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Testosterone treatment and change of categories of the International prostate symptom score (IPSS) in hypogonadal patients: 12 years prospective controlled registry study

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ABSTRACT

Functional hypogonadism is a condition characterized by low testosterone concentrations, occurring more commonly in men as they age. The International Prostate Symptom Score (IPSS) is used to categorize the severity of lower urinary tract symptoms (LUTS) and related symptoms in hypogonadal men. Testosterone therapy (TTh) has previously shown potential in improving total IPSS in men with hypogonadism. However, concerns regarding the effects of urinary function following TTh often prevent treatment in hypogonadal men. To explore this further, two population-based single-center, prospective, cumulative registry studies were combined to contribute to a total population of 1176 men with symptoms of hypogonadism. The total population was separated into a TTh group receiving testosterone undecanoate (TU) for up to 12 years and a control group that did not receive treatment. IPSS was recorded at both baseline and at final recorded visit for each patient. Long-term TTh with TU in hypogonadal men resulted in significant improvements in IPSS categories, even in patients with severe symptoms at baseline. In the control group, untreated hypogonadal men experienced a worsening of IPSS categories. These data indicate that TTh improves LUTS in men with hypogonadism and suggest that previous concerns regarding urinary function may have been overstated.

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Introduction

Functional hypogonadism is a condition characterized by low serum testosterone concentrations and symptoms in males, a condition that becomes increasingly prevalent as men age [1]. Approximately 20% of men over the age of 60 have low testosterone levels, rising to 30% over the age of 70 and 50% over the age of 80 [2]. The clinical features of functional hypogonadism include absence or regression of secondary sex characteristics, insulin resistance or type 2 diabetes (T2D), hypertension, dyslipidemia, anemia, muscle atrophy, reduced bone mass or bone mineral density, oligospermia, decreased libido, decreased sexual function and abdominal adiposity [3]. Along with T2D, other co-morbidities potentially caused by low testosterone include metabolic syndrome (MetS) and obesity, all of which are associated with increased age [4]. These co-morbidities often exacerbate the effects of hypogonadism, significantly reducing the quality of life (QoL) for patients and ultimately increasing mortality [3,4].

Lower urinary tract symptoms (LUTS) play a significant role in the reduced QoL that is observed in men with increasing age [5–7]. LUTS are a hallmark of benign prostatic hyperplasia (BPH), which has been linked to functional hypogonadism [2,8,9]. Moreover, it has been reported that approximately 20% of men with LUTS had hypogonadism, further indicating that the two conditions are linked [10]. LUTS covers a broad range of symptoms that reduce QoL including

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voiding and obstruction (hesitancy, poor/intermittent stream, straining, feeling of incomplete bladder emptying) and other storage and irritative symptoms (frequency, urgency, incontinence, nocturia) [11]. The severity of LUTS, related symptoms, and the impact of LUTS on quality of life can be assessed and categorised using the International Prostate Symptom Score (IPSS) [11]. Testosterone therapy (TTh) has previously shown potential in improving IPSS and LUTS and related symptom scores in men with hypogonadism [12]. TTh showed significant improvements in total IPSS and storage symptom score in a population of men with moderate to severe LUTS [13]. However, the voiding symptom score was not improved in the same study [13]. A meta-analysis combining the data from 14 TTh clinical trials reported changes in IPSS that were similar in the treatment and control groups [14]. While this questioned the effects of testosterone on improving LUTS, the analysis demonstrated that TTh does not worsen symptoms in men with hypogonadism [14]. Importantly, the mean follow-up period for these studies was 34.4 months which might suggest that long-term treatment is required to observe significant improvements in LUTS [14].

A perceived barrier to TTh in elderly men is often an increase in prostate volume and the subsequent deterioration of urinary function parameters. As the prostate is an androgen-dependent organ, an increase in testosterone levels may induce prostate growth and development and increase prostate volume [15]. This, therefore, raises concerns regarding LUTS and prostate cancer in men receiving TTh [15]. In order to address this issue, data were collected from two German population-based single-centre, prospective, cumulative registry studies, to give a combined population of men with symptoms of hypogonadism. The effects of testosterone undecanoate (TU) was investigated in this population, with up to 12 years follow-up, by measuring IPSS at baseline and a final recorded visit to determine if long-term TTh showed improvement in LUTS and related symptoms in hypogonadal men.

Patients and methods

Two population-based single-center, prospective, cumulative registry studies were combined to give a total population of 1176 men with symptoms of hypogonadism. This cohort was collected from two urological centers based in Germany and observation began in 2004. The baseline TT in the cohort was $\leq$3.50 ng/mL ($\leq$12.1 nmol/L). Patients had documented ED for $\geq$6 months, established using the international definition for ED, the International Index of Erectile Function (IIEF). Patients with clinically significant findings on physical exam or the presence of known clinically significant diseases that would prejudice the completion of the study or contraindicate testosterone administration were excluded from the study. Following an initial 6-week interval, 696 men received long-acting Testosterone undecanoate (TU) (Nebido®, Bayer Pharma, Berlin, Germany) as 1000 mg injections in 12-week intervals for a maximum of 12 years. The remaining 480 did not receive TTh and acted as a control group. There were two main reasons why the patients did not receive a continuation of therapy: reimbursement issues, as the therapy was not covered by insurance or other healthcare reimbursement systems, and risk aversion due to concerns about potential side effects, complications, or long-term risks associated with the treatment. IPSS scores were documented at baseline and every 3-month study visit, but are presented as the final study visit for each patient and categorized into either; mild (IPSS 1–7), moderate (IPSS 8–19), or severe symptoms (IPSS 20–35) as the primary outcome of this analysis. Patients receiving medications at baseline for comorbidities did not have therapy altered during the study. This included those receiving α-blockers, PDE5 inhibitors, and 5α-reductase inhibitors. No acute urinary retention or prostate surgery was reported during the follow-up time. Approval from the ethics committee was obtained at the institution in line with guidelines formulated by the German Ärztekammer (German Medical Association). Patients were enrolled following informed written consent and all data was treated confidentially.

Statistical analysis

IPSS categories are presented as percentage of patient populations from each treatment or control group from count data at baseline and final recorded visit. Baseline parameter values were recorded prior to the first TU injection. Chi-square tests were used to compare the differences in categorical variables between the two groups at the 2-time points and change from baseline within each group. Statistical analysis was performed using the Statistical Package for Social Sciences v.18 (SPSS Inc., Chicago, USA) and GraphPad Prism version 8.4.3 (GraphPad Software, La Jolla, CA, USA). A value of $p < .05$ was considered significant.

Results

IPSS

At baseline, 346 of the TTh group had mild symptoms (49.7%), 345 had moderate symptoms (49.6%) and 5 had severe symptoms (0.7%) (Figure 1). At the final recorded visit, 598 of the TTh group had mild symptoms (85.9%) and the number of men with moderate symptoms had significantly reduced ($p \leq .001$) to 98 (14.1%) (Figure 1). All patients that were initially categorized with severe symptoms showed an improvement to at least moderate symptoms ($p \leq .001$).

At baseline, 307 of the control group had mild symptoms (64.0%), 162 had moderate symptoms (33.8%) and 11 had severe symptoms (2.3%) (Figure 2). At the final recorded visit, 171 of the control group had mild symptoms (35.6%), 269 had moderate symptoms (56.0%) and 39 had severe symptoms (8.1%) (Figure 2).

Concomitant medication

In the TTh group, 21% of the patients had been prescribed alpha-blockers at any point in their life compared to 41.7% of patients in the control group ($p \leq .001$) (Figure 3). During the course of the observation period of the studies, one patient in the TTh group was prescribed alpha-blockers (0.1%) compared to 38 patients prescribed in the control group (7.9%, $p \leq .001$) (Figure 3).

In the TTh group, 6.5% of the patients had been prescribed 5-alpha-reductase inhibitors at any point in their life compared to 19.6% of patients in the control group ($p \leq .001$) (Figure 4). During the course of the observation period of the studies, one patient in the TTh was prescribed 5-alpha-reductase inhibitors (0.1%) compared to 42 patients prescribed in the control group (8.8%, $p \leq .001$) (Figure 4).

Discussion

There has been an ongoing debate surrounding the use of TTh and the improvement in IPSS and LUTS in men with hypogonadism and low testosterone. TTh has shown the potential to improve IPSS, and therefore the severity of LUTS, in men with hypogonadism [13]. However other studies have reported that TTh does not improve LUTS but also does not worsen any symptoms, with long-term treatment suggested in order to observe a significant improvement [14]. Concerns have also been raised regarding the use of TTh and increasing prostate volume, leading to a worsening of LUTS and acting as a barrier to prescribing TTh in elderly men [15]. The current study observed significant improvements in IPSS categories in hypogonadal men receiving TTh. Improvements were shown in patients even with severe symptoms at baseline. In contrast, untreated individuals experienced a worsening of symptoms and IPSS categories. These results are indicative of an improvement of LUTS in hypogonadal men receiving TTh over the current

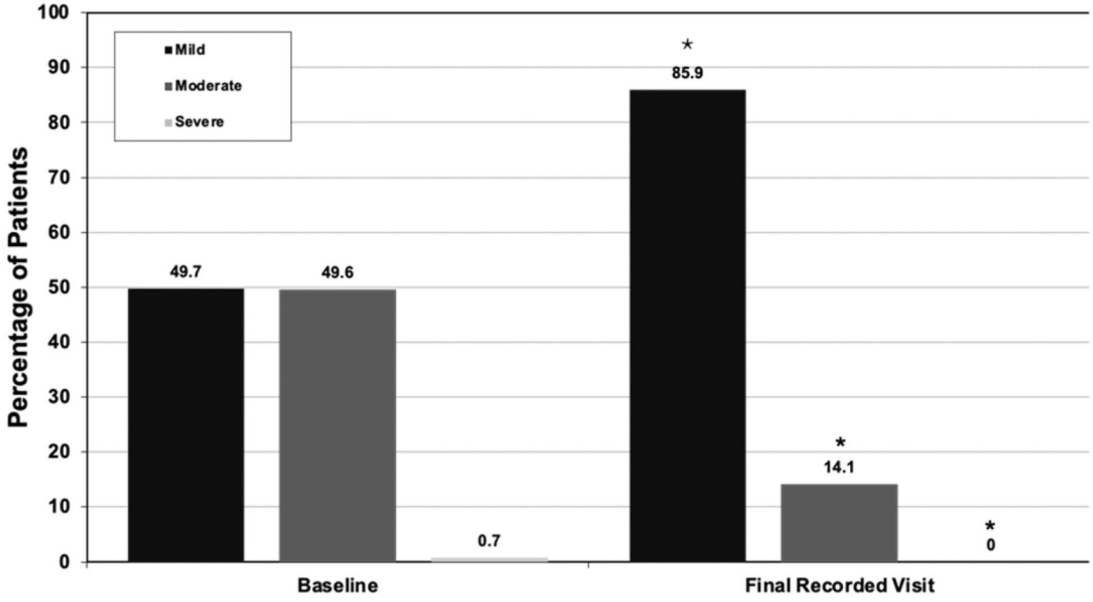

Figure 1. IPSS categories in the TTh group at baseline and the final recorded visit for each patient. Patients were categorised into mild, moderate, and severe IPSS categories. *Represents significant difference in the number of patients in an IPSS category from the baseline recording to the final recorded visit ($p \leq .05$).

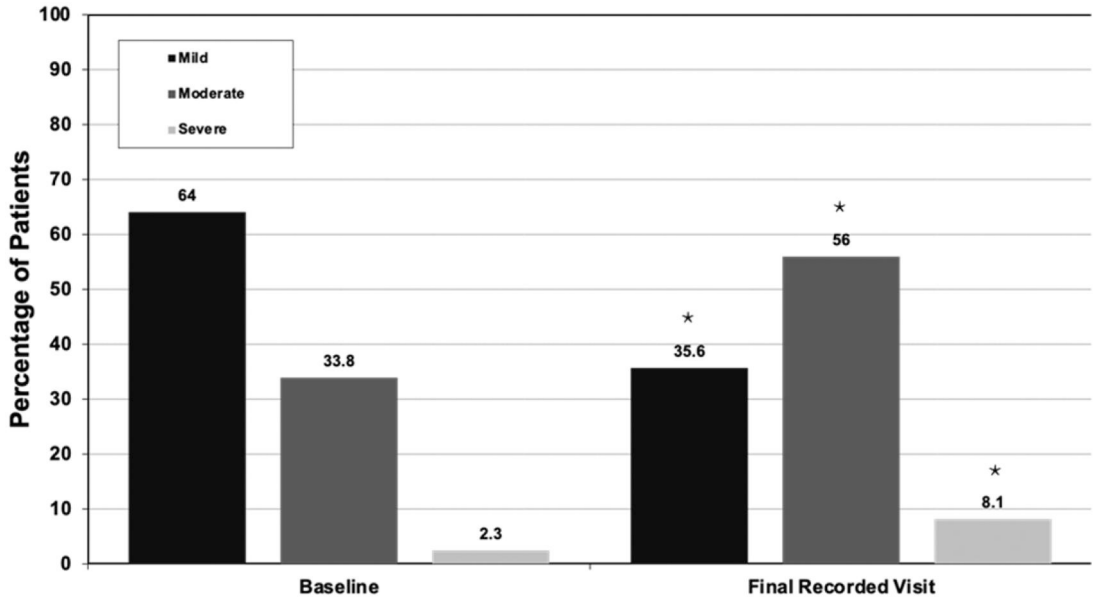

Figure 2. IPSS categories in the control group at baseline and the final recorded visit for each patient. Patients were categorised into mild, moderate, and severe IPSS categories. *Represents significant difference in the number of patients in an IPSS category from the baseline recording to the final recorded visit ($p \leq .05$).

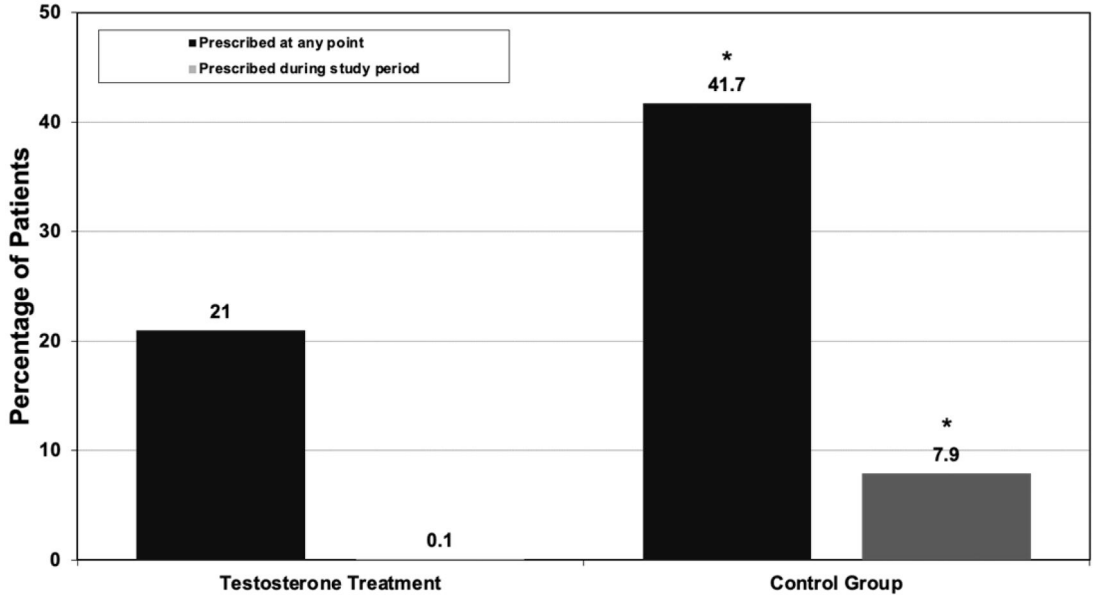

Figure 3. The percentage of patients that had been prescribed alpha blockers at any point in their life and prescribed during the course of the study period in both the TTh and control groups. *Represents significant difference between the TTh group and the control group ($p \leq .001$).

12-year study period and add to the previous discussion surrounding long-term therapy and LUTS improvement.

A previous retrospective cohort study reported that 6 months of TTh had a considerable beneficial effect on LUTS in 60 Japanese men with late-onset hypogonadism [13]. Within this study, IPSS categories were significantly improved following TTh along with improvements in IPSS sub-scores related to storage symptoms but not in voiding symptom scores [13]. TTh *via* by testosterone ointment at relatively low doses (6 mg Glowmin, daily) significantly improved all IPSS domains, as well as voiding and storage disturbance within 3 months in hypogonadal men [16]. An increase of bladder capacity and compliance (indicated by pressure-flow analysis), in addition to improvement of IPSS, has also been demonstrated in men with symptomatic late-onset hypogonadism [17]. In a randomized control study, Shigehara et al. reported that TTh resulted in a significant improvement in IPSS

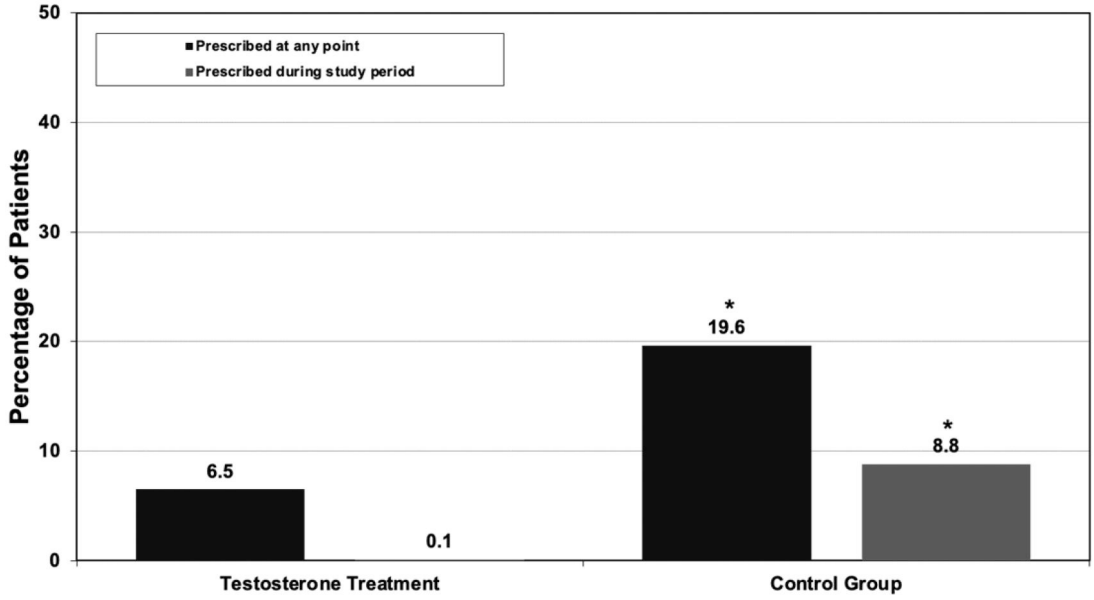

Figure 4. The percentage of patients that had been prescribed 5-alpha-reductase inhibitors at any point in their life and prescribed during the course of the study period in both the TTh and control groups. * Represents significant difference between the TTh group and the control group ($p \leq .001$).

score and flow rate in men with mild BPH [18], and subsequent improvements in nocturia have been suggested [19]. Tan et al. [20] similarly reported a non-significant improvement in IPSS following 48 weeks of TTh in a randomized placebo-controlled trial designed to evaluate the efficacy and safety of long-acting intramuscular testosterone undecanoate (TU) in aging Malaysian men with testosterone deficiency. Indeed, we have previously reported that TTh significantly decreased IPSS over time following the restoration of circulating total testosterone concentrations in 261 elderly hypogonadal men [21]. Interestingly, a meta-analysis exploring IPSS categories in hypogonadal men receiving TTh vs. placebo concluded that TTh did not improve LUTS but also did not worsen symptoms [14]. The present study adds support to suggest that TTh can improve LUTS by beneficially shifting the IPSS category to more milder symptoms regardless of baseline IPSS status and opposed to the progressive worsening of IPSS seen in hypogonadal men not receiving TTh. An advantage of the current study compared to previous studies is the length of the observation period, demonstrating for the first time that long-term TTh over 12 years is effective in improving IPSS scores in men with hypogonadism. Indeed, long-term treatment is suggested for the maintenance of endocrine parameters [22] and sustained TTh benefits on metabolic, vascular, diabetic, and obesity-related comorbidities [23].

Alpha-blockers and 5-alpha-reductase inhibitors are both commonly prescribed to BPH patients to treat the effects of LUTS [24,25]. These medications can improve LUTS by decreasing prostate volume, improving urinary symptoms and urinary retention though consequently may also reduce libido, induce erectile dysfunction, and decrease ejaculate volume in some cases, which in turn may affect QoL [25]. In the present study, a significantly lower percentage of patients were prescribed alpha-blockers and 5-alpha-reductase inhibitors in patients receiving TTh during the observation period of the study. This may suggest that TTh improves, or at least prevents, LUTS deterioration and the need for medication in hypogonadal men. This aligns with improvements in IPSS demonstrated here, and previously [4,18,21] along with beneficial effects on voiding function independent of prostate volume [4,26]. Ceasation of LUTS medication was not recorded in the present study. The TTh group, however, had significantly fewer patients prescribed these concomitant medications prescribed at any point which may demonstrate a treatment bias between the groups. As the same trends were observed for patients that had been prescribed at any point in their lives and those that had been prescribed during the observation period, it is likely that the use of concomitant medications at least did not have an effect on the differences observed in IPSS. In fact, the TTh group experienced greater improvements in IPSS with lesser concomitant medication prescription.

It is important to consider the co-morbidities commonly seen in men with hypogonadism as a mechanistic link for LUTS improvements following TTh. A

relationship exists between insulin resistance and LUTS in BPH patients [27], and individuals with diabetes experience more severe LUTS than those without, as indicated by IPSS [28]. Additionally, there is evidence suggesting that obesity and the incidence of LUTS/BPH are strongly linked, and the pathology of both obesity and MetS is underpinned by chronic inflammation which additionally plays a crucial role in BPH and LUTS [29]. Therefore, the inter-relationship between diabetes, obesity, MetS, and inflammation contribute to LUTS progression. Several studies have reported a beneficial effect of TTh on insulin sensitivity, obesity, and chronic inflammation [30–33]. Specifically, TTh reduced BMI, WC, HbA1c, and CRP in parallel to an improvement in LUTS in the same cohort of hypogonadal men as the present study over an 8-year follow-up [34]. Improvement in hypogonadism-associated co-morbidities could consequently be responsible for some of the improvements in LUTS and specifically IPSS in hypogonadal men receiving TTh. This mechanistic relationship between testosterone and LUTS is complex and remains poorly understood and therefore requires further investigation.

Limitations of the current study are recognized. A placebo-controlled group was not included in this observational study which means that the effects of TTh to non-treatment could not be directly compared. Additionally, 147 of the patients had TTh interrupted due to issues with reimbursement and/or diagnosis of prostate cancer. While this has the potential to affect the current data as testosterone returned to hypogonadal levels in some patients within the follow-up period, it has been previously reported that hormone concentrations return to a pre-interruption level when TTh is recommended [4] and in all cases, this occurred before the final recorded visit in the present study. Concerns have been raised with regard to the safety of TTh in men with suggestions that it may stimulate the growth of androgen-dependent tumors to advance or cause prostate cancer. Prostate volume and PSA measures were increased with TTh in patients in the present study, however, without the use of a placebo-controlled group we cannot ascertain whether the increase in PSA and prostate volume was significantly above that of the normal aging population. Indeed, large, controlled, long-term outcome studies are required to provide further evidence on TTh safety. Clinical practice guidelines [35] were followed throughout this study with vigilant monitoring of such prostate health parameters at baseline and subsequent treatment visits. No patient exceeded the safety levels and no complications such as acute urinary retention or prostate surgery were reported throughout the study treatment period. Importantly, TTh has not been associated with clinically significant increases in prostate-specific antigen (PSA) or an increased risk of prostate cancer, and TTh is associated with a lower risk of worsening LUTS in some studies [36].

Although IPSS is the most widely utilized tool to measure LUTS, patient perception of troublesome symptoms should be considered in parallel. A high IPSS does not always indicate poor QoL for a particular BPH patient [37–40]. Accordingly, the assessment of LUTS is a complex issue encompassing several different disorders (overactive bladder, neurogenic bladder dysfunction, bladder tumor, urinary stone disease, trauma, aging, and other diseases) each potentially impacting on QoL independently and to varying degrees. This, therefore, necessitates accurate and detailed follow-up evaluation to delineate the underlying multifactorial pathophysiology. Despite this, the treatment of hypogonadal males with TTh has been previously shown to improve QoL, ED, voiding function, and LUTS [21,34,41] with the improvement in QoL considered partially due to the improvements of LUTS symptoms (e.g. voiding dysfunction) and the associated effects on sexual function (ED, ejaculatory dysfunction, libido) [42,43]. We found no references in the literature for contraindication of testosterone treatment in patient with IPSS score higher than 19 so far.

In conclusion, the results from the current study indicate that long-term TTh with TU in hypogonadal men improves IPSS categories, even in patients with severe symptoms at baseline. In contrast, untreated hypogonadal men experienced a worsening of IPSS categories. The previous concerns regarding TTh and deteriorating urinary function in men may have been overstated and TTh may, in fact, be a useful treatment adjunct for LUTS in hypogonadal males and should be considered in recommendations on the diagnosis, treatment, and monitoring of testosterone deficiency in men [44]. No evidence for contraindication for TTh in patients with IPSS higher than 18 is found.

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Ethical approval

This study was conducted in accordance with German Ärztekammer (German Medical Association) regulations. Due to the nature of this study, explicit ethical approval was not

required. However, the researchers ensured that the study was conducted with integrity, transparency, and respect for all relevant regulations and ethical considerations.

Disclosure statement

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Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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