome per se, there have been studies investigating effects on components of the syndrome, as described above.

In summary, endogenous testosterone concentrations are generally inversely related to CAD risk factors in men, however the evidence is not conclusive regarding a generalised positive or negative treatment effect.

3. Testosterone and the blood vessel wall

Vascular tone, the degree of blood vessel constriction relative to its maximal diameter, can be a contributing factor to triggering an acute coronary syndrome in the presence of coronary atherosclerosis [1]. It is influenced by the endothelium and vascular smooth muscle as well as vasoconstrictor and vasodilator factors. Testosterone appears to affect vascular tone not via the endothelium but via large conductance, calcium-activated potassium channels, albeit at relatively high concentrations of testosterone in vitro [30]. In contrast, endogenous testosterone concentrations can regulate a voltage-gated calcium channel gene in male coronary arteries [31], and physiological doses of testosterone can increase vascular tone via endothelium-derived hyperpolarising factor modulation [32]. In the first of these studies [30] testosterone exposure was acute or short-term, and the effects on vascular tone were not mediated via the nuclear androgen receptor, but this does not exclude a role for androgen receptors on the plasma membrane or/and conversion of testosterone to oestradiol via the enzyme aromatase. Indeed a small study in men undergoing chronic aromatase inhibitor treatment, who were studied before and after stopping treatment, showed an enhancement of endothelium-dependent vasodilatation in the forearm, and a decrease in arterial compliance [33]. These effects may be due to a decrease in testosterone levels, but more likely to an increase in oestradiol concentrations.

A well-functioning endothelium is essential for the maintenance of vascular health. The requisite role of the endothelium in vasodilatation offers a mechanism whereby arterial 'health' can be assessed prior to the development of atheroma. Assessment of endothelial function in the brachial artery has been used as a surrogate marker for arterial damage preceding atheroma for-

mation [34]. Fundamental to the brachial technique is the close relationship between peripheral endothelial dysfunction and coronary atheroma [35], and endothelial dysfunction in the coronary and peripheral circulations has been shown to predict the risk of cardiovascular events in patients with CAD [36]. In hypogonadal men, reduced testosterone concentrations are associated with endothelial dysfunction in one study, yet another showed greater flow-mediated dilatation (FMD; a measure of endothelial function) of the brachial artery in hypogonadal men than in controls [22]. Testosterone treatment in hypogonadal men has mixed effects on FMD. Intramuscular testosterone treatment for a number of months, and depot testosterone for 2–4 weeks, resulted in a reduction of FMD, whereas transdermal administration had a null effect [11,22,59]. In men with coronary risk factors, endogenous testosterone concentrations were associated with endothelial dysfunction in men, independent of other risk factors [37], while oral testosterone replacement in men with established CAD had a beneficial effect on baseline endothelial dysfunction [38]. Supraphysiologic but not physiologic doses of testosterone in men with CAD enhance FMD, raising the possibility that higher concentrations of testosterone are required to induce a positive endothelial response.

Arterial stiffness is an independent predictor of CAD and cardiovascular events in healthy subjects [39]. It is well established that arterial stiffness increases with age but it is also independently related to endogenous testosterone concentrations. This may be inferred in boys at puberty when an age- and gender-associated increase in arterial stiffness occurs together with the greatly increased testosterone levels [40]. Epidemiological studies have shown an independent inverse relationship between endogenous testosterone concentrations and arterial stiffness in older men [41,42]. The few data showing effects of testosterone replacement on arterial stiffness in men with low testosterone concentrations have demonstrated a trend to normalisation of increased arterial stiffness [12,23]. Taken together, these data suggest a modulatory role for testosterone on arterial stiffness, however longer and larger studies are needed to further investigate this.

4. Testosterone and coronary blood flow, angina and myocardial ischemia

Early studies showing a favourable effect of testosterone on isolated coronary artery vasoreactivity [30] led to further investigation into the effects of testosterone on the coronary circulation in both animals and humans. Short-term testosterone administration, given at relatively high concentrations, induced vasodilatation and increases in blood flow in coronary arteries of anaesthetised animals, mediated at least in part by the dilator endothelium-derived nitric oxide [43]. In men with coronary artery disease short-term, physiological concentrations of testosterone caused epicardial coronary artery dilatation and increases in volume blood flow, but by an endothelium-independent effect [44]. Longer-term testosterone administration in men with CAD can augment myocardial perfusion in myocardium supplied by unobstructed coronary arteries, but not in areas supplied by coronary arteries with significant atherosclerosis [12]. Interestingly there was no effect on angina symptoms in this and another longer-term study of testosterone treatment [10,12], however a recent study showed a reduction in the number of angina attacks and ischemic episodes in men with CAD taking longer-term testosterone therapy [45].

Taken together, the vascular effects of testosterone are interesting in light of a study investigating longer-term testosterone treatment in men with chronic stable angina which demonstrated improvement in signs of myocardial ischemia during treadmill exercise testing [10]. Whether testosterone protects against myocardial damage during transient or prolonged ischemia is an area of recent research. An ischemia–reperfusion isolated heart model from castrated or androgen receptor inhibitor flutamide-treated male rats exhibited protection of cardiac function, decreased inflammatory cytokine production, decreased expression of apoptosis-related proteins and increased antipoptotic protein expression [46]. Cavasin et al. showed testosterone-related worsening of cardiac dysfunction and remodelling after myocardial infarction in intact male mice compared with intact female or castrated male mice [47]. These animal studies suggest a detrimental effect of endogenous testosterone on cardiac responses to myocardial ischemia and infarction. Conversely, others have demonstrated cardiomyoctye protection by testosterone via effects on mitochondrial ATP-sensitive potassium channels in a myocardial cell ischemia model [48]. Further studies investigating physiologic androgen replacement in these models and in humans would be of interest.

5. Testosterone and atherosclerosis

The inverse relationship between endogenous testosterone concentrations and extent of coronary atheroma has been well established by epidemiological studies [4]. No study has investigated the effect of testosterone replacement on atheroma development or/and progression directly in humans, however animal and in vitro studies suggest an inhibitory effect of androgen replacement on atheroma development and neo-intimal proliferation [49–51]. Testosterone has been shown to favourably affect early stages of experimental atherogenesis by inhibiting tumour necrosis factor-α-induced vascular cell adhesion molecule-1 expression, via conversion to oestradiol by aromatase [52] or interaction with the androgen receptor [53]. Interestingly though, androgen treatment in partially androgen deficient men did not affect serum inflammatory markers, including VCAM-1 [54]. In a study to explore the relative contribution of oestrogen and androgen receptors in the early pathogenesis of CAD, Liu et al. studied coronary arteries taken from males without known CAD at autopsy and found that androgen receptor expression was inversely related to plaque area whereas and oestrogen receptor-β expression had a positive association [55]. They concluded that androgen receptors and oestrogen receptors appear to both have a role, albeit opposites, in early atheroma development.

6. Risks of testosterone treatment

Testosterone administration in hypogonadal men can cause side effects such as erythrocytosis (more so with oral preparations), fluid retention, benign prostatic hyperplasia, hepatotoxic and neoplastic effects (mostly with oral preparations but not testosterone undecanoate), gynaecomastia, acne and skin reactions (mostly with patches), and benign prostatic hyperplasia [56]. There is much controversy over the association between endogenous testosterone concentrations, and testosterone treatment/replacement, and increased incidence of prostate cancer which is detailed elsewhere [56–58].

7. Conclusions

The evidence is convincing that endogenous testosterone concentrations affect risk factors for CAD, extent of CAD, and has effects directly on the blood vessel wall beyond the reproductive system of men. It would be erroneous to suggest that testosterone treatment is a panacea for men with CAD, but men with CAD who are hypogonadal or have testosterone concentrations at or below the normal range may be prime candidates for benefiting from testosterone

replacement therapy. Although the data available indicate potentially favourable effects of testosterone replacement in these men, or at least a lack of detrimental effect, the data are still relatively sparse. Testosterone treatment is not without side effects and risks, particularly relating to prostate safety, so these must be considered also. Studies encompassing longer-term treatment periods, investigating the differing types of testosterone replacement available, are required to give strong evidence for or against a clinical use for testosterone treatment in men with CAD in the future.

Provenance and peer review

Commissioned and externally peer reviewed.

Contributors

Carolyn Webb participated in the drafting and finalising of the manuscript and also has seen and approved the final version. Peter Collins participated in the writing and reviewing of the manuscript and also has seen and approved the final version.

Competing interest

None.

References

[1] Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. Lancet Infect Dis 2010;10:83–92.
[2] Turhan S, Tulunay C, Gulec S, et al. The association between androgen levels and premature coronary artery disease in men. Coron Artery Dis 2007;18:159–62.
[3] Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation 2007;116:2694–701.
[4] Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb 1994;14:701–6.
[5] Alexandersen P, Christiansen C. The aging male: testosterone deficiency and testosterone replacement. An up-date. Atherosclerosis 2004;173:157–69.
[6] Schleich F, Legros JJ. Effects of androgen substitution on lipid profile in the adult and aging hypogonadal male. Eur J Endocrinol 2004;151:415–24.
[7] Haffner SM, Mykkanen L, Valdez RA, Katz MS. Relationship of sex hormones to lipids and lipoproteins in nondiabetic men. J Clin Endocrinol Metab 1993;77:1610–5.
[8] Simon D, Charles MA, Nahoul K, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. J Clin Endocrinol Metab 1997;82:682–5.
[9] Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP, Kuller LH. Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former multiple risk factor intervention trial participants. Am J Epidemiol 1997;146:609–17.
[10] English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. Circulation 2000;102:1906–11.
[11] Kenny AM, Prestwood KM, Gruman CA, Fabregas G, Biskup B, Mansoor G. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2002;57:M460–5.
[12] Webb CM, Elkington AG, Kraidly MM, Keenan N, Pennell DJ, Collins P. Effects of oral testosterone treatment on myocardial perfusion and vascular function in men with low plasma testosterone and coronary heart disease. Am J Cardiol 2008;101:618–24.
[13] Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD, Siscovick DS. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. Am J Med 2001;111:261–9.
[14] Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006;154:899–906.
[15] Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. Sports Med 2004;34:513–54.
[16] Vitale C, Mendelsohn ME, Rosano GM. Gender differences in the cardiovascular effect of sex hormones. Nat Rev Cardiol 2009;6:532–42.
[17] Zitzmann M. Testosterone deficiency, insulin resistance and the metabolic syndrome. Nat Rev Endocrinol 2009;5:673–81.
[18] Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 1999;84:2647–53.
[19] Wiinberg N, Hoegholm A, Christensen HR, et al. 24-h ambulatory blood pressure in 352 normal Danish subjects, related to age and gender. Am J Hypertens 1995;8:978–86.
[20] Khaw KT, Barrett-Connor E. Blood pressure and endogenous testosterone in men: an inverse relationship. J Hypertens 1988;6:329–32.
[21] Fogari R, Preti P, Zoppi A, et al. Serum testosterone levels and arterial blood pressure in the elderly. Hypertens Res 2005;28:625–30.
[22] Bernini G, Versari D, Moretti A, et al. Vascular reactivity in congenital hypogonadal men before and after testosterone replacement therapy. J Clin Endocrinol Metab 2006;91:1691–7.
[23] Yaron M, Greenman Y, Rosenfeld JB, et al. Effect of testosterone replacement therapy on arterial stiffness in older hypogonadal men. Eur J Endocrinol 2009;160:839–46.
[24] Reckelhoff JF, Zhang H, Granger JP. Testosterone exacerbates hypertension and reduces pressure-natriuresis in male spontaneously hypertensive rats. Hypertension 1998;31:435–9.
[25] Yanes LL, Sartori-Valinotti JC, Iliescu R, et al. Testosterone-dependent hypertension and upregulation of intrarenal angiotensinogen in Dahl salt-sensitive rats. Am J Physiol Renal Physiol 2009;296:F771–9.
[26] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). J Am Med Assoc 2001;285:2486–97.
[27] Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683–9.
[28] Muller M, Grobbee DE, den TI, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab 2005;90:2618–23.
[29] Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. J Clin Endocrinol Metab 2006;91:843–50.
[30] Yue P, Chatterjee K, Beale C, Poole-Wilson PA, Collins P. Testosterone relaxes rabbit coronary arteries and aorta. Circulation 1995;91:1154–60.
[31] Bowles DK, Maddali KK, Ganjam VK, et al. Endogenous testosterone increases L-type Ca2+ channel expression in porcine coronary smooth muscle. Am J Physiol 2004;287:H2091–8.
[32] Gonzales RJ, Krause DN, Duckles SP. Testosterone suppresses endothelium-dependent dilation of rat middle cerebral arteries. Am J Physiol 2004;286:H552–60.
[33] Komesaroff PA, Murray R, Rajkumar C, et al. Aromatase inhibition alters vascular reactivity and arterial compliance in men: a possible vascular role for endogenous sex hormones in males. Aust N Z J Med 1999;29:265–7.
[34] Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation 1993;88:2149–55.
[35] Neunteufl T, Katzenschlager R, Hassan A, et al. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. Atherosclerosis 1997;129:111–8.
[36] Heitzer T, Schlinzig T, Krohn K, Meinertz T, Munzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. Circulation 2001;104:2673–8.
[37] Akishita M, Hashimoto M, Ohike Y, et al. Low testosterone level is an independent determinant of endothelial dysfunction in men. Hypertens Res 2007;30:1029–34.
[38] Kang SM, Jang Y, Kim JY, et al. Effect of oral administration of testosterone on brachial arterial vasoreactivity in men with coronary artery disease. Am J Cardiol 2002;89:862–4.
[39] Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113:657–63.
[40] Ahimastos AA, Formosa M, Dart AM, Kingwell BA. Gender differences in large artery stiffness pre- and post puberty. J Clin Endocrinol Metab 2003;88:5375–80.
[41] Hougaku H, Fleg JL, Najjar SS, et al. Relationship between androgenic hormones and arterial stiffness based on longitudinal hormone measurements. Am J Physiol 2006;290:E234–42.
[42] Dockery F, Bulpitt CJ, Donaldson M, Fernandez S, Rajkumar C. The relationship between androgens and arterial stiffness in older men. J Am Geriatr Soc 2003;51:1627–32.
[43] Chou TM, Sudhir K, Hutchison SJ, et al. Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. Circulation 1996;94:2614–9.
[44] Webb CM, McNeill JG, Hayward CS, de Ziegler D, Collins P. Effects of testosterone on coronary vasomotor regulation in men with coronary artery disease. Circulation 1999;100:1690–6.
[45] Cornoldi A, Caminiti G, Marazzi G, et al. Effects of chronic testosterone administration on myocardial ischemia, lipid metabolism and insulin resistance in elderly male diabetic patients with coronary artery disease. Int J Cardiol 2009.
[46] Wang M, Tsai BM, Kher A, Baker LB, Wairiuko GM, Meldrum DR. Role of endogenous testosterone in myocardial proinflammatory and proapoptotic signaling after acute ischemia–reperfusion. Am J Physiol 2005;288:H221–6.

[47] Cavasin MA, Sankey SS, Yu AL, Menon S, Yang XP. Estrogen and testosterone have opposing effects on chronic cardiac remodeling and function in mice with myocardial infarction. Am J Physiol 2003;284:H1560–9.
[48] Er F, Michels G, Gassanov N, Rivero F, Hoppe UC. Testosterone induces cytoprotection by activating ATP-sensitive K+ channels in the cardiac mitochondrial inner membrane. Circulation 2004;110:3100–7.
[49] Alexandersen P, Haarbo J, Byrjalsen I, Lawaetz H, Christiansen C. Natural androgens inhibit male atherosclerosis. A study in castrated, cholesterol-fed rabbits. Circ Res 1999;84:813–9.
[50] Hanke H, Lenz C, Hess B, Spindler KD, Weidemann W. Effect of testosterone on plaque development and androgen receptor expression in the arterial vessel wall. Circulation 2001;103:1382–5.
[51] Tharp DL, Masseau I, Ivey J, Ganjam VK, Bowles DK. Endogenous testosterone attenuates neointima formation after moderate coronary balloon injury in male swine. Cardiovasc Res 2009;82:152–60.
[52] Nathan L, Shi W, Dinh H, et al. Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. Proc Natl Acad Sci USA 2001;98:3589–93.
[53] Hatakeyama H, Nishizawa M, Nakagawa A, Nakano S, Kigoshi T, Uchida K. Testosterone inhibits tumor necrosis factor-alpha-induced vascular cell adhesion molecule-1 expression in human aortic endothelial cells. FEBS Lett 2002;530:129–32.
[54] Ng MK, Liu PY, Williams AJ, et al. Prospective study of effect of androgens on serum inflammatory markers in men. Arterioscler Thromb Vasc Biol 2002;22:1136–41.
[55] Liu PY, Christian RC, Ruan M, Miller VM, Fitzpatrick LA. Correlating androgen and estrogen steroid receptor expression with coronary calcification and atherosclerosis in men without known coronary artery disease. J Clin Endocrinol Metab 2005;90:1041–6.
[56] Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482–92.
[57] Morales A. Androgen replacement therapy and prostate safety. Eur Urol 2002;41:113–20.
[58] Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol 2006;50:935–9.
[59] Zitzmann M, Brune M, Nieschlag E. Vascular reactivity in hypogonadal men is reduced by androgen substitution. J Clin Endocrinol Metab 2002;87:5030–7.