# Improvement of the Metabolic Syndrome and of Non-alcoholic Liver Steatosis upon Treatment of Hypogonadal Elderly Men with Parenteral Testosterone Undecanoate

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Key words
- testosterone
- metabolic syndrome
- liver steatosis
- aging

## Abstract

This is a study of a cohort of 117 men aged between 34–69 years, with plasma testosterone levels between 5.9–12.1 nmol/L (N > 14.0 nmol/L) who were treated with administration of testosterone undecanoate for 1 year as the sole intervention. There was a remarkable improvement of body weight, BMI and waist size along with an improvement of lipid profiles. Liver fat is highly significantly and linearly correlated with all components of the metabolic syndrome. Hepatic inflammation secondary to liver steatosis is a potential contributor to the low-grade inflammation associated with the metabolic syndrome. Elevations of liver enzymes are associated with higher CRP concentrations. Levels of ALT (GPT) AST (GOT) and CRP had decreased significantly after one year of testosterone treatment. At baseline 74/117 met the criteria of the metabolic syndrome as defined by the NCEP and after one year of testosterone treatment this number had declined to 42/117.

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## Introduction

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 (age 20–30 years) men [2–4]. Four studies have found that a low testosterone level is a predictor of mortality in elderly men [5–8], but another study did not confirm this [9]. While disagreeing on the relationship 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 features of the metabolic syndrome and plasma testosterone [10–15]. So, while it is clear that disease, and in the context of this contribution, in particular the metabolic syndrome suppress circulating testosterone levels, it has also been documented that low testosterone induces the metabolic syndrome [16, 17], dramatically demonstrated by findings in men with prostate cancer who undergo androgen ablation therapy [18, 19]. A recent study showed convincingly that acute androgen deprivation reduces insulin sensitivity in young men [20].

Liver fat is highly significantly and linearly correlated with all components of the metabolic syndrome [21]. And the question has been asked whether nonalcoholic fatty liver disease should be included in the definition of metabolic syndrome [22], Hepatic steatosis or non-alcoholic fatty liver disease has gained attention as an important factor in the pathogenesis of insulin resistance and the metabolic syndrome [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 CRP concentrations. Hepatic inflammation secondary to liver steatosis is a potential contributor to the low-grade inflammation associated with the metabolic syndrome [24].

So, it is clear now 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 sequels such as diabetes mellitus type2 and cardiovascular disease. There is increasingly evidence of a beneficial effect of testosterone treatment on visceral fat and other elements of the metabolic syndrome [25–27]. This study investigated the effects of normalization of circulating testosterone levels in men with subnormal testosterone levels receiving treatment with parenteral testosterone undecanoate.

## Subjects and Methods

A cohort of 117 men aged between 34–69 years (mean ± SD = 59.5 ± 6.0), with plasma testosterone levels between 5.9–12.1 nmol/L (mean ± SD = 9.4 ± 1.7) were studied. They 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 they were found to have subnormal plasma total testosterone levels (5.9–12.1 nmol/L; N > 14). They received treatment with parenteral testosterone undecanoate (administration at 0 and 6 weeks and thereafter every 12 weeks) whereupon the plasma testosterone returned to the physiological range.

They were followed up for 12 months at every interval of 3 months. At each visit blood was sampled, after an overnight fast blood was collected between 8–11 a.m. Plasma testosterone, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, C-reactive protein (CRP) and liver functions (AST/ALT) were measured using standardized routine laboratory methods. Body weight, the BMI and waist circumference. 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 the weight(kg) by the square of height (meters).

Applying the definition of the metabolic syndrome of the National Cholesterol Education Program [1] (**Table 2**), it was determined how many men of this cohort met the criteria of the metabolic syndrome and how many men were still suffering from the metabolic syndrome after 12 months of testosterone treatment.

All patients gave their informed consent to be included in this study which was approved by the hospital's ethical review board for investigation in human subjects.

Statistical analysis was performed using STATA (Stata corp, College station, Texas, USA). The significance of the changes in variables of metabolism and liver function over the study period was determined by using linear mixed model (West et al, 2007). The significance of the effects of testosterone on metabolic and liver function parameters was also determined by linear mixed model (West et al., 2007). Correlation among metabolic and liver function parameters were determined using Spearman rank correlation (Dawson et al., 2004).

## Results

Following the administration of parenteral testosterone there was a significant increase in circulating levels of testosterone. Plasma testosterone rose from 9.3 ± 1.7 nmol/L to 14.0 ± 1.5 (P < 0.01)at 3 months, to 17.0 ± 2.2 P < 0.05) at 6 months whereafter levels stabilized: (18.7 ± 2.1 after 9 months and 19.4 ± 2.2 nmol/L after 12 months). All metabolic and liver function variables changed significantly over the study period of 12 months. Weight and BMI of the subject decreased significantly already over the first 3 months, while waist size began to decrease significantly after 6 months of the study. The decreases in weight, BMI and waist size were significant until the end of the study period of 12 months. (**Fig. 1**).

With regard to metabolic variables, plasma cholesterol and triglycerides significantly decreased over the full study period of 12 months. (**Fig. 2**). Plasma HDL did not increase significantly over the first 6 months, but increased significantly over the period from 6 to 12 months. By contrast, plasma LDL decreased significantly over the first six months and leveled off between

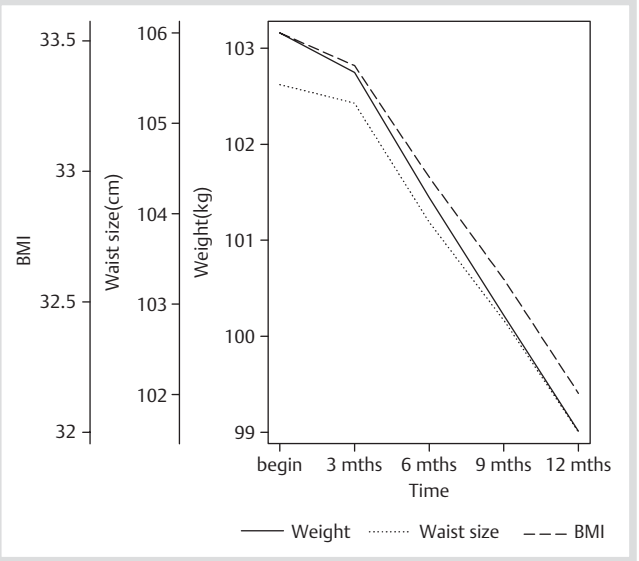


**Fig. 1** Mean weight (kg), Waist size (cm) and BMI over the study period.

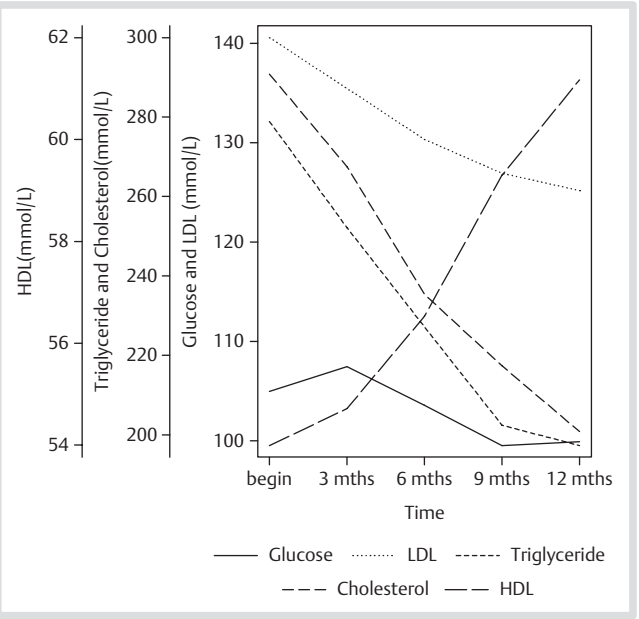


**Fig. 2** Median value of blood glucose and mean cholesterol, LDL, HDL, and triglyceride over the study period.

six and 12 months. The plasma level of glucose remained constant over the 12 month study period.

The changes in liver function indicated by AST, ALT and CRP are shown in **Fig. 3**. Plasma levels of AST and ALT decreased significantly from the beginning of the study till 9 months, then leveled off. Plasma CRP increased significantly during the first 3 months, then decreased significantly over the following 6 months and then leveled off.

Plasma testosterone levels were significantly associated with the levels of all metabolic variables except glucose. There was neither a significant association with any liver function parameter (AST, ALT and CRP) nor weight, waist size and BMI.

**Table 1** shows the correlation among all variables over the 12 months study period. Weight, waist size and BMI were not significantly correlated with any liver function parameters. Liver function parameters had high levels of correlation between them ($r^2 > 0.7$). Weight, waist size and BMI were also highly correlated with each other ($r^2 > 0.8$).

At baseline 74/117 men met the criteria of the metabolic syndrome as defined by the NCEP [1] and after one year of testosterone treatment this number had declined to 42/117 (**Table 2**).

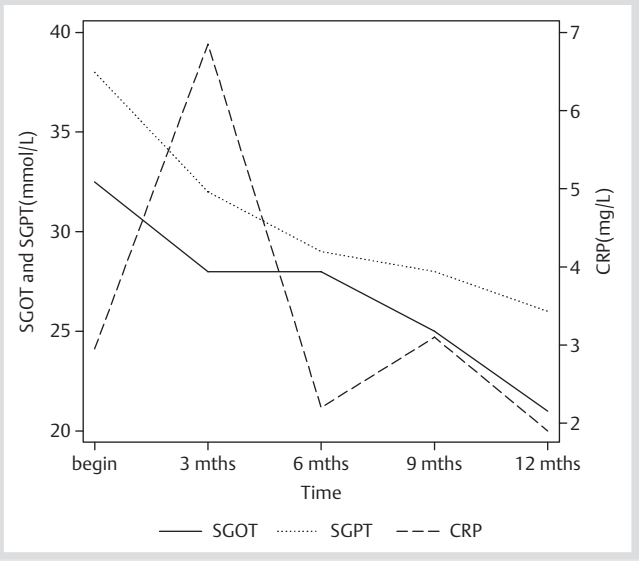


**Fig. 3** Median value of SGOT, SGPT and C-reactive protein over the study period.

## Discussion

This is a study of a cohort of 117 men aged between 34–69 years, with plasma testosterone levels between 5.9–12.1 nmol/L (N > 14.0 nmol/L) who were treated with administration of testosterone undecanoate for 1 year as the sole intervention. There was a remarkable improvement of body weight, BMI and waist size along with an improvement of lipid profiles. Liver fat is highly significantly and linearly correlated with all components of the metabolic syndrome [21]. 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 one year of testosterone treatment.

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Testosterone inhibits the expression of the activity of lipoprotein lipase, the main enzymatic regulator of triglyceride uptake in the fat cell, preferentially in abdominal fat. Several studies have indeed confirmed that testosterone treatment reduces waist circumference which, in its simplicity, appears to be a valid parameter of the degree of visceral obesity [28, 29]. A study of testosterone administration restoring testosterone levels to mid-normal values with a duration of 8–9 months found a decrease of the visceral fat mass, a decrease of fasting glucose and lipid levels and an improvement of insulin sensitivity; in addition, a decrease in diastolic blood pressure was observed [30]. In a study by Page et al testoster-

**Table 2** After 1 year of treatment with testosterone undecanoate the number of men with metabolic syndrome had decreased from 74/117 to 42/117.

| | NCEP# |
|---|---|
| | At least 2 of |
| waist circumference (cm) | >102 |
| waist hip ratio | |
| BMI | |
| triglycerides (mg/dL) | ≥150 |
| HDL-cholesterol | <40 |
| blood pressure (nmmHg) | ≥130/85 or medication |
| fasting glucose (mg/dL) | ≥110 |
| fasting insulin | |

# National Cholestorol Education Program, JAMA 2001; 285; 2486–2497

**Table 1** Correlation (Spearman) among variables in the study over 12 months period.

| | Cholesterol | HDL | LDL | Triglyceride | weight | BMI | Waist size | SGOT | SGPT | CRP | glucose |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cholesterol | 1.0000 | | | | | | | | | | |
| HDL | 0.2563* | 1.0000 | | | | | | | | | |
| LDL | 0.5054* | 0.7454* | 1.0000 | | | | | | | | |
| triglyceride | 0.8054* | 0.3699* | 0.5398* | 1.0000 | | | | | | | |
| weight | 0.4292* | 0.4559* | 0.3666* | 0.5608* | 1.0000 | | | | | | |
| BMI | 0.4175* | 0.4799* | 0.3800* | 0.5605* | 0.9642* | 1.0000 | | | | | |
| waist size | 0.4319* | 0.3614* | 0.3127* | 0.4860* | 0.8514* | 0.8081* | 1.0000 | | | | |
| SGOT | 0.2964* | 0.1091 | 0.2942* | 0.2762* | −0.0904 | −0.1036 | −0.0849 | 1.0000 | | | |
| SGPT | 0.2658* | 0.0876 | 0.2119* | 0.2213* | −0.0579 | −0.0540 | −0.0299 | 0.8837* | 1.0000 | | |
| CRP | 0.1555* | 0.1882* | 0.2766* | 0.1194 | −0.0998 | −0.1211 | −0.0861 | 0.7357* | 0.7169* | 1.0000 | |
| glucose | 0.3019* | 0.3614* | 0.3810* | 0.2534* | 0.2102* | 0.2345* | 0.2572* | 0.2087* | 0.1785* | 0.2756* | 1.0000 |

*Significant correlation ($p < 0.05$)

one 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 [31]. Also in our own earlier studies, signs and symptoms of the metabolic syndrome improved substantially following administration of long-acting testosterone undecanoate [32–35]. While part of these effects of testosterone 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 [20, 36].

A recent study of testosterone administration to elderly men found favorable effects on body composition but not on glucose and lipid metabolism [37] which is at variance with our findings. The testosterone preparation used in the study of Svartberg et al. was identical with the one used in our study: parenteral testosterone undecanaote but resulting plasma levels of testosterone have probably been higher in our study (15.3 ± 4.5 versus 19.4 ± 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 [35].

There are a number of methodological limitations to this study. The study design was not blinded and not placebo-controlled. But the results of this study are encouraging to investigate the effects of an intervention with testosterone to study its effects 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 plasma testosterone with administration of testosterone undecanoate improved features of the metabolic syndrome. 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.

**Conflicts of interest:** None.

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