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Research Article

Long-term Testosterone Therapy Improves Renal Function in Men with Hypogonadism: A Real-life Prospective Controlled Registry

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Keywords

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- Glomerular filtration rate

Abstract

Objective: Testosterone therapy (TTh) is the primary treatment for aging men with functional hypogonadism. However, the long-term effectiveness of TTh on renal function has not yet been fully investigated.

Material and Methods: In this observational, prospective, cumulative registry study, we assess the long-term effects of testosterone undecanoate (TU) administration on renal function parameters in 505 symptomatic hypogonadal men, with T levels ≤350 ng/dL. The treatment group (T-group) consisted of 321 men who received TU 1000mg/12 weeks following an initial 6-week interval for up to 12 years. The remaining 184 hypogonadal men, who opted against TTh, served as controls (C-group). We assessed renal function by measuring serum creatinine, urea, uric acid and glomerular filtration rate (GFR) according to Mayo Clinic guidelines, over 8 years.

Results: The T-group patients exhibited a decrease in serum creatinine (1.14±0.18 to 1.07±0.8 mg/dL), uric acid (6.8±1.5 to 5.5±1.6 mg/dL), urea (47.5±12.0 to 31.7±12.9 mg/dL) and an increase in GFR (86.6±12.8 to 98.5±8.6 mL/min/1.73m^2) over the study period. In contrast, the C-group patients had an increase in their serum creatinine (0.99±0.25 to 1.13±0.53 mg/dL), an increase in uric acid (5.7±1.5 to 5.2±1.5 mg/dL), and a decrease in GFR (90.8±20.2 to 87.0±26.0 mL/min/1.73m^2). There were 25 deaths (7.8%) in the T-group of which 11 (44%) were cardiovascular. In contrast, 28 patients (15.2%) died in C-group, and all deaths (100%) were attributed to cardiovascular causes.

Conclusion: The data suggest that long-term TTh improves the renal function in hypogonadal men, compared to slight worsening observed in patients without intervention. Improvements in renal function may have contributed to reduced CVD-related mortality.

ABBREVIATIONS

ALT (GOT): Alanine Transaminase; AST (GPT): Aspartate Transaminase; CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; ESRD: End-Stage Renal Disease; γ-GT: Gamma-Glutamyl Transferase; MetS: Metabolic Syndrome; QoL: Quality of Life; TT: Total Testosterone; TTh: Testosterone Therapy; TU; Testosterone Undecanoate

INTRODUCTION

In men, the age-related decline in Total Testosterone (TT) levels is a well-established phenomenon and is referred to as

functional hypogonadism when symptomatic [1-3]. The current estimates for prevalence of functional hypogonadism range between 12% for men aged 50 years, to 30% for 70-year-old men [4], and with increasing life expectancy, obesity and an aging population, the prevalence of functional hypogonadism is only going to increase [5].

The hypogonadal syndrome is characterised by symptoms such as impaired libido, infertility, fatigue, increased risk of depression and has a significant impact on quality of life (QoL) [6,7]. Furthermore, the decrease in TT levels associates with the components of metabolic syndrome (MetS) such as obesity, decrease in muscle mass, dyslipidemia, hypertension, insulin resistance and dysregulation of glucose metabolism [8-10], thereby increasing the risk of cardiovascular disease (CVD) [11]. Renal function also exhibits a marked sexual dimorphism with aging, as men experience a steady decline in Glomerular Filtration Rate (GFR) after 40-years of age, with a drop of 8ml/min/1.73m^2 every subsequent decade [12]. Interestingly, hypogonadism is overrepresented in patients with chronic kidney disease (CKD) [13], and low TT levels associate with CKD progression [14,15].

Testosterone therapy (TTh) is the primary treatment for alleviating the symptoms associated with functional hypogonadism. Indeed, several long-term studies have reported improved sexual function, body composition and reduced risk of CVD following TTh in hypogonadal men [16-20]. However, the long-term effects of TTh on renal function have not been studied to date.

Hypogonadism in men with CKD confers significant morbidity, including anemia and CVD [21]. The link between CKD and hypogonadism is likely multifactorial. Patients with LOH have comorbidities such as obesity, CVD and diabetes that can contribute to CKD, and in turn, CKD patients are likely to have dysregulation in the hypothalamic-pituitary-gonadal axis that can exacerbate hypogonadism [22-24]. To date, most studies that have investigated the effects of TTh in CKD patients have focussed on their sexual function, but not the direct effects TTh may have on the renal function of these patients. In this study, we present data on renal function of hypogonadal men, following 8-years of TTh.

MATERIALS AND METHODS

This was an observational, prospective, cumulative registry study in 505 men (mean age: 61.4 ± 9.7 years) with TT ≤350ng/dL (≤12.1nmol/L) and symptoms of functional hypogonadism. Approval from the ethics committee in line with guidelines formulated by the German Ärztekammer (German medical association) was obtained. Patients were enrolled after signing an informed written consent. In the treatment group (T-group), 321 men received 1000mg testosterone undecanoate (TU) parenterally every 12 weeks, following an initial 6-week interval, for up to 12 years. In 147 of these men, TTh had been temporarily discontinued after 5.5 years for 17 months (mean) as a result of reimbursement issues. The remaining 184 men who opted against TTh comprised the control group (C-group). There were 14 patients in the T-group with primary hypogonadism (Klinefelter's syndrome, testicular atrophy, orchiectomy following testicular cancer) but none in the control group as it was considered mandatory to treat such patients with testosterone. The remainder of the patients were considered as having "functional hypogonadism", also referred to as late onset hypogonadism. Functional hypogonadism is mainly caused by obesity and independent of age.

The effects of long-term TU on renal function was assessed by annually measuring serum creatinine, urea, uric acid and Glomerular Filtration Rate (GFR) as per the Mayo Clinic Test Guidelines. The effects of TTh on liver function were also evaluated by measuring serum Gamma-Glutamyl Transferase (γ-GT), bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT).

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) v.11 for Windows software package (SPSS Inc., Chicago, USA). Data are expressed as mean group values with standard deviations at each time point. Clinical parameters were compared between groups across the treatment periods using mixed-effects, repeated-measures model with period, group and their interaction as fixed effects. Analysis of variance (ANOVA) was used to compare continuous variables. A value of $p<0.05$ was considered significant.

RESULTS

Baseline characteristics of patients included in this registry and reported in this article are shown in Table 1 and demonstrated no significant differences between the groups, including glomerular filtration rate (GFR). The mean baseline age for T-group consisting of 321 patients was 59 ± 9.5 years, with a mean follow-up of 8.3 ± 3.5 years. In the C-group (184 patients), the mean age was 66.1 ± 7.6 years, and mean follow-up of 5.5 ± 1.6 years.

In hypogonadal men receiving TTh (T-group), an elevation in TT concentrations was observed at 1-year follow-up (7.74nmol/L to 16.11nmol/L, $p<0.0001$), which was sustained throughout

Table 1: Baseline characteristics of Testosterone treatment group (T-group) and control group (C-group). BMI, Body Mass Index; GFR, Glomerular Filtration Rate. *P<0.05, **P<0.0001.

Baseline Patient Characteristics		
	Testosterone Group	**Control Group**
N	321	184
Mean age (years)	59 ± 9.5	66.1 ± 7.6 **
Follow-up (years)	8.3 ± 3.5	5.5 ± 1.6
Testosterone (nmol/L)	7.7 ± 2.1	9.2 ± 2.4**
Waist circumference (cm)	107 ± 10	100 ± 9**
Weight (kg)	99 ± 13	91± 11**
BMI (kg/m^2)	31.5 ± 4.3	29.2 ± 3.2**
GFR (mL/min/1.73m^2)	86.6 ± 12.8	90.8 ± 20.2*
Baseline Comorbidities		
Type 2 diabetes:	94 (29.3%)	52 (28.3%)
HbA1c (in patients with Type 2 Diabetes)	7.9+/-1.0%	6.8+/-0.9%
Hypertension:	221 (68.8%)	131 (71.2%)
Hypothyreosis:	5 (1.6%)	3 (1.6%)
Hyperthyreosis	0 (0%)	1 (0.5%)

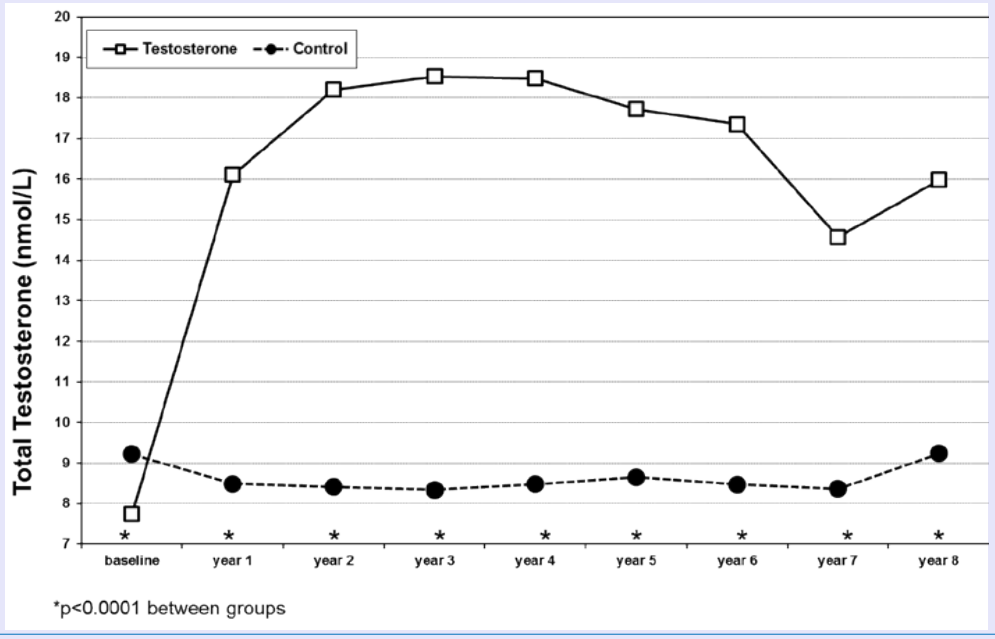

Figure 1 Total testosterone (nmol/L) in 321 hypogonadal men on long-term treatment with testosterone undecanoate (open square) and 184 untreated hypogonadal controls (black circle). *p<0.0001.

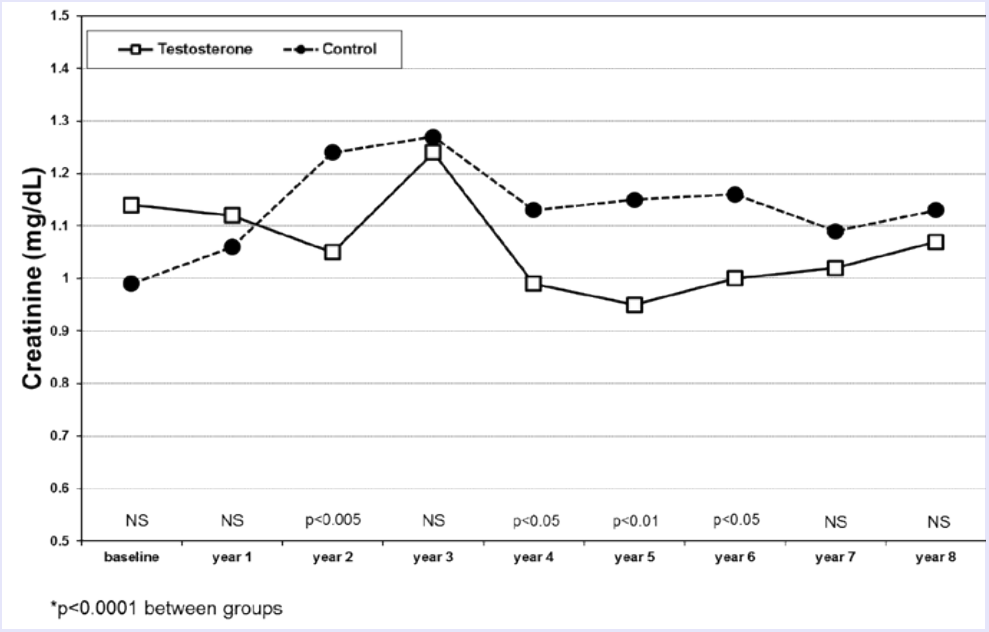

Figure 2 Serum creatinine (mg/dL) in 321 hypogonadal men on long-term treatment with testosterone undecanoate (open square) and 184 untreated hypogonadal controls (black circle). NS=not significant.

the 8-year study period (15.98nmol/L), compared to C-group patients (9.22nmol/L at baseline to 9.24nmol/L at 8-year) (Figure 1).

Serum creatinine levels in the T-group patients lowered from 1.14±0.18 at baseline to 1.07±0.8 mg/dL at 8-years, compared to the C-group which saw an increase from 0.99±0.25 to 1.13±0.53mg/dL; with years 2, 4, 5 and 6 having significantly lower serum creatinine concentrations in the T-group compared to C-group ($p<0.05$, Figure 2).

Whilst uric acid concentrations were lower at 8-years compared to the baseline, for both T-group (6.8±1.5 to 5.5±1.6mg/dL, $p<0.0001$) and C-group patients (5.7±1.5 to 5.2±1.5 mg/dL, $p<0.01$), the decrease was more pronounced for the T-group, especially in the first 5-years (6.8mg/dL to 4.68mg/dL; Figure 3). The lowering of uric acid concentrations in the T-group patients was mirrored for serum urea which decreased from 47.5±12.0 to 31.7±12.9mg/dL ($p<0.0001$, Figure 4). Serum urea data were only available for the T-group.

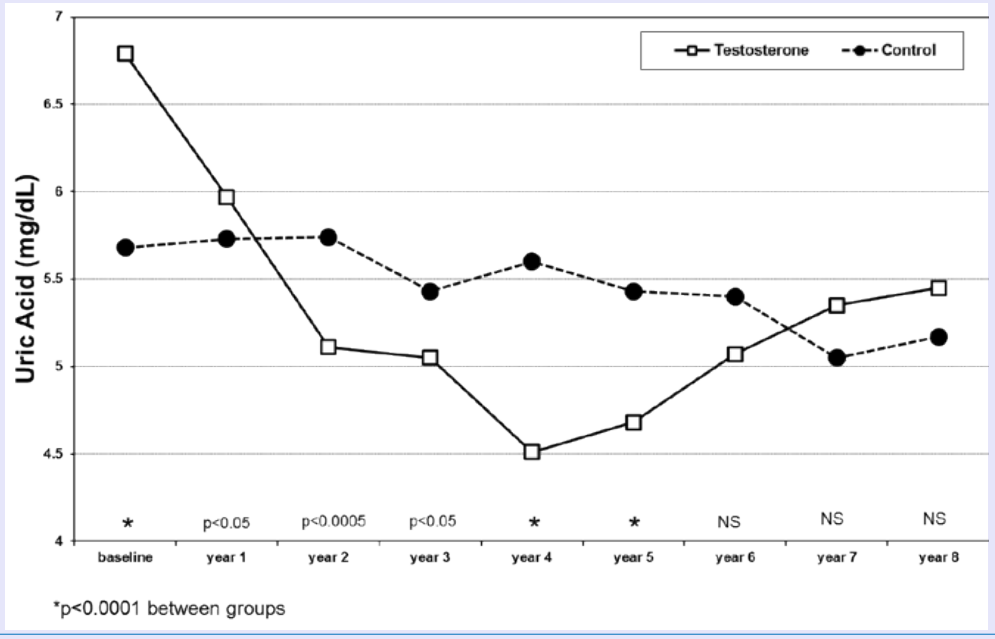

Figure 3 Uric acid (mg/dL) in 321 hypogonadal men on long-term treatment with testosterone undecanoate (open square) and 184 untreated hypogonadal controls (black circle). *p<0.0001, NS=not significant.

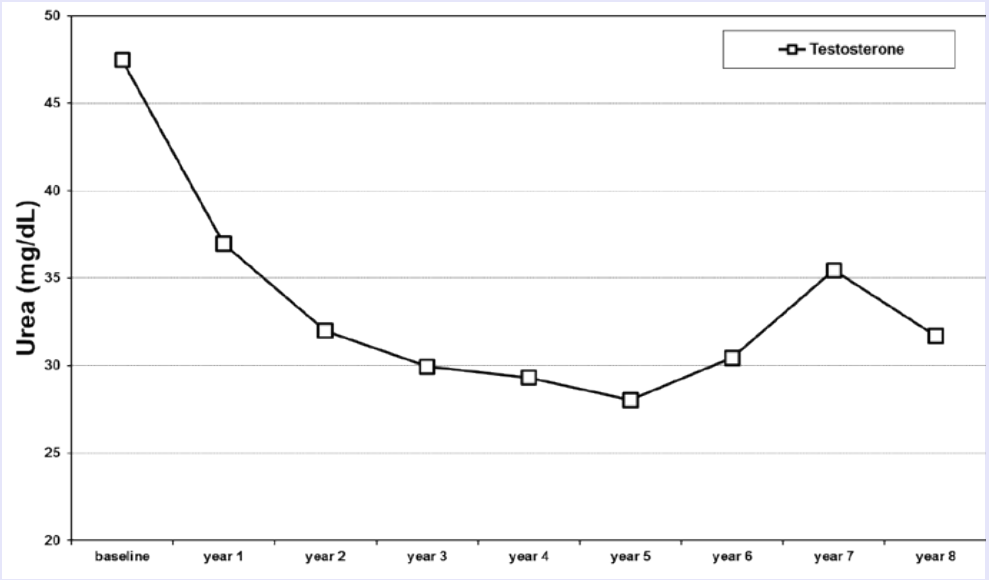

Figure 4 Serum urea (mg/dL) in 321 hypogonadal men on long-term treatment with testosterone undecanoate.

The C-group patients showed a steady decrease in GFR over the study period, from 90.8±20.2 at baseline to 87.0±26.0mL/min/1.73m^2 at 8-year follow-up (p<0.0001). In contrast, the patients in T-group showed an increase in GFR from baseline of 86.6±12.8 to 98.5±8.6 mL/min/1.73m^2 at 8-years (p<0.0001), with significantly higher GFR compared to C-group at all time-points (p<0.0001, Figure 5).

In T-group patients, the γ-GT decreased from 39.31±11.62 at baseline to 28.95±7.57U/L at 8-years (p<0.0001), whilst it increased from 37.79±29.55 to 39.5±26.71U/L in the C-group (p<0.0005; Figure 6A). A similar reduction in bilirubin levels was observed for T-group patients from 1.64±4.13 to 1.21±1.89 mg/dL (p<0.05), with C-group patients remaining unchanged (1.04±7.08 to 1.12±1.96 mg/dL; p>0.05, Figure 6B). Additionally, we observed that the AST levels remained stable for both groups, while ALT levels declined slightly for both patient-groups (Figure 6C-D).

Furthermore, in the C-group, there were 28 deaths (15.2%), all of which were attributed to CVD. In contrast, in the T-group, a significantly lower number of 25 deaths (7.8%, p=0.0351) occurred, of which a lower proportion that untreated men in the C-group were attributed to CVD with 11 (44%, p=0.001) reported (Table 2).

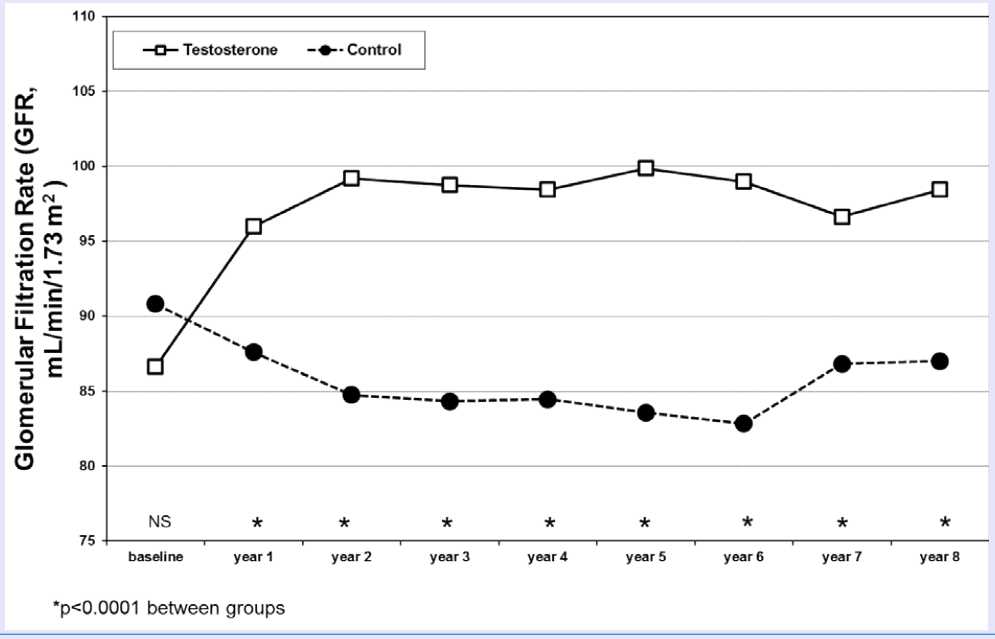

Figure 5 Glomerular filtration rate (GFR, mL/min/1.73m^2) in 321 hypogonadal men on long-term treatment with testosterone undecanoate (open square) and 184 untreated hypogonadal controls (black circle). *p<0.0001, NS=not significant.

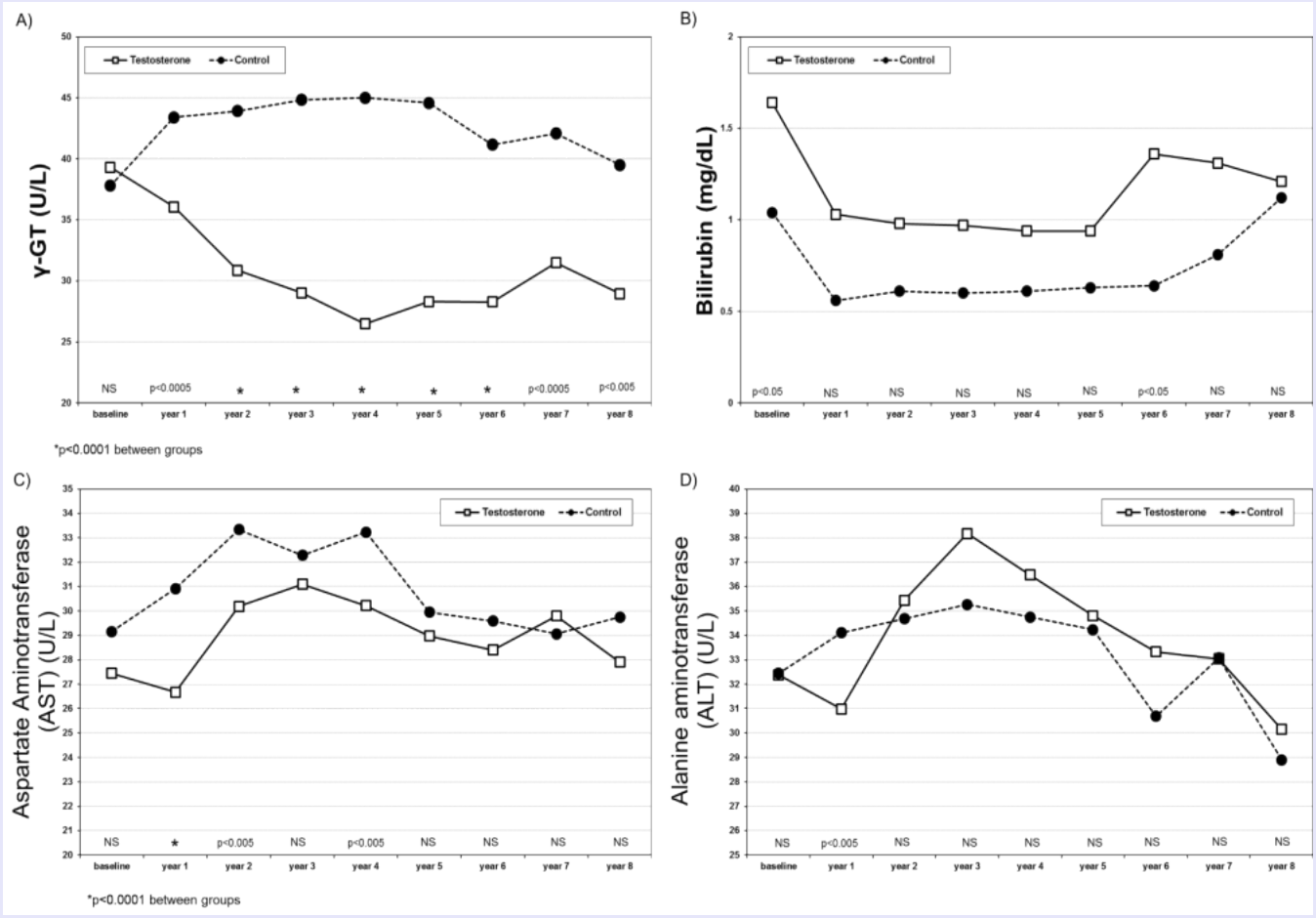

Figure 6 Liver function in 321 hypogonadal men on long-term treatment with testosterone undecanoate (open square) and 184 untreated hypogonadal controls (black circle) as measured by A) γ-GT, B) bilirubin, C) AST, and D) ALT. *p<0.0001, NS=not significant.

DISCUSSION

The lowering of testosterone levels in aging men, and the resultant hypogonadism associates with components of Metabolic Syndrome (MetS), and risk for cardiovascular disease (CVD) [9-11]. The risk of chronic kidney disease (CKD) and renal complications is also significantly higher in men and, at least in part, is independent of the well-documented strong causal link with CVD [25,26]. Whilst the beneficial effects of testosterone therapy (TTh) on components of MetS and CVD have been widely reported [27-29], studies on the effects of TTh on renal function in CKD are limited. In this observational, prospective, registry study we demonstrate beneficial effects of long-term TTh on markers of renal function: serum creatinine, uric acid, serum urea and glomerular filtration rate in hypogonadal men.

Majority of studies that have investigated hypogonadism in the context of renal function, focused on its association with morbidity and mortality in populations with CKD and End-Stage Renal Disease (ESRD). The primary focus of TTh in these patient populations has been restoration of sexual function and improvements in metabolic parameters such as insulin resistance, lean muscle mass and did not focus on parameters of renal function [30,31]. The effects of TTh on renal function have been largely unexplored. In a report by Tomaszewski et al. [32], an inverse relationship between serum testosterone concentrations and creatinine clearance as an indication of renal function has been described. The population investigated was healthy eugonadal young men (mean age 18.5 years) displaying total testosterone levels within the normal range and, while not comparable to our study population of older hypogonadal men, suggests that the beneficial effects of testosterone on renal function may exist independently of age and beyond the confines of hypogonadism. Kurita et al. [33] observed a similar protective effect of endogenous testosterone levels on kidney function in elderly Japanese men undergoing routine health checks. A study by Fukami et al. [34] observed that in patients with renal disease requiring hemodialysis, free testosterone levels were lower compared to healthy controls.

The rapid reduction in uric acid observed in patients that received TTh in this study, accompanied with an increase in GFR, which corresponds with the increase in their serum TT, suggests a direct effect of testosterone on renal function. Urea and uric acid are two of the four major non-protein nitrogen fractions in circulation, with creatine and creatinine being the other two. Whilst urea is a by-product of protein metabolism, and uric acid a result of purine catabolism, they are primarily cleared from the body via the kidneys and therefore their serum concentrations are a reflection of renal function. Mechanistically testosterone has been implicated in altering uric acid reabsorption by the kidneys by downregulating GLUT-9, a transporter protein primarily responsible for uric acid [35,36]. In contrast, serum uric acid levels have been shown to increase following TTh in patients with gender identity disorder, and is attributed to increase in muscle mass and turnover - a major source of purines [37,38]. Consistent with a protective role on renal function, at several time points across the duration of the present study, creatinine levels were shown to be significantly lower in testosterone treated men Supporting this, it has been reported in a large cohort of veterans diagnosed with low total testosterone that normalisation of testosterone decreased risk of ESRD (as defined by a serum creatinine level greater than 6.0 mg/dL) by 24% and a 25% reduction in risk of mortality [39,40].

Table 2: Adverse events observed in Testosterone treatment group (T-group) and control group (C-group). CVD, Cardiovascular Disease. $^{*}p<0.05$, $^{**}p<0.001$.

Adverse Events		
	Testosterone Group	**Control Group**
N	321	184
Deaths (%)	25 (7.8%)	28 (15.2%)*
Deaths due to CVD (%)	11 (44%)	28 (100%)**

The effect of TTh on renal function could also be mediated via improvements in the various components of MetS as outlined previously [17,18]. The inverse association of renal function with MetS components such as obesity, hypertension and dyslipidemia, observed in previous studies further supports this hypothesis [41,42]. Moreover, the improved liver function in the TTh group as evidenced by lower γ-GT and bilirubin levels does suggest improved metabolic parameters in the TTh group compared to the controls. Indeed, testosterone administration has been shown to reduce serum urea concentrations in hypogonadal men by inhibiting the hepatic urea cycle and increasing protein anabolism [43], and could in part contribute towards the decrease in serum urea observed in the treatment group in this study. Measuring whole-body protein turnover using established techniques such as leucine oxidation assays may help gauge the extent of this phenomenon for this cohort in future analysis. However, the association between testosterone and improved renal function demonstrated by Kurita et al. [33] remained even after adjusting for pathological covariates including obesity, diabetes, and dyslipidemia. Direct effects of testosterone deficiency on kidney function may result from renal ischemia induced by endothelial dysfunction as testosterone induces vasodilation in the renal vessels via the production of nitric oxide [44] and demonstrates vasodilatory effects on renal afferent arterioles in an arteriole culture model [45]. Alternatively, testosterone may protect against inflammation induced kidney injury as levels of inflammatory cytokines or inflammatory markers have been found to be reduced by testosterone administration in testosterone deficient men [46]. Further studies are warranted to decipher the exact biological mechanism responsible for the observed effects in this study.

Finally, the marked reduction in CVD related deaths in the treatment group is in keeping with previous reports of improved cardiovascular health and reduced mortality in hypogonadal men that receive TTh [47-49]. Although not directly investigated, it is suggested that the improvements in renal function may have contributed to reduced CVD-related mortality. In a cross-sectional analysis of non-dialysis elderly male patients with chronic kidney disease, a reduction in endogenous testosterone level was related to the progressiveness of the disease and was inversely associated with brachial artery endothelial dysfunction exacerbating the risk of future cardiovascular events [50]. A low total testosterone level was also associated with higher mortality in men with CKD stages 3-4 in a retrospective, cohort study [51].

The present study has a few limitations including the nature of the registry design. This single-centre, observational study was not a Randomized Controlled Trial (RCT) with a placebo arm and therefore did not allow direct effects of treatment

versus non-treatment to be compared limiting the scope of interpretation. However, this was not the primary focus of the study. Furthermore, ethical issues of not treating hypogonadal men who presented at our clinic would be raised. Whilst there is a justification for further prospective randomized controlled studies, the large patient cohort and long-term follow-up-period of up to 12-years permits clinically meaningful data. As indicated in the methods, several patients discontinued TTh temporarily during the course of the follow-up period due to reimbursement issues. This interruption in treatment may have reduced the inter-group differences in renal function and may explain some of the trend reversals demonstrated in treated patients between 4-7 years for several parameters in this study. Indeed, we have previously shown that TTh withdrawal results in a loss of beneficial effects on body weight, obesity, glycaemic control, voiding function and prostate safety parameters in hypogonadal men and re-treatment restores the positive effects [52-54].

CONCLUSION

We believe that this study highlights the beneficial effects long-term TTh may have on the renal function in men with chronic low testosterone levels. Furthermore, it also suggests that improvement in renal function may translate to lower CVD-related mortality in these patients. Nevertheless, large, randomised and placebo-controlled trials may be necessary to elucidate the impact of TTh on renal and cardiovascular function in hypogonadal men.

DISCLOSURES

AY has received partial compensation for data entry and occasional honoraria from Bayer AG, Ferring Pharmaceuticals and GSK. FS is a consultant to Bayer AG. No other conflicts of interest to report.

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