Androgens, ageing and vascular function

Circulating testosterone in males is well known to decline progressively with advancing age, a decline that is paralleled by a number of physiological changes including loss of bone and muscle mass; increased fat mass; impairment of physical, sexual and cognitive functions; loss of body hair; and decreased hemoglobin levels. Indeed, early-onset androgen deficiency produces similar changes [1]. In addition, androgens have an important influence on vascular function: the human androgen receptor is expressed in all vascular tissues, including endothelium, smooth muscle and myocardium [2]. Besides traditional modifiable cardiovascular risk factors, androgens have also been implicated in the relatively higher rate of cardiovascular disease in men. Excess exogenous androgens certainly seem to increase cardiovascular morbidity [3], however, there is growing evidence that at physiological levels androgens appear to be associated with reduced cardiovascular risk [2, 4].

Arteriosclerosis is associated with increased large artery stiffness (or reduced compliance), which inhibits optimal coronary and peripheral perfusion [5]. Simultaneous endothelial degeneration, with impaired release of vasoactive substances has an effect mainly on peripheral vessels where smooth muscle content is higher. These processes interact to contribute to increased cardiovascular morbidity and mortality (Figure 1).

Non-invasive measurement of arterial properties that reflect the severity of arteriosclerosis allows both safe and meaningful assessment of the extent of vascular damage and overall vascular performance. Pulse wave velocity (PWV), which measures large artery stiffness, is the most widely used and independently predicts cardiovascular morbidity and mortality [6]. Other methods for measuring large artery stiffness include augmentation index (AI) [7], systemic arterial compliance (SAC) [8], and measurement of QKD (ECG Q wave to Korotkoff sound) [9]. Impaired endothelial function, assessed non-invasively, has also been shown to predict cardiovascular risk [10]. Endothelial function may also influence large central arteries, and thus, measurements such as PWV and endothelial function are closely related, but not necessarily interchangeable, as they measure different aspects of vessel function [11, 12].

Because arterial stiffness is closely related to chronological age, any deviations from age-predicted normal
values could represent a more meaningful reflection of biological age, which may be more predictive of cardiovascular pathology [13]. Moreover, measures such as PWV and endothelium-dependent vasodilatation have consistently revealed a significant role of androgens in arteriosclerosis [2].

For some time, gender disparity in cardiovascular morbidity and mortality has largely been attributed to hormonal differences. Indeed, until recently, oestrogens were thought to be cardioprotective. However, the Women’s Health Initiative study, and several studies since, have convincingly demonstrated higher rates of non-fatal heart attacks, stroke and thromboembolic disease in association with HRT [14]. The effects of androgens on vascular function, and consequently their impact on cardiovascular morbidity are less well understood [15]. Non-invasive techniques are, however, rapidly filling gaps in this field.

Much evidence for the detrimental cardiovascular effects of androgens is derived from studies of exogenous anabolic steroid abuse by athletes. Supraphysiological androgen concentrations cause hypertension and ventricular remodelling, and are linked to myocardial ischaemia and sudden cardiac death [3]. In smaller vessels, impaired vasodilatory responsiveness (e.g. to nitro-glycerine) is recognised both with anabolic steroid abuse [16], and in female-to-male transsexuals receiving large androgen doses [17]. However, other authors have reported enhanced vascular reactivity with supraphysiological testosterone doses [18].

At the other extreme, the vascular effects of abnormally low androgen levels have been investigated following pharmacological androgen blockade in the treatment of prostatic carcinoma. In this context, arterial stiffness is increased [19].

Moving the focus from exogenous androgen manipulation in extremes of range towards endogenous physiological androgen levels, several observational studies have shown lower testosterone concentrations in men with cardiovascular disease [20, 21]. A systematic review suggested a neutral or favourable effect of high physiological testosterone concentrations on coronary heart disease risk [2], and there is evidence that even in low doses, testosterone acts as a coronary vasodilator, with the ability to reverse myocardial ischaemia [22, 23]. Low androgen levels have also been associated with increased aortic stiffening [24] and reduced systemic arterial compliance [4]. A larger longitudinal study following 206 men for approximately 33 years also showed that a lower free testosterone index was significantly associated with increased arterial stiffness [25]. Therefore, it would seem that states of extreme androgen excess or deficiency cause increased cardiovascular morbidity, but physiological androgen levels may well be cardioprotective.

The decrease in serum testosterone with age renders a substantial proportion of middle-aged and older men hypogonadal. The term ‘andropause’ has been coined to describe cases when this decline in androgenicity is associated with troublesome symptoms such as diminished libido, erectile dysfunction, fatigue and depression [26]. Whether declining androgen levels are also related to increased cardiovascular morbidity in older men is an important question, which requires further elucidation. It seems likely that non-invasive assessments of vascular function will continue to play a key role in this field.

Despite the growing attention of testosterone replacement in hypogonadal older men in the literature, its perceived influence on physical and cognitive function remains controversial [27, 28]. Additionally, cardiovascular implications of testosterone administration are not completely understood [15], and lessons learned from hormone replacement therapy in females understandably fuel anxieties surrounding adverse side effects. Clearly, further work is needed to fully understand the trade-off between health-related outcomes and long-term risks of androgen replacement, but given the substantial epidemiological burden presented by cardiovascular disease, the potential value to the entire male population of clarifying whether such therapies increase or reduce cardiovascular morbidity certainly justifies more high-quality randomised placebo controlled trials in this area.

References


Editorials
ACE inhibitors for sarcopenia— as good as exercise training?

Sarcopenia is a major health problem for older people. Progressive impairment in muscle strength and loss of muscle mass are key contributors to falls, fractures and reduced physical function, is a key risk factor for death, and for the need for assistance with activities of daily living [1, 2]. Finding effective ways to prevent and reverse sarcopenia, therefore, has great importance as a way of attempting to reduce falls and immobility, avoid institutionalisation and enhance healthy ageing.

No consensus threshold for diagnosing sarcopenia has yet been arrived at, but the pathophysiological hallmarks of the condition are becoming better defined. Reduced cross-sectional muscle area, fibre loss and reduced muscle quality all play a part; mitochondrial dysfunction occurs together with preferential loss of type I (slow twitch) fibres and changes in calcium handling by the sarcoplasmic reticulum [3]. These changes lead to reductions in maximal muscle strength, affecting predominantly explosive power but also leading to increased fatigability.

The biological mechanisms underlying the pathophysiological changes of sarcopenia are still not well understood, but basic science and epidemiological studies have given us important insights in the last few years. Satellite cells in muscle, which usually provide the substrate for muscle regeneration, are lower in number in older people [4]. Chronic inflammation is linked to sarcopenia, with pro-inflammatory cytokines, including IL-6 and TNF alpha, thought to have deleterious actions on muscle [5]. Hormonal