



Review Article

Long-Term Testosterone Treatment Improves Fatty Liver and Kidney Function with Safe Outcomes on Cardio-, Metabolic and Prostate Health in Men with Hypogonadism. Prospective Controlled Studies

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Citation: Yassin A, Albaba B, Talib R, Aboumarzouk O, Alwani M, et al. (2022) Long-Term Testosterone Treatment Improves Fatty Liver and Kidney Function with Safe Outcomes on Cardio-, Metabolic and Prostate Health in Men with Hypogonadism. Prospective Controlled Studies. Curr Trends Intern Med 6: 163. DOI: 10.29011/2638-003X.100063

Received Date: 01 September, 2022; **Accepted Date:** 07 September, 2022; **Published Date:** 10 September, 2022

Abstract

Hypogonadism is receiving recognition for being a risk factor for fatty liver and impaired kidney function [1,2]. Emerging data, summarized here, suggest that long-term treatment with testosterone undecanoate injection may improve both liver and kidney function as well as metabolic deterioration with favorable safety profile on metabolism and prostate health [3,4].

Key Points

- Low testosterone is a risk factor for fatty liver and reduced kidney function (assessed with the glomerular filtration rate).
- Previous randomized controlled trials of testosterone therapy have shown conflicting results on fatty liver, and studies investigating the effects of testosterone therapy on kidney function are sparse.
- A real-life evidence study shows that treatment with testosterone undecanoate injection for up to 12 years reduces fatty liver index and improves glomerular filtration rate, suggesting improved liver and kidney function.
- Improvement in liver and kidney function with testosterone therapy was linked to a reduced risk of myocardial infarction, stroke and premature mortality.

What is known about testosterone, liver and kidney function

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of liver disease globally [5,6]. Global prevalence of NAFLD is 25% (95% CI: 22-29%) [5] with obesity, type 2 diabetes and metabolic syndrome being particularly strong risk factors for NAFLD development. In a meta-analysis of 24 studies involving 35,599 patients with type 2 diabetes, the pooled prevalence of NAFLD was 60% (range 30-87%) [7].

An analysis of NHANES III data of a nationally representative sample of U.S. adults (n=4,758) found an association between low testosterone levels and an increased risk of NAFLD in men, even after adjustment for obesity and other metabolic risk factors [8]. Another study of 495 men found that the association between low testosterone and NAFLD persisted even after controlling for visceral abdominal fat (measured by computed tomography) and insulin resistance [9]. The 2012 Practice Guideline on the Diagnosis and Management of Non-alcoholic Fatty Liver Disease by the American Gastroenterological Association and American College of Gastroenterology acknowledged that hypogonadism is a risk factor for NAFLD. All NAFLD histological stages are associated with significantly increased overall mortality, and this risk increases progressively with worsening NAFLD histology [10,11].

Age-associated loss of kidney function has been recognized for decades [12]. With aging, many people experience progressive decrease in glomerular filtration rate and kidney blood flow, with wide variability among individuals [12]. Overall, a decline in GFR of approximately 8 mL/min per 1.73 m² per decade, starting between the ages of 30 and 40 years can be considered an average kidney function decline [13]. Decreased kidney function, defined as eGFR less than 60 mL/min/1.73 m² and urine albumin-to-creatinine ratio 1.1 mg/mmol (10 mg/g) or more, is an independent predictor of mortality risk in the general population [14].

Population studies have found an association between lower testosterone levels and reduced kidney function among men in general population [2,15] as well as increased CKD stages, even in younger men and middle-aged men [16]. Importantly, the Diabetes Prevention Program (DPP) Outcomes Study found that in 889 men with overweight and glucose-intolerance who underwent a follow-up period of 11 years, low testosterone is a risk factor for abnormal kidney markers, even after adjustment for multiple other risk factors for kidney disease [2].

Despite evidence showing that low testosterone is a risk factor for both NAFLD and reduced kidney function, two medical conditions that are becoming more and more common due to the epidemic of obesity and type 2 diabetes, the effects of testosterone therapy in men with hypogonadism on liver and kidney function have not been adequately studied.

What this study adds

A real-world evidence study was conducted in 505 men (mean age: 61 ± 10 years) with testosterone levels ≤350 ng/dL (≤12.1 nmol/L) and symptoms of hypogonadism, of whom 321 men received treatment with testosterone undecanoate injection every 12 weeks (following an initial 6-week interval), for up to 12 years (3, 4). The remaining 184 men opted against testosterone therapy and served as the control group.

Testosterone therapy was temporarily discontinued for 17 months in 147 men in the testosterone group after 5.5 years, due to reimbursement issues, and re-started upon resolution of reimbursement issues.

Kidney function was assessed by measuring serum creatinine, urea, uric acid and glomerular filtration rate (GFR), while hepatic steatosis was assessed with the fatty liver index, a predictor of NAFLD, which is calculated by inputting values for waist size, BMI, triglyceride and gamma-glutamyl transferase [17]. The fatty liver index score ranges from zero to 100. Fatty liver index < 30 rules out fatty liver (negative likelihood) while a score of ≥ 60 indicates a high likelihood that fatty liver is present.

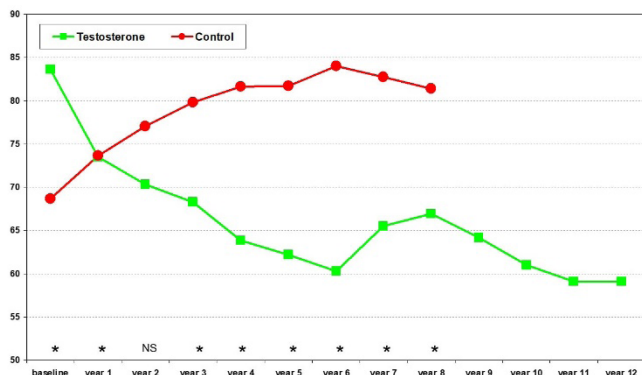
Results showed that men receiving testosterone therapy had a decrease in serum creatinine (1.14 to 1.07 mg/dL), uric acid (6.8 to 5.5 mg/dL), urea (47.5 to 31.7 mg/dL) and an increase in GFR (86.6 to 98.5 mL/min/1.73 m²) over the study period. The reduction in uric acid was mirrored for serum urea, which decreased from 48 to 32 mg/dL (serum urea data were only available for the testosterone group). In contrast, men not receiving testosterone therapy had an increase in serum creatinine (0.99 to 1.13 mg/dL) and a decrease in GFR (90.8 to 87.0 mL/min/1.73 m²). There was a slight reduction in uric acid (5.7 ± 1.5 to 5.2 ± 1.5 mg/dL).

Men in the testosterone group had decreased fatty liver index (84 to 59), gamma-glutamyl transferase (39 to 25 U/L), bilirubin (1.64 to 1.21 mg/dL) and triglycerides (252 to 175 mg/dL) over 12 years. In contrast, men not receiving testosterone therapy had an increase in fatty liver index (69 to 81), gamma-glutamyl transferase (38 to 40 U/L), bilirubin (1.04 to 1.12 mg/dL) and triglycerides (196 to 244 mg/dL). ALT levels declined slightly in both groups. Between group difference in AST was at year 1 (p<0.0001), year 2 (p<0.005) and year 4 (p<0.005), with the testosterone group having lower levels.

Waist size and BMI decreased in the testosterone group (107 to 94 cm and 31 to 28 kg/m²) and increased in the control group (100 to 105 cm and 29 to 31 kg/m²).

Mortality was 15% in the control group; all deaths were due to cardiovascular disease; myocardial infarction (13, 48%), stroke (7, 27%), heart failure (3, 11%), aortic aneurysm (2, 7%) and lung embolism (2, 7%). In contrast, mortality was only 8%

in the testosterone group, of which a lower proportion of deaths (44%) were due to cardiovascular disease; myocardial infarction (5, 20%), stroke (2, 8%), heart failure (2, 8%), aortic aneurysm (1, 4%) and lung embolism (1, 4%).



*p<0.0001 between groups. TTh; testosterone therapy

Figure 1: Fatty Liver Index (y-axis) in 321 men with hypogonadism receiving long-term treatment with testosterone undecanoate injection and 184 men with untreated hypogonadism.

From Yassin AA, Alwani M, Talib R, et al. Long-term testosterone therapy improves liver parameters and steatosis in hypogonadal men: a prospective controlled registry study. The aging male: the official journal of the International Society for the Study of the Aging Male. Dec 2020;23(5):1553-1563.

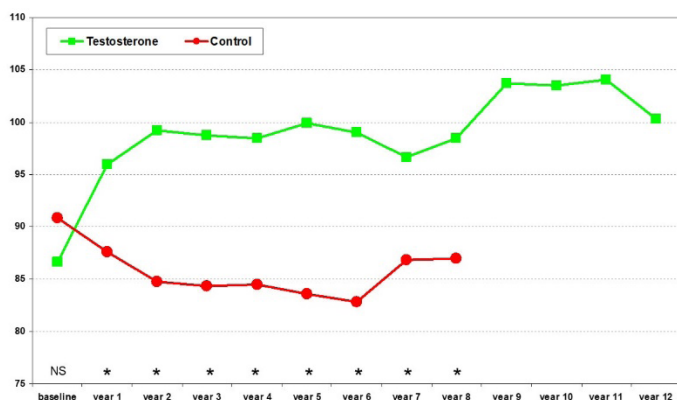


Figure 2: Glomerular filtration rate (GFR, mL/min/1.73m², y-axis) in 321 men with hypogonadism receiving long-term treatment with testosterone undecanoate injection (open square) and 184 men with untreated hypogonadism (black circle). *p<0.0001, NS=not significant.

From Yassin A, Almehmadi Y, Alwani M, Mahdi M, Jaber A, et al. Long-term Testosterone Therapy Improves Renal Function in Men with Hypogonadism: A Real-life Prospective Controlled Registry. J Clin Nephrol Res. 2020;7(1)

It was concluded that long-term testosterone therapy improves liver function, hepatic steatosis and kidney function in hypogonadal men, compared to men with hypogonadism not receiving testosterone therapy, in whom a worsening is observed in most parameters. It is likely that the improvements in liver and kidney function contributed to reduced cardiovascular mortality [3,4].

Commentary

This is the first study showing that long-term treatment with testosterone undecanoate injection in men with hypogonadism has beneficial effects of on hepatic steatosis, liver function and kidney function, and is associated with reduced mortality [34]. Importantly, men with hypogonadism who did not receive testosterone therapy had a significant increase in fatty liver index and worsening of GFR.

An important observation was the worsening in parameters of both fatty liver and kidney function in testosterone treated men who had an interruption in testosterone therapy due to reimbursement issues, which then resumed improving when testosterone therapy was re-started upon resolution of reimbursement issues. This confirms previous findings showing that continuous testosterone therapy is required for achievement and maintenance of health benefits of testosterone therapy, as benefits disappear after discontinuation of testosterone therapy [18-24]. As pointed out in the British Society for Sexual Medicine guidelines on Adult Testosterone Deficiency, cessation of testosterone therapy results in reappearance of symptoms and reversal of benefits within 6 months, hence, testosterone therapy is likely required lifelong for persistent symptom resolution and maintenance of health benefits [25].

Previous randomized controlled trials of testosterone therapy have shown conflicting results on fatty liver. This could be due to small study sample, short testosterone treatment duration, different liver fat measurements and of different testosterone preparations (long-acting testosterone undecanoate injection vs. short-acting testosterone injection vs. gels) [26-30].

Available randomized controlled trials which showed that testosterone therapy reduces fatty liver used testosterone undecanoate injection [26,27]. The study presented above was conducted in a larger number of men who received treatment with testosterone undecanoate injection for up to 12 years, which is the longest reported follow-up. The finding that treatment with testosterone undecanoate injection resulted in a significant reduction in fatty liver index from 84 to 59, while men with hypogonadism not receiving testosterone treatment had a worsening of fatty liver index from 69 to 81, and the large difference in mortality among groups, is notable and congruent with data from other studies. A large-scale population-based study including over 3 million people

who had undergone health screening with repeated assessment of fatty liver index four times between 2009 and 2013 found that changes over time in fatty liver index were significantly associated with risk of all-cause mortality (aHR, 1.86; 95% CI, 1.75-1.98; $P < 0.001$) and incidence of myocardial infarction (aHR, 1.3; 95% CI, 1.21-1.40; $P < 0.001$), and stroke (aHR, 1.27; 95% CI, 1.19-1.37; $P < 0.001$), even after adjustment for age, sex, smoking, alcohol consumption, income, hypertension, dyslipidemia, diabetes, BMI and physical activity [31].

In the study above, testosterone therapy did not appear to have a large effect on ALT levels [4]. Interestingly, previous studies have found that half of patients with type 2 diabetes and normal ALT levels have NAFLD [32]. This suggests that liver enzymes are not a reliable indicator of fatty liver status.

Type 2 diabetes is one of the top six underlying causes of NAFLD-related deaths [11]. This makes testosterone therapy a particularly promising treatment, as it can reduce both fatty liver 4 and prevent and possibly reverse type 2 diabetes [33-35].

For more information, see:

Testosterone therapy for prevention and reversal of type 2 diabetes in men enrolled in a lifestyle program

Remission of type 2 diabetes during long-term treatment with testosterone undecanoate injections

Testosterone therapy in men with hypogonadism prevents progression from prediabetes to type 2 diabetes

Most studies that have investigated hypogonadism and testosterone therapy in the context of kidney function focused on its association with morbidity and mortality in men with chronic kidney disease and end-stage kidney disease. The primary aim of these studies was to examine the effects of testosterone therapy in these patient populations on restoration of sexual function and improvements in metabolic parameters, lean muscle mass and mortality, and not parameters of kidney function [36,37]. Hence, the effect of testosterone therapy on kidney function is an understudied area. A large population study of US veterans, including 48,461 men, found that testosterone therapy resulted in a significant delay in progression of chronic kidney disease to end-stage kidney disease, and prolonged survival time, corresponding to 25% reduced risk of mortality [38].

The study presented above is the first long-term study investigating the effect of testosterone therapy on kidney function, evaluated by GFR. The rapid reduction in uric acid observed in men receiving treatment with testosterone undecanoate injection, accompanied with an increase in GFR, suggests a direct beneficial effect of testosterone therapy on kidney function.

The reduction in myocardial infarction, stroke and mortality in the testosterone group confirms findings from previous studies [34,35,39]

For more information, see:

“Survival and cardiovascular events in men treated with testosterone”

The significant reduction in fatty liver index and mortality seen in testosterone treated men compared to untreated men is a highly important finding, as there currently are no approved medications available for treatment of fatty liver disease.

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