



Therapeutic Benefits of Testosterone Replacement Therapy in Men in the Anti-Aging Clinical Setting: A Review of Recent Scientific Literature (2004-2005)

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Anti-Aging for Professionals, published by the European Society of Anti-Aging Medicine (ESAAM)

The 14,500 physicians, health practitioners, and scientists representing 80 countries worldwide who are members of the American Academy of Anti-Aging Medicine (A4M), the world's leading professional medical society involved in addressing the issues of global aging, focus on the use of high-tech diagnostic and treatment biomedical technologies for the very earliest detection and most aggressive care of disease. Anti-aging physicians aim not only to help people to live longer, healthier lives, but A4M's scientific members also seek to improve the quality of their patients' lives. Such is the case with aging men and the use of testosterone replacement therapy (TRT) in the anti-aging clinical setting.

Testosterone levels in men begin to decline in the late third or early fourth decade, and diminish at a constant rate thereafter. Across various studies, the median rate of decline in total testosterone is 0.5-0.8% per year. Concurrently, Sex Hormone Binding Globulin (SHBG) levels rise, at an approximate rate of 1-3% per year for men age 40 and over. As a result of the combined rise in SHBG and fall in total testosterone, free testosterone levels decrease by approximately 2-3% per year. As a result, men may experience symptoms and findings of testosterone deficiency are similar to those associated with aging, such as:

- Atherosclerotic profile, including adverse lipid markers
- Stroke
- Decreased muscle mass and strength
- Increased fat mass
- Frailty, osteopenia, and osteoporosis
- Erectile dysfunction
- Depressed mood

Several small clinical trials indicate that testosterone replacement therapy can improve many of these findings. In this article, we will review some of the recent scientific literature — published clinical studies from 2004 and 2005 — that demonstrate the multi-modal benefits of TRT. While testosterone replacement therapy has been shown to confer multiple physiological benefits to men in middle age and beyond who are diagnosed with androgen deficiency, anti-aging physicians have also been successful with using TRT to treat the subtle age-associated declines in serum testosterone levels to boost quality of life and overall well-being.

Because two of the strongest independent risk factors for coronary heart disease (CHD) are increasing age and male sex, Dr. RD Jones and colleagues from the University of Sheffield (United Kingdom) investigated the cardioprotective role of TRT. As men age, serum levels of testosterone decline; low testosterone is positively associated with other cardiovascular risk factors. The researchers submit a lengthy list of proven beneficial effects of TRT, such as to:

- "Reduce serum levels of the pro-inflammatory cytokines interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha
- Increase levels of the anti-inflammatory cytokine IL-10
- Reduce vascular cell adhesion molecule (VCAM)-1 expression in aortic endothelial cells
- Promote vascular smooth muscle and endothelial cell proliferation
- Induce vasodilatation and to improve vascular reactivity, to reduce serum levels of the pro-thrombotic factors plasminogen activator inhibitor (PAI)-1 and fibrinogen
- Reduce low-density lipoprotein-cholesterol (LDL-C)
- Improve insulin sensitivity

- Reduce body mass index and visceral fat mass"

The team suggests that these actions of testosterone may confer cardiovascular benefit since testosterone therapy reduces atheroma formation in cholesterol-fed animal models, and reduces myocardial ischemia in men with CHD. Dr. Jones and team submit that "age-related decline in testosterone contributes to the atherosclerotic process. This is supported by recent findings, which suggest that as many as one in four men with CHD have serum levels of testosterone within the clinically hypogonadal range." They conclude that the "restoration of serum levels of testosterone via testosterone replacement therapy could offer cardiovascular, as well as other, clinical advantages to these individuals."

In a study by Dr. J. Mäkinen and colleagues from the University of Turku (Finland), researchers explored the role of male sex hormones in the pathogenesis of atherosclerosis. The team studied 239 men, ages 40-70 (mean 57 years); 99 men were considered andropausal (i.e., serum testosterone <9.8 nmol/l or luteinizing hormone [LH] >6.0 U/l and testosterone in the normal range). The andropausal men were found to have a higher maximal carotid artery intima-media thickness (IMT), compared with controls in the common carotid (1.08 +/- 0.34 vs. 1.00 +/- 0.23, $p < 0.05$) and in the carotid bulb (1.44 +/- 0.48 vs. 1.27 +/- 0.35, $p = 0.003$). Common carotid IMT correlated inversely with serum testosterone ($p = 0.003$) and directly with LH ($p = 0.006$) in multivariate models adjusted for age, total cholesterol, body mass index, blood pressure, and smoking. The researchers concluded that "Middle-aged men with symptoms of andropause, together with absolute or compensated (as reflected by high normal to elevated LH) testosterone deficiency, show increased carotid IMT. These data suggest that normal testosterone levels may offer protection against the development of atherosclerosis in middle-aged men."

Dr. F. Schleich and team from the University of Liege (Belgium) reported on "conflicting but favorable ... studies concerning the effect of androgen substitution therapy on lipids." Small decreases in high-density lipoprotein cholesterol result from TRT, accompanied by significant decrease in total cholesterol (CT) and low-density lipoprotein cholesterol. Consequently, Dr. Schleich's team concludes that "A counterbalancing of these [aforementioned] effects plausibly accounts for the absence of increase cardiovascular risk."

Dr. CJ Malkin and co-researchers from the Royal Hallamshire Hospital (United Kingdom) studied TRT in 10 men with ischaemic heart disease and hypogonadism. Baseline total testosterone and bioavailable testosterone were respectively 4.2 (0.5) nmol/l and 1.7 (0.4) nmol/l. After a month of testosterone, delta value analysis between testosterone and placebo phase showed that mean (SD) trough testosterone concentrations increased significantly by 4.8 (6.6) nmol/l (total testosterone) ($p = 0.05$) and 3.8 (4.5) nmol/l (bioavailable testosterone) ($p = 0.025$), time to 1 mm ST segment depression assessed by Bruce protocol exercise treadmill testing increased by 74 (54) seconds ($p = 0.002$), and mood scores assessed with validated questionnaires all improved. The researchers reported that "Compared with placebo, testosterone therapy was also associated with a significant reduction of total cholesterol and serum tumour necrosis factor alpha with delta values of -0.41 (0.54) mmol/l ($p = 0.04$) and -1.8 (2.4) pg/ml ($p = 0.05$) respectively." Further, Dr. Malkin's team concludes that "Testosterone replacement therapy ... delays time to ischaemia, improves mood, and is associated with potentially beneficial reductions of total cholesterol and serum tumour necrosis factor alpha."

In one of this year's most compelling studies on the benefits of TRT, Dr. Y. Pan and co-researchers from Saint Louis University Hospital (Missouri, USA) studied the effect of testosterone on functional recovery after stroke (May 2005). The team focused on the role of testosterone during recovery from neurological deficits in a rat focal ischemia model. In two groups of castrated rats, stroke was induced; the group that received testosterone showed significant improvement in neurological deficits, while those that did not receive testosterone did not. Moreover, less GFAP expression and reactive astrocyte hypertrophy were found around the infarct area in testosterone-treated rats compared with control rats. The researchers concluded that "Testosterone replacement [can exert a] potential[ly] therapeutic role for testosterone replacement in stroke recovery."

Explaining TRT in older men with low serum testosterone levels increases lean body mass and decreases fat mass, Dr. ST Page and team from Wesley Woods Health Center (Georgia, USA) explored whether testosterone therapy could improve functional outcome in older men. In their study of 70 men

over a 36-month period, TRT significantly improved timed physical performance, grip strength, and lower extremity strength. In particular, the researchers reported that "testosterone therapy also increased lean body mass (3.77 +/- 0.55 kg) decreased fat mass, and significantly decreased total cholesterol, low-density lipoprotein, and leptin, without affecting high-density lipoprotein, adiponectin, or fasting insulin levels. The researchers concluded that "These results demonstrate that testosterone therapy in older men with low serum testosterone improves physical performance and strength."

Dr. JS Mayes and colleagues from Oklahoma State University (USA) studied the role of sex steroid hormones in the metabolism, accumulation and distribution of adipose tissues. Hypothesizing that sex steroid hormones carry out their function in adipose tissues by both genomic and nongenomic mechanisms, they observed that leptin and lipoprotein lipase are two key proteins in adipose tissues that are regulated by transcriptional control with sex steroid hormones. Dr. Mayes and team explained that in the presence of sex steroid hormones, a normal distribution of body fat exists, but with a decrease in sex steroid hormones, as occurs with aging, there is a tendency to increase central obesity, a major risk for cardiovascular disease, type 2 diabetes and certain cancers. Because sex steroid hormones regulate the amount and distribution of adipose tissues, they or adipose tissue-specific selective receptor modulators might be used to ameliorate obesity. In their observation, this team states that "testosterone replacement therapy in older men appear[s] to reduce the degree of central obesity."

Dr. M. Audran and colleagues from the CHU & faculté de médecine Angers (France) encourage physicians to tend to the potential for osteoporosis in men. Reporting that the condition in men may be idiopathic, in 60% of patients, secondary osteoporosis contributes to bone loss and fractures. Dr. Audran and team conclude that " In primary or secondary male osteoporosis, [TRT] prevent[s] bone loss and reduce[s] the incidence of future fractures."

Dr. E. Amar and co-researchers from the Hôpital de Bicêtre (France) reported that erectile dysfunction (ED) can benefit from TRT. The team explained that androgens have an action on penile tissue innervation, on the structure and function of penile trabecular smooth muscle, on penile endothelial function, as well as on the fibroelastic properties of the penile corpus cavernous, finding that "The addition of testosterone improves a great number of androgen deficiency in the aging male (ADAM)."

Age-related decline in testosterone levels is associated with depressive symptoms. Low testosterone levels are present in men with treatment-refractory depression and older men with dysthymia. Low testosterone levels may also increase the risk of incident depression in older males. Dr. RM Carnahan and colleagues from the University of Iowa (USA) found testosterone monotherapy to be tolerable and efficacious in appeared effective in treating late-onset but not early-onset major depressive disorder in older males. They also found TRT augmented the efficiency of antidepressants in treatment-refractory depression in adult males.

About 15 to 25% of men over the age of 50 years will experience serum testosterone levels well below the threshold considered normal for men between 20 and 40 years of age. Approximately 30% of men 60 to 70 years of age and 70% of men 70 to 80 years of age have low bioavailable or free testosterone levels. The number of men in the United States age 65 and over is projected to increase from 14.4 million in 2000 to 31.3 million in 2030. Taken collectively, these demographics mandate the safe and judicious use of testosterone replacement therapy in the anti-aging clinical setting.

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