

Age, obesity and inflammation at baseline predict the effects of testosterone administration on the metabolic syndrome

Farid Saad^{1,2,*}, Ahmad Haider³, Erik J. Giltay⁴ and Louis J.G. Gooren⁵

¹ Bayer Schering Pharma, Scientific Affairs Men's Healthcare, Berlin, Germany

² Gulf Medical University School of Medicine, Ajman, United Arab Emirates

³ Private Urology Praxis, Bremerhaven, Germany

⁴ Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands

⁵ Endocrinology, VUmc, Amsterdam, The Netherlands

Abstract

Background: Testosterone administration to hypogonadal men improves the metabolic syndrome. This study analyzed whether age, serum testosterone, body mass index/waist circumference, increment in testosterone values and C-reactive protein (CRP) predicted the outcome of testosterone administration.

Materials and methods: A total of 110 mainly elderly men, aged between 18 and 83 years (mean \pm SD = 59.6 \pm 8.0) with baseline serum testosterone of 5.8–12.1 nmol/L (mean \pm SD = 9.3 \pm 1.7) ($n > 14.0$ nmol/L), received parenteral testosterone undecanoate whereupon serum testosterone normalized between 3 and 24 months.

Results: (i) The lower the baseline testosterone, the stronger the decreases in waist size and triglycerides. (ii) The greater the increment in serum testosterone, the stronger the decreases in low-density lipoprotein (LDL) cholesterol, triglycerides and glucose. (iii) Older age was associated with stronger beneficial effects on waist size, glucose and all lipids, but a small negative effect on high-density lipoprotein cholesterol. (iv) Obese men and men with the largest waist circumference showed the strongest declines over 2 years in weight, waist circumference and body mass index (BMI), and also in total cholesterol, triglycerides and glucose. Baseline BMI predicted a stronger decline in LDL cholesterol, but a smaller decline in CRP levels. (v) Higher baseline CRP predicted larger declines in levels of triglycerides, glucose and CRP. (vi) In the multivariate model, age, BMI and CRP were independent predictors of the strongest benefit of testosterone treatment on the metabolic syndrome.

Conclusions: Older men, particularly when obese with chronic low-grade inflammation benefited most of normal-

izing their testosterone levels, preferably if they reached mid-normal reference values.

Keywords: body mass index; lipids; testosterone; treatment effect.

Introduction

Aging can be viewed as a time-related functional decline of health into the frailty of old age, with an ever-increasing vulnerability to disease and eventually to death. Among the many processes of aging, endocrine changes are relatively easy to identify and quantify. With aging a significant percentage of men over the age of 60 years have serum testosterone levels that are below the lower limits of young adult men (aged 20–30 years) [1–3]. This is not solely of theoretical significance. Several recent studies have found that low testosterone level is a predictor of mortality in elderly men [4–9]. The latter study found that this is related to cardiovascular disease (for review see [9]).

Numerous studies have found inverse associations between features of the metabolic syndrome and plasma testosterone [10–16]. It has also been documented that low testosterone levels induce the metabolic syndrome [17, 18], dramatically demonstrated by findings in men with prostate cancer who undergo androgen ablation therapy [19, 20]. One study showed convincingly that acute androgen deprivation reduces insulin sensitivity in young men [21].

The question arises then whether testosterone treatment has a role to play in the prevention and/or treatment of the metabolic syndrome and its sequelae such as diabetes mellitus type 2 and cardiovascular disease, in particular in men with lower-than-normal testosterone levels. A recent discontinued trial showed an increased rate of cardiovascular-related events in elderly hypogonadal men treated with testosterone gel versus placebo [22], which could be related to edema, hypertension and congestive heart failure. However, in this study, men with an adverse cardiovascular risk profile were treated with unusually high doses of testosterone. Nevertheless, there is also increasing evidence of a beneficial effect of testosterone treatment on visceral fat and other elements of the metabolic syndrome [23–27] (for review see [9]). Evidently, the justification for testosterone treatment lies in a proper diagnosis of testosterone deficiency, and this can be problematic.

A diagnosis of androgen deficiency should be based on consistent symptoms and signs and unequivocally low serum testosterone levels [28]. There is as yet no true consensus what constitutes low testosterone values [29] and it could turn out to be impossible to define precise normal/abnormal

*Corresponding author: Professor Farid Saad, BU Primary Care/Men's Healthcare, Scientific Affairs, c/o Bayer Schering Pharma AG, D-13342 Berlin, Geb. S101, 09, 226, Germany
Phone: +49-30-46815057, Mobile: +49-151-16715428, Fax: +49-30-46895057, E-mail: Farid.Saad@bayerhealthcare.com
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values owing to inherent properties of the biological action of testosterone in an individual person. Blood testosterone thresholds for androgen deficiency symptoms are highly consistent within a person but do differ, to a degree, between men [30]. The factors which define this symptomatic threshold are as yet unknown but, as indicated above, it is reasonable to assume that genetic polymorphisms of the androgen receptors influencing androgen sensitivity play a significant role [31, 32].

The metabolic syndrome and its components have been consistently associated with the presence of “low grade” systemic inflammation [33]. Inflammation is recognized as one of the central features of atherosclerosis [34]. The acute phase reactant C-reactive protein (CRP) is a sensitive marker of systemic inflammation [33]. Elevated concentrations of CRP, although they can still be in the normal range, are not only independent predictors of future cardiovascular disease in adults and older individuals but have been also associated with different features of metabolic syndrome [34]. The aging process in itself has also been associated with a progressive and significant increase in CRP plasma levels [35].

This is a study of mostly elderly hypogonadal men with symptoms of the metabolic syndrome. The men were treated with parenteral testosterone undecanoate (1000 mg) administered at 0 and 6 weeks and thereafter at intervals of 12 weeks [36]. In earlier studies, we have reported beneficial effects of administration of testosterone on a set of features of the metabolic syndrome: body weight, body mass index (BMI), waist circumference, serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides [23]. In the present study, we refined these research questions as follows: (i) how are the above effects of testosterone in the study population related to baseline testosterone values. As argued above, it is difficult to define a threshold value for androgen deficiency. (ii) Further, to the age of the recipient of testosterone administration. The metabolic syndrome is a multifactorial condition, and aging itself is a factor in its emergence [37]. Therefore, we tested whether age of the subject receiving testosterone treatment had an impact on the improvements of features of the metabolic syndrome following testosterone administration. (iii) Next, we tested whether indicators of obesity, such as BMI and waist circumference at baseline, and (iv) the degree of increase of serum testosterone after testosterone administration were relevant. (v) Finally, we tested whether baseline levels of CRP had a predictive effect of the outcome of testosterone administration.

Materials and methods

The study comprised a cohort of 123 men aged between 35 and 70 years (mean \pm SD = 60 ± 6.7), with plasma testosterone levels between 5.8 and 12.1 nmol/L (mean \pm SD = 9.3 ± 1.7) ($n > 14.0$ nmol/L). Because 13 men also had Crohn’s disease, a chronic inflammatory disease of the intestine of unknown etiology, these men were excluded from the present analysis, resulting in a study population of 110 (89.4%) hypogonadal men. These men had sought urological consultation for several reasons: erectile dysfunction,

questions about their testosterone status or a variety of urological complaints. Upon clinical and laboratory investigation they were found to have subnormal plasma total testosterone levels. They received treatment with parenteral testosterone undecanoate whereupon the plasma testosterone returned to the physiological range.

They were followed-up for 24 months at intervals of 3 months. At each visit blood was sampled; after an overnight fast blood was collected between 08:00 and 11:00 h. Plasma testosterone, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were measured using standardized routine laboratory methods. The waist circumference was measured midway between the upper hip bone and the uppermost border of the right iliac crest. Waist circumference measurements were always done by the same expert nurse. Weight and height were measured, and BMI was calculated by dividing the weight (kg) by the square of height (meters).

Ethical guidelines as formulated by the German “Ärzttekammer” (the German Medical Association) for observational studies in patients receiving standard treatment were followed. After receiving an explanation regarding the nature and the purpose of the study, all subjects consented to be included in the research of their treatment protocol.

Statistical analysis

Because of positively skewed data, CRP levels were logarithmically transformed before analyses, and back-transformed means [95% confidence intervals (CIs) of the mean in parentheses] are presented. For other variables percentages or means [\pm standard deviation (SD)] were given. CRP levels at baseline were available for 107 (97%) of 110 men (but after 2 years of testosterone administration only 57 men were available). Using z-scores for baseline testosterone, change in testosterone over 2 years, baseline age, baseline BMI, baseline waist and baseline CRP, we examined the relationship between baseline characteristics and changes over time in the different metabolic parameters.

The z-scores, derived by dividing the difference between the raw score and the mean by the SD ($z\text{-score} = [x - \text{mean}] / \text{SD}$), were used because of their ease of interpretation as the effect sizes in Table 1 can be compared to one another (as they are unit free). If effect sizes in Table 1 are above 0 then a higher value of the predictor variable is associated with a relative increase in the metabolic variable compared to men with lower values of the predictor variable. In opposition, if it is below 0 then there is a relative decrease in the metabolic variable over 2 years in men with high values compared to low values of the predictor variable. The effects of an increase of one standard deviation (1 SD) in predictor variables was explored by analyzing the interaction terms for time-by-predictor in the multilevel regression analysis (i.e., mixed models), using a compound symmetry covariance model. The course of changes over the study period of 2 years was compared between subjects. Measurements in each subject were performed up to 9 times, and therefore a two-level structure consisted of the observations (i.e., lower level) and the subject (i.e., higher level). To facilitate presentation of data, categorization of predictor variables into quintiles were used only in the figure. For other analyses continuous variables were used which maximizes the statistical power.

For the multivariable analysis, a metabolic syndrome composite score was calculated as the mean of z-scores of body waist, body mass index, total cholesterol, LDL cholesterol, HDL cholesterol (inverted), triglycerides, glucose, and CRP (partially based on the components of the metabolic syndrome as defined by the National Cholesterol Education Program) [38]. The effects of increases of a 1 SD increase in predictor variables were explored by analyzing

Table 1 Potential predictors of changes over 2 years in features of the metabolic syndrome during testosterone supplementation.

	Predictor variables					
	Baseline testosterone	Change in testosterone	Baseline age	Baseline BMI	Baseline waist	Baseline CRP
Body weight, kg	0.004 (SE: 0.008) (p=0.62)	0.007 (SE: 0.008) (p=0.392)	-0.003 (SE: 0.008) (p=0.661)	-0.081 (SE: 0.007) (p<0.001)	-0.047 (SE: 0.008) (p<0.001)	-0.001 (SE: 0.008) (p=0.888)
Body waist, cm	0.025 (SE: 0.007) (p=0.001)	-0.005 (SE: 0.007) (p=0.522)	-0.016 (SE: 0.007) (p=0.028)	-0.060 (SE: 0.007) (p<0.001)	-0.069 (SE: 0.007) (p<0.001)	0.000 (SE: 0.007) (p=0.992)
Body mass index, kg/m ²	0.008 (SE: 0.008) (p=0.298)	-0.002 (SE: 0.008) (p=0.818)	-0.015 (SE: 0.008) (p=0.051)	-0.085 (SE: 0.007) (p<0.001)	-0.047 (SE: 0.008) (p<0.001)	0.001 (SE: 0.008) (p=0.915)
Total cholesterol, mg/dL	0.059 (SE: 0.038) (p=0.119)	0.013 (SE: 0.038) (p=0.745)	-0.131 (SE: 0.037) (p<0.001)	-0.136 (SE: 0.037) (p<0.001)	-0.119 (SE: 0.037) (p=0.001)	-0.071 (SE: 0.038) (p=0.061)
LDL cholesterol, mg/dL	0.020 (SE: 0.016) (p=0.219)	-0.062 (SE: 0.016) (p<0.001)	-0.093 (SE: 0.016) (p<0.001)	-0.068 (SE: 0.016) (p<0.001)	-0.026 (SE: 0.016) (p=0.109)	0.014 (SE: 0.016) (p=0.382)
HDL cholesterol, mg/dL	0.023 (SE: 0.016) (p=0.164)	-0.005 (SE: 0.017) (p=0.757)	-0.041 (SE: 0.016) (p=0.010)	-0.027 (SE: 0.016) (p=0.079)	0.016 (SE: 0.016) (p=0.327)	-0.004 (SE: 0.016) (p=0.791)
Triglycerides, mg/dL	0.079 (SE: 0.026) (p=0.002)	-0.087 (SE: 0.026) (p=0.001)	-0.163 (SE: 0.025) (p<0.001)	-0.197 (SE: 0.025) (p<0.001)	-0.131 (SE: 0.025) (p<0.001)	-0.095 (SE: 0.026) (p<0.001)
Glucose, mg/dL	0.051 (SE: 0.035) (p=0.147)	-0.080 (SE: 0.035) (p=0.024)	-0.152 (SE: 0.034) (p<0.001)	-0.112 (SE: 0.035) (p=0.001)	-0.170 (SE: 0.034) (p<0.001)	-0.101 (SE: 0.035) (p=0.004)
C-reactive protein, mg/dL	0.008 (SE: 0.016) (p=0.621)	-0.011 (SE: 0.016) (p=0.499)	0.020 (SE: 0.016) (p=0.208)	0.044 (SE: 0.015) (p=0.004)	0.012 (SE: 0.016) (p=0.443)	-0.072 (SE: 0.015) (p<0.001)

SE indicates standard error of the mean; CI indicates confidence interval. C-reactive protein values were naturally log-transformed to normalize the distribution. Data are β -coefficients by multilevel regression analyses (i.e., linear mixed models) of the time \times predictor interaction term, which can be interpreted as the relative change in SD of the feature of the metabolic syndrome per year [with standard errors (SEs) and p-values in parentheses] according to 1 SD increase in the predictor variable. Conversion factors: for total cholesterol, LDL cholesterol and HDL cholesterol: mg/dL \times 0.0259 = mmol/L; for triglycerides: mg/dL \times 0.0114 = mmol/L.

interaction terms for all time-by-predictor variables in the multilevel regression analysis. Results are considered statistically significant if $p < 0.05$ (two-sided). The software used was SPSS for windows version 17.0 (SPSS, Chicago, IL, USA).

Results

Table 2 shows the baseline characteristics of the 110 men participating in this study. Men had a mean age of 60 years (SD 7). The mean BMI was 34.7 kg/m² (SD 4.6), with 73 men (67.0%) being obese with a BMI of 30–40 kg/m², and 19 men (17.4%) having extreme obesity with a BMI ≥ 40 kg/m². Plasma testosterone increased from 9.3 ± 1.7 nmol/L to 14.9 ± 4.5 nmol/L ($p < 0.01$) at 3 months, then stabilized at 19.2 ± 4.6 nmol/L after the first 6 months ($p < 0.05$) over the remaining period of the study.

Figure 1 shows the changes over 2 years in the metabolic syndrome composite score (means with error bars representing standard error of the mean) during testosterone supplementation according to quartiles of the independent baseline predictors of age, body mass index and CRP.

Table 1 shows the associations between potential predictors of changes over 2 years in features of the metabolic syndrome during testosterone supplementation. Baseline testosterone was positively predictive of changes in body waist and triglycerides. These associations indicate that lower testosterone levels were associated with stronger decreases in body waist and triglycerides, thus the beneficial effects of testosterone were most evident in men with the lowest baseline total testosterone levels compared to men with low normal testosterone levels. The change in testosterone levels over 2 years was inversely associated with changes in LDL cholesterol, triglycerides and glucose. This indicates that a strong increase in testosterone after supplementation resulted in the strongest declines in these metabolic factors.

Next, we focused on the predictive value of baseline age, BMI, waist circumference and CRP. Baseline age was inversely associated with changes in waist circumference, glucose and all lipids (including a small effect on HDL cholesterol). This indicates that older age was associated with stronger beneficial metabolic effects, notwithstanding a small less beneficial effect on HDL cholesterol than in younger men. Baseline BMI and waist showed largely consistent

Table 2 Baseline characteristics and endocrine, metabolic and Aging Male Symptoms (AMS) changes over 2 years for 110 hypogonadal men.

	Baseline		2 years		p-Value
	Mean or percentage	Range	Mean or percentage	Range	
Age	60.3 ± 6.9	35–70	–	–	
Current smoker	79%	–	–	–	
Current alcohol user	80%	–	–	–	
Total testosterone level, nmol/L	9.3 ± 1.7	5.8–12.1	18.3 ± 2.6	14.2–23.4	<0.001
Body height, cm	175.8 ± 4.4	168–192	–	–	
Body weight, kg	107.3 ± 14.5	72–139	98.2 ± 12.8	77–131	<0.001
Body mass index, kg/m ²	34.7 ± 4.6	24–47	31.8 ± 4.1	22–42	<0.001
Body waist, cm	108.4 ± 9.7	86–129	102.3 ± 8.9	84–125	<0.001
Total cholesterol, mg/dL	292.6 ± 38.3	209–389	204.7 ± 106.8	135–1293	<0.001
LDL cholesterol, mg/dL	148.8 ± 43.2	63–216	113.9 ± 37.6	36–183	<0.001
HDL cholesterol, mg/dL	58.5 ± 28.8	22–154	72.9 ± 27.4	28–179	<0.001
Triglycerides, mg/dL	285.7 ± 53.3	201–439	194.5 ± 26.3	149–328	<0.001
Glucose, mg/dL	103.3 ± 18.9	69–165	95.6 ± 12.7	60–132	<0.001
C-reactive protein, mg/dL	3.5 (0.8–19.1)	0.7–23.8	1.4 (0.2–9.4)	0.2–20.4	<0.001
Aging Male Symptoms (AMS) score	63.5 ± 7.5	46–95	18.1 ± 1.4	17–25	<0.001

Data are mean ± standard deviation, geometric mean [5% and 95% percentiles; (P₅–P₉₅)] for C-reactive protein, and percentages for dichotomous variables. The p-value is by multilevel regression analysis (i.e., mixed models) for the effects of time over 2 years. Conversion factors: for total cholesterol, LDL cholesterol and HDL cholesterol: mg/dL × 0.0259 = mmol/L; for triglycerides: mg/dL × 0.0114 = mmol/L.

results. As expected, obese men and men with the largest waist circumference showed the strongest declines over 2 years in weight, waist and BMI. Moreover, both BMI and waist circumference predicted for stronger declines in total cholesterol, triglycerides and glucose, with large effect sizes. In addition, baseline BMI predicted for a stronger decline in LDL cholesterol, but a smaller decline in CRP levels. Finally, higher baseline CRP predicted for declines in levels of triglycerides, glucose and CRP.

Table 3 shows the results from the multivariable model with a metabolic syndrome composite score as the dependent variable. These results indicate that baseline age, BMI and CRP independently predicted the strongest beneficial effects on metabolic derangements in hypogonadal men (all p-values <0.05). The effect sizes for baseline age, BMI and CRP were largely comparable, indicating that all three predictor variables contributed to a similar extent. Baseline waist was not statistically significantly associated with stronger beneficial metabolic effects, but the direction and size of the effect size were only slightly smaller than that of baseline BMI (p=0.11).

Discussion

This study answered several questions regarding testosterone supplementation in hypogonadal men. First, it was found that testosterone administration to elderly hypogonadal men had beneficial effects on several components of the metabolic syndrome. Second, a combination of age, BMI and CRP levels can be used as independent predictors of the strongest beneficial effects on metabolic derangement.

The first question was whether age was a determinant of the beneficial effects. This appeared to be the case; the high-

er the age the larger the benefits of testosterone administration. Other studies have shown that the beneficial effects of testosterone in older men are similar to those in younger men: for instance, on muscle, bone, fat, libido and mood [39]. Also, other studies have demonstrated that the benefits of testosterone administration on gains of fat-free mass and muscle strength in elderly men are as large as in younger men [40]. The improvements in physical performance, grip strength and lean body mass were of the same magnitude in older men as in younger men [27]. Testosterone administration prevented gain in visceral adipose tissue and loss of skeletal muscle equally well in younger and older people [26]. Thus, there is now a body of information supporting the administration of testosterone to hypogonadal men regardless of age.

The following question was whether the baseline testosterone value predicted the outcome of the intervention with testosterone. The higher the baseline testosterone, the less benefit of testosterone treatment on body waist and triglycerides. Thus, on the contrary, the lower the baseline testosterone, the greater the improvements of these two metabolic factors. Inclusion into the study was determined by testosterone levels lower than the reference range. In one study [41], it was shown that the lower the pretreatment serum testosterone concentration, the greater the effect of testosterone treatment on lumbar spine bone mineral density. Bone mineral density was not measured in our study. But in a later study [42] of the effect of testosterone administration on serum lipids and apolipoproteins, no such effect was reported. Changes in body composition did not correlate with baseline total testosterone levels in other studies [27].

On the basis of recent insights into the biological action of testosterone, there could be limitations to measured serum levels of testosterone as a reliable indicator of androgen defi-

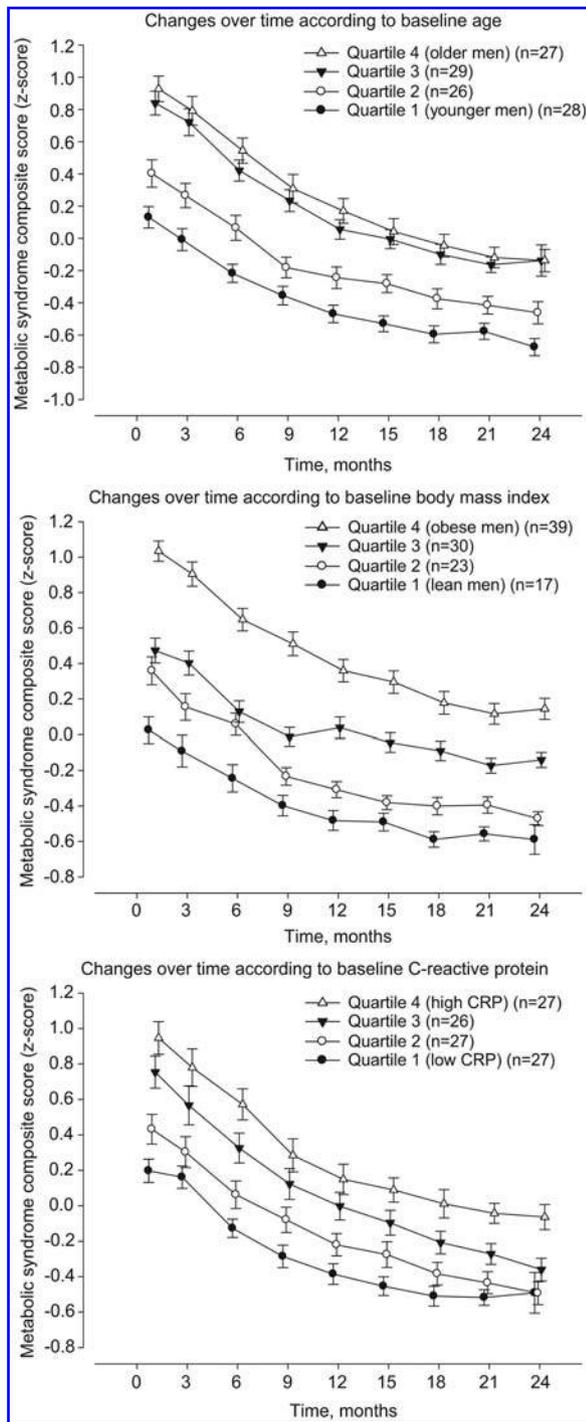


Figure 1 Changes over 2 years in the metabolic syndrome composite score (means with error bars representing standard error of the mean) during testosterone supplementation according to quartiles of the independent baseline predictors of age, body mass index and CRP.

ciency. Blood testosterone thresholds for androgen deficiency symptoms are highly consistent within a person but differ between men [30]. The factors which define this symptomatic threshold are as yet unknown but, as indicated above, it is reasonable to assume that genetic polymorphisms of the

androgen receptor influencing androgen sensitivity play a significant role [31, 43].

BMI was significantly associated with the benefit of testosterone treatment on all variables measured except on CRP. This is encouraging for patients with a high degree of obesity and subnormal testosterone levels, who are likely to benefit from treatment with testosterone. Waist circumference also showed these associations, but BMI appeared to be a slightly stronger predictor than baseline waist circumference. There is, so far, no confirmation of this finding in the literature.

We found that baseline BMI predicted for a stronger decline in LDL cholesterol, but a smaller decline in CRP levels. Higher baseline CRP predicted for declines in levels of triglycerides, glucose and CRP. Elevated concentrations of CRP, although they could still be in the normal range, are not only independent predictors of future cardiovascular disease in adults and older individuals, but have also been associated with different features of the metabolic syndrome [34]. A reduction in CRP levels could indicate a lower degree of systemic inflammation and represent an improvement in the risk profile of cardiovascular disease.

A third question we attempted to answer was whether the increment of plasma testosterone above baseline values following administration of testosterone was a determinant of the observed beneficial effects. Incremental increase of testosterone over the study period of 24 months was significantly associated with the benefit of testosterone treatment on HDL cholesterol, triglycerides and glucose. The lower the incremental increase of testosterone, the more benefit of testosterone treatment on these metabolic factors. It should be noted, however, that the increase of testosterone was no longer a significant predictor in the multivariable model, indicating that the effects of age, BMI and CRP largely explained the changes in variables of the metabolic syndrome over time. Nevertheless, this was not found in a study [42] testing the effects of testosterone administration on serum lipids and apolipoproteins. But in another study [27], changes in lean body mass correlated significantly with changes from baseline in total testosterone levels. It is of note that the treatment modality provided (parenteral testosterone undecanoate) produced a significant increase from baseline testosterone values (baseline 9.3 ± 1.7 nmol/L to 17.0 ± 2.2 nmol/L at 6 months and 19.4 ± 2.2 nmol/L at 12 months of testosterone administration). Thus, the increments in plasma testosterone were of a magnitude that restored plasma testosterone to the mid-normal range, supposedly sufficient to restore androgen-dependent functions in these men. This might be relevant. In an earlier study, the effects of administration of testosterone gel and parenteral testosterone undecanoate were compared. Serum testosterone increased significantly more with parenteral testosterone undecanoate than with testosterone gel and the effects on the International Index of Erectile Function and on waist circumference and on plasma lipids were significantly more favorable with testosterone undecanoate than with testosterone gel [44]. This observation was recently confirmed in a study using a range of testosterone preparations concluding that testosterone preparations achieving medium-high levels of serum testosterone are more efficacious [45].

Table 3 Independent predictors of changes over 2 years in the metabolic syndrome composite score during testosterone supplementation.

	β -Coefficient	SE	95% CI	p-Value
Baseline testosterone	0.006	0.014	-0.022; 0.034	0.67
Change in testosterone	0.001	0.014	-0.025; 0.028	0.91
Baseline age	-0.032	0.013	-0.057; -0.007	0.01
Baseline BMI	-0.035	0.016	-0.068; -0.003	0.03
Baseline waist	-0.025	0.016	-0.056; 0.006	0.11
Baseline CRP	-0.027	0.012	-0.050; -0.005	0.02

SE indicates standard error of the mean; CI indicates confidence interval. C-reactive protein (CRP) values were naturally log-transformed to normalize the distribution. Data are β -coefficients by multilevel regression analyses (i.e., linear mixed models) of the time \times predictor interaction term, which can be interpreted as the relative change in SD of the metabolic syndrome composite score per year [with standard errors (SEs) and p-values in parentheses] according to 1 SD increase in the predictor variable.

In summary, this study found that age, BMI and CRP levels, in addition to hypogonadism, can be used clinically to predict which men benefit the most from testosterone supplementation with regard to components of the metabolic syndrome. Moreover, features of the metabolic syndrome present in elderly men need not be a limiting factor in allowing elderly men benefit from the improvements that normalization of testosterone levels can achieve in men with evidence of hypogonadal testosterone values. Yet, future studies in hypogonadal men above the age of 70 years are needed, with particular focus on cardiovascular side effects.

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