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# Beneficial effects of 2 years of administration of parenteral testosterone undecanoate on the metabolic syndrome and on non-alcoholic liver steatosis and C-reactive protein

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## Abstract

**Background**: Elderly men often show a concurrence of a decline of testosterone with attributes of the metabolic syndrome. This study tested the effects of normalization of testosterone.

**Materials and methods**: A total of 122 hypogonadal men (18–83 years, mean 59.6±8.0 years; n=11<45 years, n=25<55 years, n=53<65 years) were included in the study. Their baseline testosterone levels were between 0.14 and 4.51 ng/mL (n>4.90 ng/mL) and were treated with parenteral testosterone undecanoate for 2 years as the sole intervention (administration at 0 and 6 weeks, and thereafter every 12 weeks).

**Results**: Plasma testosterone increased from 3.3±1.9 ng/mL to 4.1±1.5 ng/mL ($p<0.01$) at 3 months, and then stabilized at 6.8±1.3 ng/mL after the first 6 months. There was a remarkable progressive linear decline in body weight, body mass index, and waist circumference over the entire study period. Plasma cholesterol decreased significantly over the first 12 months, and then stabilized. Plasma glucose, triglycerides, low-density lipoprotein cholesterol, and C-reactive protein decreased significantly and high-density lipoprotein cholesterol increased significantly over the 24-month study period in a non-linear manner. There was a significant decrease in aspartate aminotransferase and alanine aminotransferase levels over the first 9 and 12 months, and then values leveled off. Changes in variables were largely correlated with changes in testosterone levels. At baseline, 47 out of 122 subjects fulfilled the metabolic syndrome criteria as defined by the National Cholesterol Education Program (2001); after 2 years of testosterone treatment, this number had declined to 11 out of 122 subjects.

**Conclusion**: With testosterone treatment over 2 years, the most significant improvement of the metabolic syndrome was noted over the first 12 months, but over the following 12 months further improvement was also observed. With regard to safety of testosterone administration to mainly elderly men, a number of safety measures were carried out.

**Keywords:** aging; liver steatosis; metabolic syndrome; testosterone.

## Introduction

It is now well established that 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). Four studies have found that a low testosterone level is a predictor of mortality in elderly men (4–7), but another study did not confirm this (8). While disagreeing regarding the relationship between plasma testosterone and overall mortality, the latter study demonstrated that a low testosterone level was predictive of mortality from ischemic heart disease and respiratory disease and that research into this relationship may be warranted. It would seem that a low testosterone level is a marker, an indicator of disease, and it is plausible that disease predicts mortality. Obviously, epidemiological studies cannot unravel cause relationships, but the evidence is convincing that the decline in testosterone levels with aging is accounted for rather by (age-related) disease than the calendar age of men. Intervention studies provide potential answers to the causality of the relationship.

Numerous studies have found associations between attributes of the metabolic syndrome and plasma testosterone (9–14). Thus, while it is clear that disease, and in the context of this contribution, in particular the metabolic syndrome suppresses circulating testosterone levels, it has also been documented that low testosterone levels induce the metabolic syndrome (15, 16), dramatically demonstrated by findings in men with prostate cancer who undergo androgen ablation therapy (17, 18). A recent study convincingly showed that

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**Table 1** NCEP-ATPIII[a] criteria for clinical metabolic syndrome (having at least three of the criteria listed below).

| Risk factor | Male | Female |
|---|---|---|
| Waist circumference | >102 cm (>40 in) | >88 cm (>35 in) |
| Triglycerides | ≥150 mg/dL | |
| HDL-cholesterol | <40 mg/dL | <50 mg/dL |
| Blood pressure | ≥130/≥85 mm Hg | |
| Fasting glucose | ≥110 mg/dL | |

[a]The National Cholesterol Education Program (NCEP) Expert Panel (2001). Detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). NIH publication #01-3670, p. 26.

acute androgen deprivation reduces insulin sensitivity in young men (19).

Liver fat is highly significantly and linearly correlated with all components of the metabolic syndrome (20,21). And the question has been asked whether non-alcoholic fatty liver disease should be included in the definition of the metabolic syndrome (21,22). Hepatic steatosis or non-alcoholic fatty liver disease has been the focus of much attention as an important factor in the pathogenesis of insulin resistance and the metabolic syndrome (21,23). Peptides and cytokines secreted by adipocytes in the visceral compartment may cause a decrease in peripheral insulin mediated glucose uptake and may increase hepatic fat accumulation. Elevations of liver enzymes are associated with higher C-reactive protein (CRP) concentrations. Hepatic inflammation secondary to liver steatosis is a potential contributor to the low-grade inflammation associated with the metabolic syndrome (24).

Thus, it is now clear that low levels of testosterone are a factor in the etiology of common ailments of elderly men, such as the metabolic syndrome and its associated diseases, such as diabetes mellitus and atherosclerotic disease. The question arises then whether testosterone treatment has a role to play in the treatment of the metabolic syndrome and its associated diseases, such as diabetes mellitus type 2 and cardiovascular disease. There is increasing evidence of a beneficial effect of testosterone treatment on visceral fat and other elements of the metabolic syndrome (25–28). This study investigated the effects of normalization of circulating testosterone levels in men with subnormal testosterone levels receiving treatment with parenteral testosterone undecanoate over 2 years. In general, this is a longer period of time than that reported in the majority of studies.

## Subjects and methods

A cohort of 122 mainly elderly men, aged between 18 and 83 years (mean ± SD = 59.6 ± 8.0), were studied. Their age distribution was as follows: n = 11 < 45 years, n = 25 < 55 years, and n = 53 < 65 years. All subjects were recruited from the same clinic. The subjects had sought urological consultation for a number of reasons: erectile dysfunction, questions about their testosterone status, or a variety of urological complaints. Upon clinical and laboratory investigation, the subjects were found to have subnormal plasma total testosterone levels (0.14–4.51 ng/mL; mean ± SD = 3.3 ± 1.9). The subjects received treatment with parenteral testosterone undecanoate 1000 mg (administration at 0 and 6 weeks and thereafter every 12 weeks) at which point the plasma testosterone levels returned to the physiological range.

All subjects were followed-up for 24 months at intervals of 3 months. At each visit, after an overnight fast, blood was collected between 08:00 and 11:00 h. Plasma testosterone, cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), triglycerides, CRP, and liver functions (aspartate aminotransferase (AST)/alanine aminotransferase (ALT)) were measured using standardized routine laboratory methods. Body weight, body mass index (BMI), and waist circumference were also measured. 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 recorded and BMI was calculated by dividing weight (kg) by the square of height (m).

According to the definition of the metabolic syndrome of the National Cholesterol Education Program (NCEP) (29) (Table 1), the number of male subjects who fulfilled the criteria of the metabolic syndrome at the beginning of the study and at 3 month intervals was determined. The number of male subjects who were still enduring the metabolic syndrome under testosterone treatment was also determined.

With regard to safety of testosterone administration to mainly elderly men, the following safety measures were carried out: before inclusion in the study, all male subjects had a digital rectal examination of the prostate, an ultrasound of the prostate, and a PSA measurement, and hemoglobin and hematocrit values were also measured. These measurements were repeated at 3 month intervals.

All patients gave their informed consent to be included in the study. The study was approved by the hospital's Ethical Review Board for investigation in human subjects.

Statistical analysis was performed using STATA (STATA Corp., College Station, TX, USA). The significance level of the relationship between testosterone and metabolic or liver function parameters over the study period were determined by the linear mixed model (30). Correlation among metabolic and liver function parameters were determined using the Spearman rank correlation (31).

## Results

Plasma testosterone levels significantly increased ($p < 0.01$) from $3.3 \pm 1.9$ ng/mL to $4.1 \pm 1.5$ ng/mL at 3 months and $4.6 \pm 1.1$ ng/mL at 6 months, and stabilized over the remaining period of the study. Weight, waist circumference, and BMI of the subjects started to decrease linearly and significantly 6 months after initiation of testosterone administration treatment. The decreases in weight, BMI, and waist circumference showed significant progression until the end of the study period of 24 months (Table 2 and Figure 1).

All metabolic and liver function variables changed significantly over the study period of 24 months (Figures 2 and 3; Table 2). Plasma cholesterol levels decreased significantly over the first 12 months, and then levels became stable over the remaining 12 months of the study (Figure 2). Plasma triglyceride and LDL levels significantly decreased and HDL levels significantly increased over the 24 month study period in a non-linear manner. Such changes could not be tracked as a result of significant changes over the 3-month intervals of variables measurements in this study (Table 2). This applied also to changes in CRP (Table 2 and Figure 3). The changes in liver function indicated by AST and ALT are shown in Table 2 and Figure 3. There was a significant decrease in AST and ALT levels over the first 9 and 12 months, and then values leveled off over the remaining study period (Table 2 and Figure 3).

Plasma testosterone levels were significantly and inversely associated with the levels of cholesterol, triglycerides, AST, ALT, and CRP (Table 2).

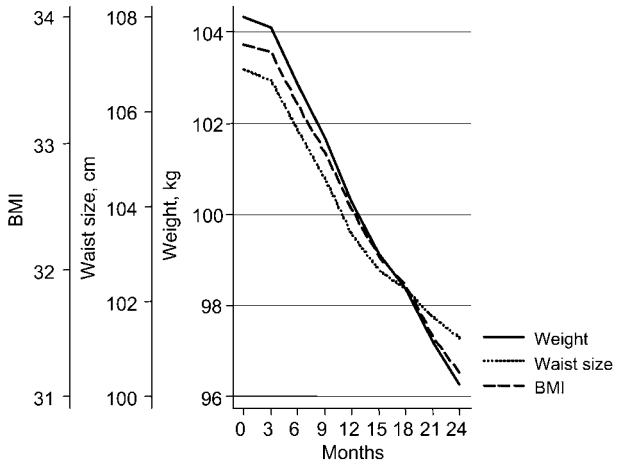


**Figure 1** Average weight (kg), waist size (cm), and BMI over the study period.

Table 3 shows the correlations among all measured variables over the 24-month study period. Almost all correlations were significant. There was a low level of significant correlations between weight, waist circumference, and BMI and the liver function variables. Liver function parameters had high levels of correlations between each variable. Weight, waist circumference, and BMI were highly correlated with each other. Testosterone level was moderately correlated with levels of cholesterol.

At baseline, 47 out of 122 male subjects fulfilled the clinical metabolic syndrome criteria according to the NCEP (29)

**Table 2** Significance level of changing parameters over testosterone level and time determined by linear mixed modeling.

| | Testosterone | BMI | Weight | Waist size | Glucose | Cholesterol |
|---|---|---|---|---|---|---|
| Testosterone | N/A | 0.339 | 0.444 | 0.152 | 0.726 | 0.000 |
| Time | 0.000 | 0.000 | 0.000 | 0.000 | 0.003 | 0.000 |
| 0–3 months | 0.000 | 0.852 | 0.722 | 0.000 | 0.730 | 0.001 |
| 3–6 months | 0.000 | 0.000 | 0.000 | 0.000 | 0.126 | 0.000 |
| 6–9 months | 0.069 | 0.000 | 0.000 | 0.000 | 0.214 | 0.000 |
| 9–12 months | 0.229 | 0.000 | 0.000 | 0.000 | 0.966 | 0.004 |
| 12–15 months | 0.644 | 0.000 | 0.000 | 0.000 | 0.891 | 0.433 |
| 15–18 months | 0.453 | 0.000 | 0.000 | 0.000 | 0.164 | 0.672 |
| 18–21 months | 0.082 | 0.000 | 0.000 | 0.000 | 0.898 | 0.919 |
| 21–24 months | 0.274 | 0.000 | 0.000 | 0.000 | 0.730 | 0.365 |
| 0–24 months | 0.000 | 0.000 | 0.000 | 0.000 | 0.004 | 0.000 |
| | HDL | LDL | Triglycerides | AST | ALT | C-reactive protein |
| Testosterone | 0.125 | 0.150 | 0.000 | 0.001 | 0.001 | 0.000 |
| Time | 0.000 | 0.001 | 0.000 | 0.000 | 0.000 | 0.000 |
| 0–3 months | 0.573 | 0.569 | 0.415 | 0.004 | 0.173 | 0.198 |
| 3–6 months | 0.465 | 0.566 | 0.063 | 0.002 | 0.000 | 0.294 |
| 6–9 months | 0.004 | 0.032 | 0.087 | 0.002 | 0.008 | 0.575 |
| 9–12 months | 0.982 | 0.410 | 0.594 | 0.027 | 0.325 | 0.267 |
| 12–15 months | 0.247 | 0.863 | 0.491 | 0.450 | 0.482 | 0.434 |
| 15–18 months | 0.340 | 0.813 | 0.891 | 0.087 | 0.004 | 0.676 |
| 18–21 months | 0.169 | 0.876 | 0.672 | 0.208 | 0.099 | 0.308 |
| 21–24 months | 0.306 | 0.593 | 0.189 | 0.224 | 0.286 | 0.610 |
| 0–24 months | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

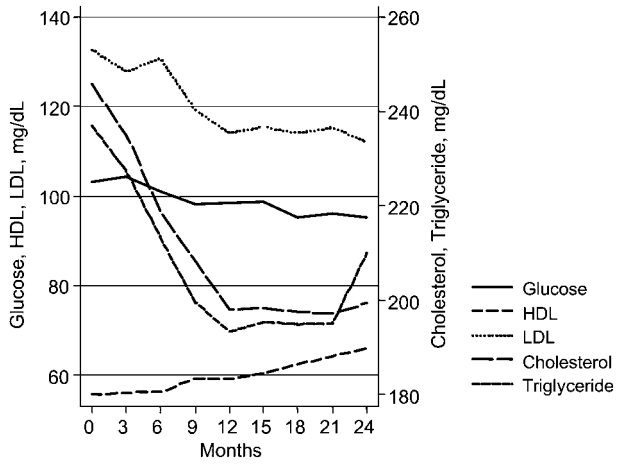


**Figure 2** Average value of blood glucose and mean cholesterol, LDL, HDL, and triglycerides over the study period.

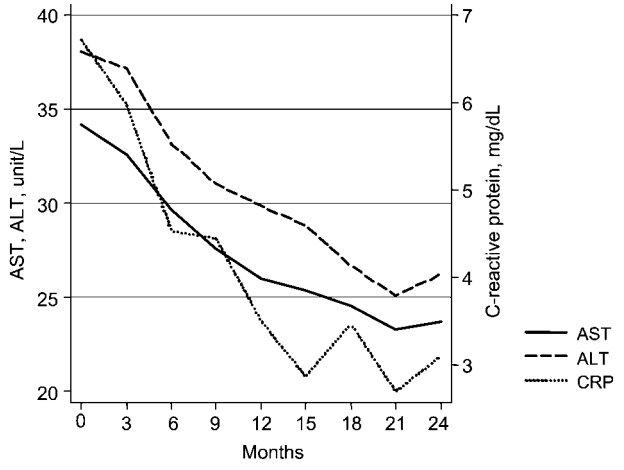


**Figure 3** Average value of AST, ALT, and C-reactive protein over the study period.

(Table 1). This number declined to 17 out of 122 male subjects after 1 year of testosterone treatment (Tables 4 and 5) and declined further to 11 out of 122 male subjects after 2 years of treatment (Tables 4 and 5).

With regard to safety, prostate specific antigen (PSA) levels increased initially but returned to baseline values at the end of the 2 years. At the beginning of the study, PSA levels were $1.53 \pm 1.91$ ng/mL, and at the end of the 24 months PSA levels were $1.59 \pm 1.1$ ng/mL (n.s.). Prostate volume did not change significantly over the study period (from $27.98 \pm 12.90$ mL to $29.66 \pm 12.59$ mL). The International Prostate Symptom Score (IPSS) and residual bladder volume decreased significantly over the 24 month study period (from $6.95 \pm 4.05$ to $3.57 \pm 2.24$ and from $42.58 \pm 20.12$ mL to $25.76 \pm 9.33$ mL, respectively). There were five measurements of elevated levels of hemoglobin and hematocrit, which returned to reference values without special measures, such as dose reduction of testosterone.

## Discussion

The present study consists of a cohort of 122 mainly elderly men, aged between 18 and 83 years (mean $\pm$ SD $= 59.6 \pm$ 8.0 years), with plasma testosterone levels below the lower limit of reference values. The subjects were treated with administration of parenteral testosterone undecanoate for 2 years as the sole intervention. There was a remarkable linear improvement in body weight, BMI, and waist circumference size over the 24 month study period, along with a (non-linear) improvement of lipid profiles particularly evident over the first 9–12 months of the study. The latter also applied to fasting glucose levels. Liver fat is highly significantly and linearly correlated with all components of the metabolic syndrome (20). Hepatic inflammation secondary to liver steatosis is a potential contributor to the low-grade inflammation associated with the metabolic syndrome (24). Elevations of liver enzymes are associated with higher CRP concentrations. Levels of ALT, AST, and CRP had decreased significantly after 2 years of testosterone treatment. Overall, there was a high degree of correlations between changes in variables and plasma testosterone levels. Thus, it seems relevant that testosterone treatment results in plasma testosterone levels that reach mid-normal levels of reference values (32), which was the case in this study.

At baseline, 47 out of 122 male subjects fulfilled the metabolic syndrome criteria as defined by the NCEP (29), and after 1 year of testosterone treatment this number had declined to 17 out of 122 male subjects, with a further decline to 11 out of 122 male subjects after 24 months.

Our results offer a timetable of beneficial effects of testosterone administration on indices of the metabolic syndrome. Most beneficial effects are apparent after the first year of treatment but continue upon further treatment at least for 1 year, be it at a slower pace.

With regard to the potential mechanisms of the favorable effects of testosterone in the metabolic syndrome, testosterone inhibits the expression of lipoprotein lipase activity, the main enzymatic regulator of triglyceride uptake in the fat cell, preferentially in abdominal fat. Indeed, several studies have confirmed that testosterone treatment reduces waist circumference which, in its simplicity, appears to be a valid parameter of the degree of visceral obesity (33,34). A study of testosterone administration restoring testosterone levels to mid-normal values with a duration of 8–9 months revealed a decrease in the visceral fat mass, a decrease in fasting glucose and lipid levels, and an improvement in insulin sensitivity; in addition, a decrease in diastolic blood pressure was observed (35). In a study by Page et al., testosterone administration improved body composition (reduction in trunk fat, increase in lean body mass, improvement of plasma triglycerides, total cholesterol and LDL, no impairment of HDL (36)). Also, in our own earlier studies, signs and symptoms of the metabolic syndrome improved substantially following administration of long-acting testosterone undecanoate (32,37–39). While part of these effects of testoster-

**Table 3** Spearman rank correlation among variables in the study over a 24-month period.

| | Testosterone | BMI | Weight | Waist size | Glucose | Cholesterol |
|---|---|---|---|---|---|---|
| Testosterone | 1 | | | | | |
| BMI | –0.0951* | 1 | | | | |
| Weight | –0.1305* | 0.9517* | 1 | | | |
| Waist size | –0.1218* | 0.7933* | 0.8189* | 1 | | |
| Glucose | –0.1257* | 0.2256* | 0.2033* | 0.2346* | 1 | |
| Cholesterol | –0.5553* | 0.3985* | 0.3909* | 0.4082* | 0.3021* | 1 |
| HDL | 0.1478* | 0.3947* | 0.3546* | 0.3509* | 0.2418* | 0.2040* |
| LDL | –0.2481* | 0.3744* | 0.3301* | 0.3532* | 0.3242* | 0.6089* |
| Triglycerides | –0.4783* | 0.4824* | 0.4784* | 0.4470* | 0.2452* | 0.7981* |
| AST | –0.4852* | 0.0589* | 0.0684* | 0.1188* | 0.1980* | 0.4961* |
| ALT | –0.4363* | 0.0604* | 0.0716* | 0.1383* | 0.1660* | 0.3688* |
| C-reactive protein | –0.2981* | 0.0066 | 0.0251 | 0.0245 | 0.2901* | 0.3229* |
| | HDL | LDL | Triglyceride | AST | ALT | C-reactive protein |
| HDL | 1 | | | | | |
| LDL | 0.5899* | 1 | | | | |
| Triglycerides | 0.2805* | 0.5912* | 1 | | | |
| AST | 0.0611* | 0.3974* | 0.4361* | 1 | | |
| ALT | –0.0372* | 0.2256* | 0.2838* | 0.8014* | 1 | |
| C-reactive protein | 0.1770* | 0.3705* | 0.2704* | 0.6623* | 0.5883* | 1 |

*Significant correlation ($p < 0.05$).

**Table 4** Number of patients with metabolic syndrome classified by NCEP-ATPIII.

| Time | n | Metabolic syndrome | % |
|---|---|---|---|
| Begin | 122 | 47 | 38.52 |
| 3 months | 122 | 35 | 28.69 |
| 6 months | 122 | 24 | 19.67 |
| 9 months | 122 | 20 | 16.39 |
| 12 months | 122 | 17 | 13.93 |
| 15 months | 122 | 16 | 13.11 |
| 18 months | 122 | 9 | 7.38 |
| 21 months | 122 | 8 | 6.56 |
| 24 months | 122 | 11 | 9.02 |

one may be indirect (via an improvement of body composition: less adipose tissue, more lean body mass), there is also evidence that testosterone directly improves insulin sensitivity (19, 40).

A recent study of testosterone administration to elderly men revealed favorable effects on body composition but not on glucose and lipid metabolism (41), which is at variance with our findings. The testosterone preparation used in the study of Svartberg et al. (41) was identical with the one used in our study: parenteral testosterone undecanoate, but resulting plasma levels of testosterone are probably higher in our study ($15.3 \pm 4.5$ vs. $19.4 \pm 2.2$ nmol/L in our study). In a recent study, we could show that effects of testosterone administration on variables of the metabolic syndrome are more pronounced with higher plasma testosterone levels (32).

There are a number of methodological limitations to this study. The study design was not blinded and was not placebo-controlled. But the numbers of male subjects included in the study are high and results consistently point in the same direction. While the results of this study are encouraging, better designed studies are needed to investigate the effects of an intervention with testosterone in elderly men with proven subnormal plasma testosterone levels.

In summary, in a large cohort of elderly men with hypogonadal values of plasma testosterone, normalization of

**Table 5** Number of patients and metabolic syndrome risk factors identified by NCEP-ATPIII.

| Time | 0 | 1 | 2 | 3 | 4 | Total |
|---|---|---|---|---|---|---|
| Begin | 0 | 20 | 55 | 46 | 1 | 122 |
| 3 months | 0 | 28 | 60 | 35 | 0 | 122 |
| 6 months | 1 | 31 | 67 | 24 | 0 | 122 |
| 9 months | 1 | 45 | 57 | 20 | 0 | 122 |
| 12 months | 0 | 56 | 50 | 17 | 0 | 122 |
| 15 months | 0 | 58 | 49 | 16 | 0 | 122 |
| 18 months | 0 | 57 | 57 | 9 | 0 | 122 |
| 21 months | 5 | 53 | 57 | 8 | 0 | 122 |
| 24 months | 2 | 59 | 51 | 11 | 0 | 122 |

plasma testosterone with administration of testosterone undecanoate improved attributes of the metabolic syndrome, most evident over the first year of testosterone administration but progressing after the first 12 months. Together with the increasing evidence of a role of testosterone in body composition and the metabolic syndrome, further studies are needed to substantiate this beneficial effect of testosterone. It is likely that changes of lifestyle and diet would have additional beneficial effects on the actions of testosterone. The potential mood-elevating effects of normalization of testosterone levels might boost motivation and stamina of men undergoing such treatment.

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