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Cohort Study

The impact of long-term Testosterone Therapy (TTh) in renal function (RF) among hypogonadal men: An observational cohort study

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ABSTRACT

Objectives: Testosterone therapy (TTh) is the main treatment for elderly men with hypogonadism. No evidence of the long-term effectiveness of TTh on renal function is reported to date.

Methods: In this study, we evaluated the long-term TTh of testosterone undecanoate (TU) administration on renal function parameters in 496 symptomatic hypogonadal men, with T levels ≤350 ng/dL. The treatment group (T-group) consisted of 312 patients and obtained TU 1000 mg for 12 weeks followed by 6-week intervals and for up to 8 years. The remaining 184 hypogonadal men, who opted against TTh, served as a control group (C-group). The two groups were similar in criteria prior to treatment. We evaluated renal function by calculating serum creatinine, urea, uric acid, and glomerular filtration rate (GFR) according to Mayo Clinic guidelines for 8 years. This study obeys the ethical guidelines of German medical association according to Section 15 of the Professional Code, document for AY- Ref. EK/CH/AU signed on Jun 2015.

Results: During the study period, the T-group exhibited lower levels of urea (47.0 ± 11.8 to 34.0 ± 13.9 mg/dL), uric acid (6.57 ± 1.2 to 5.49 ± 1.5 mg/dL), serum creatinine (0.90 ± 0.10 to 1.12 ± 0.9 mg/dL), and higher-level in GFR (87.0 ± 12.9 to 98.0 ± 8.0 mL/min/1.73 m^2), which were significant. Alternatively, the C-group exhibited an increase in their serum creatinine (1.16 ± 0.31 to 1.19 ± 0.58 mg/dL), an increase in uric acid (5.54 ± 1.2 to 5.44 ± 1.7 mg/dL), and a decrease in GFR (92.0 ± 20.1 to 87.0 ± 26.1 mL/min/1.73 m^2). A total of 25 deaths (7.8%) was recorded in the T-group, among them 11 (44%) were cardiovascular. On the other hand, 28 patients (15.2%) died in C-group and all deaths (100%) were found to cardiovascular causes.

Conclusion: The results suggest that long-term TTh could improve renal function in hypogonadal men comparing to slight deterioration observed in patients without intervention. In addition to reduce mortality in cardiovascular patients, almost to the half.

1. Introduction

Functional hypogonadism is known as age-related decrease in total testosterone (TT) levels with sexual symptoms [1–4]. The prevalence of functional hypogonadism range is estimated from 12% for 50 year-old, to 30% for 70-year-old men [5], and the chance increased with obesity and aging [6].

Symptoms for hypogonadal syndrome such as infertility, impaired libido, fatigue, and risk of depression have a great impact on the quality of life (QoL) [7,8]. Additionally, several components of metabolic syndrome (MetS) such as dyslipidemia, hypertension, obesity, decrease in muscle mass, insulin resistance, and dysregulation of glucose metabolism are also associated with the low TT levels [9–11], and hence increased the risk of cardiovascular disease (CVD) [12,13].

Many studies have shown that Testosterone Therapy (TTh) in hypogonadal men improved body composition, sexual function and reduces risk of CVD [14–27]. It is worth noting that long-term treatment of TTh and the effect on renal have not been reported to date.

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Hypogonadism in men with Chronic Kidney Disease (CKD) has significant morbidity with CVD and anemia [28]. The link between hypogonadism and CKD is likely to be multifactorial. Other comorbidities with LOH are known as CVD, diabetes, and obesity, which can be linked to CKD with a dysregulation in the hypothalamic-pituitary-gonadal axis [29–31]. Although many studies were concentrated on the sexual function and the effects of TTh on CKD, limited protocols on the direct effects of TTh on renal function were published so far.Herein, we present the renal function data of hypogonadal men with 8-years of long-term TTh.

2. Methods

2.1. Design and setting

A cohort prospective observational study was conducted at Institute of Urology and Andrology, Segeberger Kliniken, Norderstedt-Hamburg, Germany, and Men's Health Department, Hamad Medical Cooperation, Doha, Qatar.

A convenience sampling method were used to include 496 men (mean age: 59 ± 9.5 years) who suffers from low testosterone level ≤350 ng/dL (≤12.1 nmol/L) and hypogonadism. Any other patients were excluded. Observational data registry started in November 2004 till January 2015.

2.2. Sample

A total of 312 men have enrolled in the treatment group (T-group) and received 1000 mg testosterone undecanoate (TU) every 12 weeks, followed for 6 weeks and for up to 8 years. Among them, 140 men had discontinued treatment for 17 months after 5.5 years for reimbursement issues. The remaining 184 patients were selected for the control group (C-group). The two groups were mostly similar medically and demographically prior to treatment. The assessment of the long-term effect of TU on renal function as per Mayo Clinic test guidelines was evaluated by measuring uric acid, serum creatinine, urea and Glomerular Filtration Rate (GFR).

2.3. Ethical consideration

Institutional Review Board (IRB) approval were obtained from the ethics committee in the German medical association (Ärztekammer) (EK/CH/AU/June 1, 2015). All patients have signed the informed consent before enrolling in this study. In accordance with the declaration of Helsinki, the research was registered at ResearchRegistry.com with unique identifying number (researchregistry6769) [59]. This study written under STROCSS 2019 Guideline [58].

2.4. Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences, v.12, Windows package, USA) and GraphPad Prism V.8.4.3 (GraphPad Software, La Jolla, California, USA). Data were expressed as mean ± SD or as a simple number. Clinical parameters were studied between both groups over the treatment periods by linear mixed effect, repeated-measures model with period, group and their interaction considered as fixed effects. Data were compared using the X^2 test or Fisher's exact test as appropriate. Correlations were performed using Spearman's correlation coefficient. Regression was used for multivariate test analysis and as designated. A p-value < 0.05 were considered statistically significant.

3. Results

The characteristics of patients included in this study are described in Table 1. No significant differences between both groups are found using glomerular filtration rate (GFR). The mean for T-group including 312 patients was 59 ± 9.5 years, whereas the mean for C-group including 184 patients was 66.1 ± 7.6 years.

Table 1
Baseline characteristics of Testosterone treatment group (T-group) and the 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	312	184
Mean age (year)	59 ± 9.5	66.1 ± 7.6**
Testosterone (nmol/L)	7.90 ± 2.32	9.22 ± 3.41**
Waist Circumference (cm)	107.51 ± 9.95	100.76 ± 9.54**
Weight (kg)	98 ± 12	92 ± 09**
BMI (kg/m^2)	31.54 ± 4.51	29.50 ± 3.31**
GFR (mL/min/1.73m^2)	87.0 ± 12.8	92.0 ± 20.2*
Baseline Comorbidities		
Type II diabetes	94 (29.3%)	52 (28.3%)
HbA1c (for patients with type-II 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%)

The elevation in TT levels for hypogonadal men with TTh (T-group) was observed during 1-year follow-up period (7.90 nmol/L – 15.98 nmol, P < 0.0001), and compared to 9.10 nmol/L to 9.20 nmol/L (C-group) as shown in Fig. 1.

The change in serum creatine levels was also investigated between the two groups for 8-years period. Clearly, it shows a lowering level of serum creatine in the T-group (0.90 ± 0.10 to 1.12 ± 0.9 mg/dL) compared to C-group, where it shows an increase in serum creatine levels in C-group from 1.16 ± 0.31 to 1.19 ± 0.58 mg/dL with p < 0.05 and especially for years 4–7 compared to C-group as described in Fig. 2.

The uric acid level was dropped dramatically within the first 5-years for the T-group and from 6.57 mg/dL to 5.49 mg/dL (Fig. 3), whereas a steady decrease in uric acid levels for an 8-year study period for both groups giving (6.57 ± 1.2 to 5.49 ± 1.5 mg/dL, p < 0.0001) for T-group and (5.54 ± 1.2 to 5.44 ± 1.7 mg/dL, p < 0.01) for C-group. Furthermore, the dropping of uric acid levels in the T-group is likely engaged with the decrease of serum urea and from 47.0 ± 11.8 to 34.0 ± 13.9 mg/dL (p < 0.0001) as described in Fig. 4.

Moreover, the results also showed a continuous decrease in GFR levels over the 8-years follow-up in C-group patients and from 92.0 ± 20.1 to 87.0 ± 26.1 mL/min/1.73 m^2 (p < 0.0001). Alternatively, the T-group patients showed an increase in GFR levels over the 8-years from 87.0 ± 12.9 to 98.0 ± 8.5 mL/min/1.73 m^2 (p < 0.0001). It is worth to note that GFR level was significantly higher for T-group and in all years compared to C-group (p < 0.0001) as shown in Fig. 5.

Furthermore, 28 deaths were recorded for the C-group (15.2%) compared to significantly lower death cases for the T-group (25 deaths,

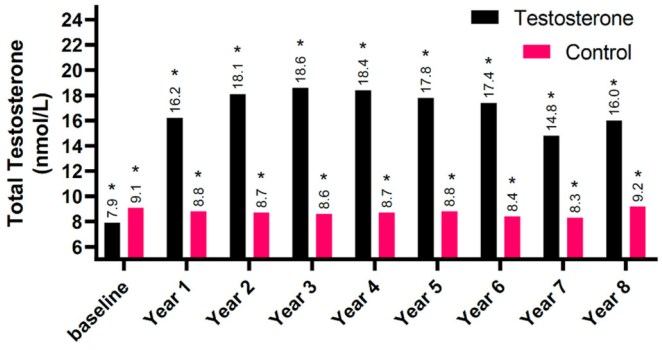

Fig. 1. The long-term treatment of testosterone undecanoate versus total testosterone (nmol/L) for 312 hypogonadal men and 184 untreated hypogonadal controls (*p < 0.0001).

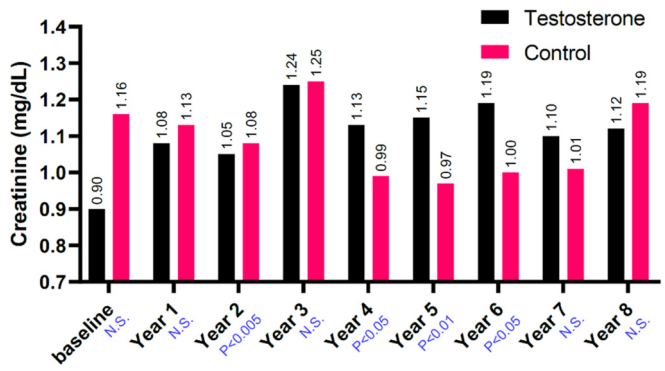

Fig. 2. The long-term treatment of testosterone undecanoate versus serum creatinine (mg/dL) for 312 hypogonadal men and 184 untreated hypogonadal controls. N.S. = not significant.

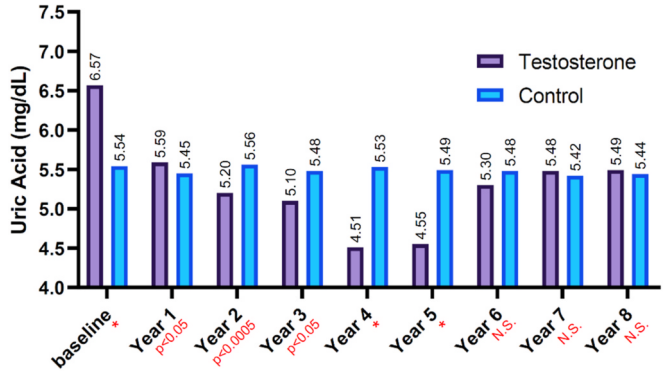

Fig. 3. The long-term treatment with testosterone undecanoate versus Serum Uric acid (mg/dL) for 312 hypogonadal men and 184 untreated hypogonadal controls, (*p < 0.001), N.S. = not significant.

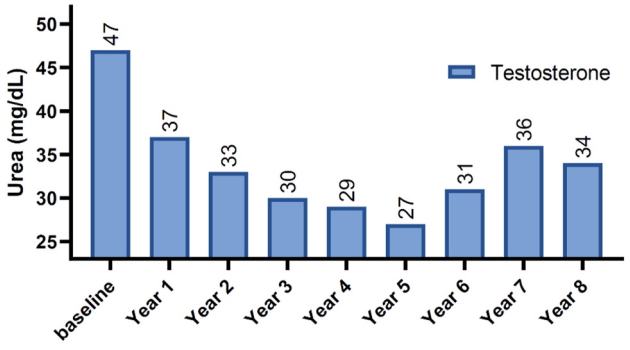

Fig. 4. The long-term treatment with testosterone undecanoate versus serum urea (mg/dL) for 312 hypogonadal men.

7.8%, p = 0.0351), in which most reported deaths from both groups were attributed to CVD (Table 2).

4. Discussion

The low testosterone levels in aging men and the subsequent hypogonadism are associated with different complications such as metabolic syndrome (MetS) and increase risk of cardiovascular disease (CVD) [10–13]. Also, others are significantly higher in men such as chronic kidney disease (CKD) and renal complications even though a well-documented causal link with CVD, in accordance to cardiorenal syndrome [32,33]. While the long-term effects of TTh on MetS and CVD

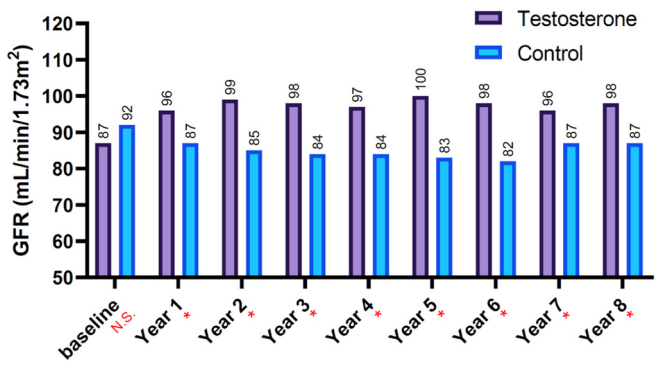

Fig. 5. The long-term treatment with testosterone undecanoate versus glomerular filtration rate (GFR, mL/min/1.73m2) for 312 hypogonadal men and 184 untreated hypogonadal controls (*p < 0.0001), N.S. = not significant.

Table 2
Adverse events observed in Testosterone treatment group (T-group) and control group (C-group). CVD, Cardiovascular Disease. *P < 0.05, **P < 0.0001.

Adverse Events		
	Testosterone Group	Control Group
N	312	184
Death (%)	25 (7.8%)	28 (15.2%)*
Death due to CVD (%)	11 (44%)	28 (100%)**

have been widely reported [34–37], the effect of TTh on renal function in CKD is still limited. Herein, we presented an observational study on the long-term effect of TTh on renal function biomarkers like uric acid, serum creatinine, serum urea and glomerular filtration rate in hypogonadal men.

Most of the published protocols of hypogonadism effect on renal function focused on the association with mortality and morbidity of patients including end-stage renal function (ESRD) and CKD [38–40]. The major objectives of TTh in these studies have been sexual function restoration (Treatment of functional hypogonadism) and enhancement of metabolic parameters (lean muscle mass and insulin resistance) [41,42] and no consideration for renal function parameters were mentioned. For instance, in 2009, Tomaszewski et al. reported a baseline study on the correlation between serum testosterone levels and creatinine as an indicator for renal function on eugonadal healthy young men (mean age 18.5 years) [43]. It revealed a normal range for total testosterone concentrations for selected young population, thus it suggests that the effect of testosterone on renal function may endure autonomously of age and beyond the limitations of hypogonadism. Another study by Kurita and co-workers revealed a similar protective effect of endogenous levels of testosterone on kidney function beyond elderly men in Japan [44]. Furthermore, Fukami et al. reported that testosterone levels were significantly lower in the T-group compared to the C-group for patients with renal disease receiving hemodialysis, all of the aforementioned were consistent with our study [45].

The reduction in uric acid levels for patients receiving TTh in this study, along with the increase in GFR, revealed a strong and direct effect of testosterone on renal function. Uric acid, urea, creatine and creatinine are the four non-protein nitrogen fractions in circulations. Uric acid is known because of catabolism, while urea is a by-product of protein metabolism, and both are excreted by the kidney and their serum concentrations reflect the status renal function. Testosterone has a large implication on altering uric acid reabsorption in kidneys by down-regulation the transporter protein channel GLUT-9 [39,40]. Moreover, creatinine levels were also found to be lower in patients under testosterone treatment, which is supported by the larger number of published cohort studies [48–50]. The improvement of various components of MetS such as obesity, hypertension and dyslipidemia could be also used

as an indication on the effect of TTh on renal function as previously reported [15,16]. However, it was reported that reducing the serum urea concentration in hypogonadal men by increasing the protein anabolism and inhibiting the hepatic urea cycle, which could be in part the cause for having lower levels of serum urea in this study. The deficiency of testosterone has a direct effect on kidney function, it could results from renal ischemia induced by endothelial dysfunction as testosterone demonstrated vasodilatory effects on the renal by the production of nitric acid [51]. Furthermore, testosterone administration suggests that deficient testosterone levels may protect from inflammation-induced by kidney injury by reducing levels of inflammatory markers [52]. Lastly, the reduction in deaths related to CVD in the T-group suggests a direct contribution to the improvement in renal function (Cardiorenal syndrome) [53–55]. Although, it is in-line with previously published studies of reduced mortality and improved cardiovascular health in hypogonadal patients receiving TTh. Yalmiz et al. reported a cross-sectional study of elderly men with chronic kidney disease (CKD). It revealed that the progressiveness of CKD stage related to increased hypogonadism, as well as testosterone levels were inversely related to endothelial dysfunction and the risk of CVD in non-dialysis CKD patients [56]. Although, we found that 100% deaths from C-group due to CVD causes in comparison to 44% in T-group, which emphasis the protective role of testosterone in CVD.Moreover, a retrospective cohort study published by Khurana and co-workers revealed that higher CKD-related deaths in men patients were associated with low testosterone levels [57].

Even though this observational study is not a Randomized Controlled Trial (RCT) and has few limitations such as the nature of registry design and scope of interpretation, the large patient cohort study and the long-term follow-up for 8 years provide essential clinical facts. Other ethical issues could be raised for not treating hypogonadal patients at our clinic. As mentioned in our methodology, the large number of discontinuing TTh patients during the treatment course and the hard-to-follow-up due to reimbursement issues limited the group differences in renal function and explained some of the parameters in the treatment group between 4 and 7 years.

5. Conclusion

This study highlights the long-term TTh beneficial effects on renal function in men with low levels of testosterone. Moreover, it also highlights the low CVD-related mortality rate with improvement renal function. Indeed, RCT with placebo-controlled trials is still needed to elucidate the impact of TTh on cardiovascular and renal functions in hypogonadal men.

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Provenance and peer review

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Declaration of competing interest

No Conflict of Interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102748.

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Please state any conflicts of interest

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

No Conflict of interest at all.

Please state any sources of funding for your research

All sources of funding should be declared as an acknowledgement at the end of the text. Authors should declare the role of study sponsors, if any, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. If the study sponsors had no such involvement, the authors should so state.

No funding

Ethical approval

Research studies involving patients require ethical approval. Please state whether approval has been given, name the relevant ethics committee and the state the reference number for their judgement.

Institutional Review Board (IRB) approval were obtained from the ethics committee in the German medical association (Ärztekammer) (EK/CH/AU/June 1, 2015).

Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper.

Authors must obtain written and signed consent to publish a case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Patients have a right to privacy. Patients' and volunteers' names, initials, or hospital numbers should not be used. Images of patients or volunteers should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. If such consent is made subject to any conditions, the Editor in Chief must be made aware of all such conditions.

Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

Written informed consent were signed by the patients before enrolled to the study.

Author contribution

Mustafa Alwani: writing the paper, study concept, data analysis, and final revision.
Raed M. Al-Zoubi: writing the paper, and final revision.
Ahmad Al-Qudimat: writing the paper, and final revision.
Aksam Yassin: study concept and design, supervision, writing the paper and final revision.
Omar Aboumarzouk: writing the paper and final revision.
Khaled Al-Rumaihi: supervision and writing the paper.
Raidh Talib: supervision and writing the paper.
Abdulla Al-Ansari: supervision and writing the paper.

Registration of research studies

In accordance with the Declaration of Helsinki 2013, all research involving human participants has to be registered in a publicly accessible database. Please enter the name of the registry and the unique identifying number (UIN) of your study.

You can register any type of research at http://www.researchregistry.com to obtain your UIN if you have not already registered. This is mandatory for human studies only. Trials and certain observational research can also be registered elsewhere such as: ClinicalTrials.gov or ISRCTN or numerous other registries.

1. Name of the registry: The Impact of Testosterone Therapy (TTh) in Renal Function (RF) among Hypogonadal Men: Long-Term Treatment Observational Study
2. Unique Identifying number or registration ID: researchregistry6769
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): Browse the Registry - Research Registry

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Aksam Yassin.

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