

The benefit and risk of testosterone replacement therapy in older men: effects on lipid metabolism

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Abstract. Over the last decades, testosterone replacement therapy for middle-aged and older men has been gaining increasing and widespread attention and popularity. Although several benefits of testosterone replacement therapy are well established, including but not limited to improvement in libido, body composition, and bone density, concerns for multiple potential adverse effects remain. In particular, concerns are frequently raised regarding the possibility that testosterone replacement therapy may increase the risks of prostate cancer and cardiovascular disease as consequence of a potential detrimental effect of testosterone on cardiovascular risk factors. This mini-review will present and discuss the current knowledge on the relationship between testosterone replacement therapy and change in lipid fractions in older men. (www.actabiomedica.it)

Key words: testosterone, men, aging, lipids

Introduction

There has been considerable recent interest in testosterone replacement therapy in men. This interest has been fuelled by growing scientific and medical awareness of the negative effects of hypogonadism, together with media attention regarding hormone replacement therapy in older persons, the marketing of new testosterone preparations, and the increasing desire of middle-aged men to maintain vigor and health into their more mature years.

Severe male hypogonadism, defined as chronic androgen deficiency, has a low prevalence but, epidemiological studies revealed that the aging process is paralleled by a progressive decline in free and total testosterone levels (1). In addition to physiological aging, the comorbidities occurring in older age and the several medications used to treat them further contribute to lower circulating testosterone levels. Despite the publication of several studies examining the potential beneficial effects of testosterone on multiple

aspect of the aging process and although reports indicate that testosterone replacement therapy may produce a wide range of benefits for hypogonadal men that include improvement in libido, bone density, muscle mass body composition, mood, erythropoiesis, and cognition, considerable controversy remains regarding indications for testosterone therapy in aging men (2). Major concerns have arisen because testosterone is not a 'risk-free' treatment and literature lacks the publication of properly designed, controlled trials enrolling thousand of patients to evaluate effects and safety of long-term treatment.

Testosterone and lipid metabolism

The observation that men have higher incidence of cardiovascular events than women raised the hypothesis that higher testosterone levels may represent an etiologic factor in atherosclerosis and coronary heart disease (3). Indeed, there are consistent differ-

ences in lipid profile between sex, which can potentially contribute to sex-related differences in cardiovascular risk documented in epidemiological studies. An unfavourable lipid profile, characterized by an increase in total plasma cholesterol, Low Density Lipoprotein-cholesterol (LDL-C) and triglycerides, and/or High Density Lipoprotein-cholesterol (HDL-C) reduction, represents a major risk factor for atherosclerosis and for cardiovascular events. HDL-C plasma levels decrease in men after puberty and stay lower than in women; the latter, on the other hand, have high HDL-C concentrations during their reproductive years, with a progressive decline after menopause. Total cholesterol increases with age in both sexes from 20 to 70 yr: subsequently it decreases in men while continuously increasing in women. This different behaviour may be due to modifications of endogenous sex-hormones and suggests a negative role for testosterone in lipoprotein metabolism (3).

Several mechanisms may explain a pharmacological effects of androgen replacement therapy on plasma lipids (4). These effects can be defined as direct or indirect effects. Indirect effects are due to the metabolic action of estradiol after testosterone aromatization in adipose tissue. Two genes involved in HDL catabolism are upregulated by testosterone: namely, hepatic lipase and scavenger receptor B1 (SR-B1). SR-B1 mediates the selective uptake of HDL-C lipids into hepatocytes and steroidogenic cells, including Sertoli and Leydig cells of the testes, as well as cholesterol efflux from peripheral cells, including macrophages. Testosterone up-regulates SR-B1 in human hepatocytes and in macrophages, thereby stimulating selective cholesterol uptake and efflux, respectively. Hepatic lipase hydrolyzes phospholipids on HDL surface, facilitating the selective uptake of HDL lipids by SR-B1. The activity of hepatic lipase is increased after administration of exogenous testosterone. The increases in both SR-B1 and hepatic lipase activities are consistent with the reported HDL-C lowering effect of testosterone. The activity of hepatic lipase enzyme is inhibited by estrogen and this mechanism might explain why serum HDL-C levels are lower in men than in premenopausal women (5). Finally, testosterone administration results in increased lipolysis by adipocytes and stimulation of androgen receptors (6).

Exogenous testosterone is aromatized in vivo to estradiol, which plays a key role in maintaining HDL concentrations among men. The beneficial effect on LDLs is perhaps the result of an increase in estradiol concentration after aromatization of androgen in the adipocytes. Estrogen stimulates LDL receptor expression and therefore its clearance. This hypothesis is indirectly supported by the observations that aromatizable androgen (testosterone) has less detrimental effects on serum lipids than non-aromatizable androgen (dihydrotestosterone).

Effect of testosterone replacement therapy on serum lipid profile

Data from early intervention studies suggest that androgens can increase LDLs and/or decrease HDLs, with negative effects on the global cardiovascular risk profile. These effects were found after administration of different hormone preparations at supraphysiological doses in individuals with different characteristics (healthy volunteers, body-builders, transsexuals, young and old hypogonadic patients); however most of these trials were neither controlled nor randomized and were of short duration (7-9). A positive effect of testosterone enanthate (200 mg im every 2 weeks) on the lipid profile, showing a reduction in total and LDL-C, and no change in HDL-C and HDL sub-fractions, has been reported in a non-controlled trial, on a sample of geriatric and pre-geriatric hypogonadic patients (10). Some randomized controlled trials on the efficacy of testosterone substitution in the elderly considered changes in lipid levels among their outcomes: they must be taken cautiously since the investigational groups are of small size and were followed for a short time. Sih et al. (11) could find no change in the lipid pattern after 1 yr treatment with intramuscular testosterone cypionate (16 men >50 yr *vs* 16 control subjects). Parenteral testosterone enanthate significantly decreased both serum total cholesterol and LDL-C while HDL-C and triglycerides remained unchanged (12, 13). Another trial confirmed these results after treatment with testosterone undecanoate per os (14). Also transdermal testosterone treatment does not seem to have unequivocal effects

on plasma lipoprotein concentration. Kenny et al. (15) treated 67 hypogonadal old men with testosterone patches or placebo for 1 yr: total cholesterol, triglyceride, and LDL-C levels did not significantly change, whereas HDL-C and, specifically, HDL2-C decreased in men receiving testosterone supplementation. Ly et al. (16), however, reported only a reduction in total cholesterol and LDL-C after 3-month treatment with transdermal dihydrotestosterone while Snyder et al. found that, among 108 healthy men >65 yr of age with low serum testosterone, those assigned to testosterone transdermally for 36 months did not have any modification of total cholesterol, LDL-C, HDL-C, ApoA1, ApoB and lipoprotein(a) (Lp[a]) plasma levels (17).

On the whole the results of these particular studies on the effects of testosterone replacement therapy on lipids profile are conflicting and of difficult interpretation because of the limited number of enrolled older men, the small sample size of the studies, different inclusion criteria, and different study design. In order to overcome this methodological limitations three significant meta-analysis have been published in the last few years (Table 1).

In the first one, published in 2001, Whitsel and colleagues (18) analyzed 19 studies that focused on male subjects with hypogonadism and treated with intramuscular testosterone ester. They found that intramuscular administration of testosterone esters was

associated with a small, dose-dependent decrease in HDL-C and also in total cholesterol and LDL-C. Of the 19 studies included in the meta-analysis, however, only 3 were specifically focused on older subjects. Isidori and colleagues (19) analyzed the effect of testosterone replacement therapy on total cholesterol, LDL-C and HDL-C as a function of pre-treatment gonadal status. Overall, the pooled analysis of 16 different trails demonstrated a mean reduction of 8.9 mg/dl (95% C.I. -14.4 to -3.9) of total cholesterol. The effect of testosterone on serum total cholesterol however, were more pronounced in hypogonadal men (baseline testosterone < 286 ng/dl; mean difference; -16 mg/dl, CI: -25.4 to -7.4 mg/dl), than in eugonadal men (mean difference -5.5 mg/dl, CI: -11.7 to 1.2 mg/dl). With regard to HDL-C, a small reduction (mean difference -3.5 mg/dl, CI: -6.6 to 0.0 mg/dl) was observed in the group of studies performed in men with higher baseline testosterone concentrations. HDL-C reduction, corresponding roughly to a 4-6% reduction in baseline levels, was of borderline statistical significance. Nevertheless, in the overall analysis where data from men with low and normal baseline testosterone levels were pooled, HDL-C reduction was minimal and not statistically significant. Additional sensitivity analysis suggested that HDL-C modification may be affected by treatment preparation. Indeed, the decrease in HDL-cholesterol was lower in the studies

Table 1. Effect of testosterone replacement therapy on lipid fractions: results of published meta-analyses

	Total Cholesterol			LDL-Cholesterol			HDL-Cholesterol		
	N of RCT	MD	95% C.I.	N of RCT	MD	95% C.I.	N of RCT	MD	95% C.I.
Whitsel et al (2001)	3/19	-12 mg/dl	-22 to -2	3/19	-8 mg/dl	-21 to 5	3/19	-4 mg/dl	-6 to -2
Isidori et al. (2005)									
Low testosterone	4/7	-16.2 mg/dl	-25.1 to -7.3	2/3	-12.8 mg/dl	-31.2 to 5.5	3/5	0.39 mg/dl	-1.9 to 7.0
Normal testosterone	7/9	-5.4 mg/dl	-11.6 to 1.2	6/8	0.8 mg/dl	-5.9 to 7.0	6/8	-3.5 mg/dl	-6.63 to 0.0
		SMD	95% C.I.		SMD	95% C.I.		SMD	95% C.I.
Haddad et al (2007)									
Low testosterone	3/5	-0.22	-0.71 to 0.27	3/3	0.06	-0.30 to 0.42	3/4	-0.04	-0.39 to 0.30
Low-normal/normal testosterone	6/8	-0.47	-0.77 to -0.17	5/8	-0.25	-0.57 to 0.08	5/8	-0.21	-0.43 to 0.01

N of RCT: number of trials enrolling older patients out of the total number of trials
MD: mean difference; SMD: standardized mean difference

using T-esters with respect to other formulations. Finally, testosterone had no effect on LDL-C plasma concentration. In a more recent meta-analysis of randomized placebo-controlled trials, Haddad and colleagues (20) evaluated the effect of testosterone replacement therapy on the main serum lipid fractions as a function of baseline testosterone levels and comorbidity status. Table 1 show nonsignificant effects of testosterone preparations on all lipid fractions in men with low testosterone levels. Although important between-study differences regarding total cholesterol were found, these data excluded unfavourable elevations in total cholesterol levels of more than 9 mg/dl, in LDL-C levels of more than 14 mg/dl, and also exclude unfavourable reductions in HDL-C levels of greater than 5 mg/dl. In men with low-normal or normal pre-treatment testosterone levels testosterone significantly reduced total cholesterol levels by 16 mg/dl (95% confidence interval, 6-26 mg/dl); all other lipid fractions were not significantly affected. Globally taken the results of this meta-analysis suggest minimal and clinically negligible effects of testosterone use on lipid fractions in men with different degrees of androgen deficiency.

Conclusions

Strong methodological limitations affect the interpretation of the findings of studies exploring the effect of testosterone replacement therapy on lipid fractions in older men. These limitations include the small number of studies dedicated to older men and number of older subjects enrolled in these studies, the lack of studies with lipid profile as primary outcome of the trial, and a great degree of heterogeneity in studies' results. However published studies suggest that testosterone replacement therapy might decrease LDL-C without adversely affecting HDL cholesterol, particularly in men with severe pre-treatment hypogonadism. These findings provide a measure of reassurance concerning potential adverse heart effects of testosterone substitutional therapy in older men, even if more specific trials than reported are needed to definitively rule out potential adverse effects on lipid metabolism and, more important, on the global cardiovascular risk profile.

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