ORIGINAL ARTICLE

Open Access

Design and Conduct of a Real-World Single-Center Registry Study on Testosterone Therapy of Men with Hypogonadism

Karim Sultan Haider,¹ Ahmad Haider,¹ Gheorghe Doros,² and Farid Saad^{3,4,*}

Abstract

Aims: Despite the prevalence of hypogonadism (testosterone deficiency [TD]) and widespread use of testosterone therapy (TTh), the effectiveness and safety of long-term testosterone use remains highly contested. Over the past 15 years, we have conducted a registry study of men with TD with a focus on several health outcomes associated with TTh.

Design: Observational patient disease registry study.

Materials and Methods: Noninterventional disease registry with prospective longitudinal data on a large sample of adult hypogonadal men ($n = 858$) who were treated in a single Urology Clinic. The registry evaluates men with symptomatic TD during a urological exam of patients who have not been previously treated with TTh. There were no inclusion/exclusion criteria. All hormone assays are carried out in a single laboratory. Standard-of-care treatment of each patient is the sole responsibility of the attending clinician. The registry data consist of comprehensive medical records and questionnaire data collected during patient visits. The registry has a dedicated statistician to ensure adequate statistical analyses of all outcome measures assessed.

Main Outcome Measures: We measured the following parameters: height, weight, waist circumference, hemoglobin, hematocrit, fasting glucose, glycated hemoglobin, insulin, systolic and diastolic blood pressure, heart rate, lipids (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides), highly sensitive C-reactive protein, and total testosterone (T). We assessed quality of life, erectile and urinary function. Clinical parameters were measured two to four times a year. Data are analyzed in regular intervals.

Results: As of 2019, 858 men have been enrolled, of whom 85 patients exhibited primary hypogonadism, and the remaining 773 exhibited secondary or functional hypogonadism. Findings from this registry study on the benefit of TTh on anthropometric parameters, cardiometabolic function, diabetes, and prostate health have been reported.

Conclusions: This registry study has provided real-world clinical evidence and produced new important findings regarding the effectiveness and safety of long-term TTh in hypogonadal men.

Keywords: hypogonadism; real-world evidence; long-term therapy; testosterone; observational study

¹Private Urology Practice, Bremerhaven, Germany.

²Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA.

³Gulf Medical University School of Medicine, Ajman, United Arab Emirates.

⁴Dresden International University, Dresden, Germany.

*Address correspondence to: Farid Saad, DVM, PhD, Hinsbleek 1, Hamburg 22391, Germany, Email: farid.saad@bayer.com

Introduction

Clinical evidence suggests that testosterone therapy (TTh) is a long-term, if not lifelong, treatment. Although a number of randomized controlled trials (RCTs) have been carried out in hypogonadal men receiving TTh, most of these trials are of very short duration ranging from 1 to 36 months.¹ To date, there are only three prospective RCTs with a duration of 3 years.^{2–4} Two of those clinical trials were not restricted to hypogonadal men,^{2,4} and one trial included a group of men receiving a combination of T and finasteride, and only 24 men each received testosterone (T) or placebo.³ Other long-term studies with 42 and 60 months' duration were not placebo-controlled.^{5,6}

Many RCTs on TTh screen a large number of men, exceeding thousands of patients, in their recruitment process after establishing substantial lists of inclusion and exclusion criteria. This results in exclusion of thousands of patients producing study populations that significantly differ from the patient populations often presenting in physicians' offices and clinics in their everyday practice.

Although RCTs are considered the gold standard of clinical research, they are not entirely free from all forms of bias.⁷ In addition, the high associated costs of long-term RCTs, especially those that are expected to recruit a large number of patients, make such trials prohibitive to execute, and therefore, such trials have yet to surface in the TTh field.

Recently, increased attention has focused on observational, so-called “real-life” or “real-world” studies reflecting daily clinical practice.⁸ Indeed, relevant clinical information had been attained from large observational studies that had contributed to the advancement of clinical research. Such trials provide additional knowledge to RCTs.

In the early 2000s, urologists became aware of the concept of the metabolic syndrome, a cluster of cardiometabolic risk factors, since they are managing patients with such risk factors. In fact, the relationship between metabolic syndrome and androgen deficiency was recognized as early as 1990.⁹ Further, studies conducted in the field of erectile dysfunction (ED) that were triggered by the introduction of phosphodiesterase type 5 inhibitors showed that ED was an early predictor of cardiovascular events.¹⁰

The absence of long-term RCTs in hypogonadal men to investigate the effects of long-term TTh and the concept that TTh requires a long duration to produce the

expected clinical outcomes due to the pathophysiology of hypogonadism and the remodeling and repair in response to androgen treatment necessitated new approaches to investigating TTh in men with TD. Our registry study was initiated in 2004 with the objective of investigating long-term effectiveness and safety of a novel depot injection of testosterone undecanoate (TU) in otherwise unselected, adult patients with symptomatic hypogonadism. Patients were considered symptomatic if they had at least moderate symptoms on the Aging Males' Symptoms (AMS) Scale¹¹ and T levels below 12.1 nmol/L. At that time, it had become routine in our urological office to also measure parameters that may not always be assessed by urologists but were related to the metabolic syndrome (e.g., weight, waist circumference [WC], body mass index [BMI], lipid profiles, glucose levels, and insulin), a common condition in the vast majority of our patients. In this communication, we wish to provide details of our registry study and summaries of major findings reported from this registry.

There is an ongoing discussion about testosterone deficiency (TD) due to organic (classical or pathological) hypogonadism arising from disorders of the hypothalamus, pituitary, or testes, or functional hypogonadism due to obesity and comorbidities.¹² Whether this is clinically relevant or an academic discussion remains to be seen. There is recent evidence suggesting that obesity may lead to hypothalamic inflammation,¹³ which, in turn, leads to suppression of testosterone production.¹⁴ This would mean that functional hypogonadism is in reality secondary hypogonadism. Zitzmann et al. have shown that there is little difference in response to TTh regardless of whether a patient is diagnosed with primary, secondary, or functional hypogonadism.¹⁵

Materials and Methods

The “Ethical guidelines as formulated by the German ‘Ärztekammer’ (the German Medical Association) for observational studies in patients receiving standard treatment” were followed. After receiving a detailed and informative explanation regarding the nature and the purpose of the study, all subjects provided written consent, regardless whether or not they decide for TTh.

Patients who displayed or reported symptoms or who requested to have their testosterone levels measured are routinely screened for TD (hypogonadism). Men with two total testosterone measurements ≤ 12.1 nmol/L (350 ng/mL) were informed about their laboratory results during a personal consultation. They are then offered

treatment and informed about different testosterone preparations, including transdermal gels and short-acting injections. The majority of patients opted for treatment with TU 1000 mg injections (Nebido®; Bayer AG, Berlin, Germany) in 12-week intervals after an initial 6-week interval as one of the treatment options.

All patients were informed that they had the option to receive or not receive testosterone medication based on their own level of understanding of the benefits of this medication to their overall health. Patients were encouraged to continue to follow up with their urologist to treat their urological complaints and/or routine check-ups, irrespective of the choice to receive or not to receive TTh. The patients were given ample time to think through which option to choose or to consider obtaining a second opinion before their next appointment. Patients who opted to undergo TTh made their decision based on a number of reasons, including well-known effects of TTh on increased vitality, energy and sexual function, as well as improved mood. More recently, an increasing number of patients with type 2 diabetes were referred to our clinic by a local diabetes center after they had seen beneficial changes in many of their patients receiving testosterone at our clinic. Additional referrals come from local orthopedists who refer patients with osteoporosis, especially younger men, with a suspicion of hypogonadism. Most patients in our clinic opted for TU 1000 mg injectable over transdermal gels for convenience, as it is only one injection every quarter instead of daily self-administration.

Patients who opted not to be treated with testosterone were concerned about adverse cardiovascular effects of testosterone, the increased risk for prostate cancer, as well as negative effects on liver metabolism, in many cases after consultation with their general practitioners (GPs). Most patients presenting with hypogonadal symptoms exhibited overweight, obesity, and/or poor lifestyle habits. These patients are encouraged to improve their lifestyles and start exercising through an educational program that was devised for this study. Patients were provided with an educational pamphlet (Supplementary Appendix SA1), including exercise suggestions as well as dietary recommendations and daily routine recommendations.

Patients were asked to fill and complete the following three questionnaires:

1. The AMS scale.¹⁶
2. The International Prostate Symptom Score (IPSS).¹⁷

3. The International Index of Erectile Function—Erectile Function Domain (IIEF-EF 5 + 1).¹⁸

At each visit, all patients are asked to complete a form for current changes in their medication, medical incidences, or other major events that have occurred since their last visits. In addition, blood pressure (BP) and heart rate are measured in each patient. Blood samples are taken from each patient and sent to a commercial laboratory (Synlab, Hamburg, Germany). The parameters are measured, and the methods are summarized in Table 1. Urine samples are also obtained from each patient. Weight and WC are measured in each patient. All patients receive an ultrasound examination (Samsung Ultrasound System H60) of the kidneys, testes, and the bladder, including measurement of residual bladder voiding volume and suprapubically of the prostate. If the ultrasound is unable to calculate the testes volume, a Prader orchidometer is used to estimate the testicular volume. A digital rectal examination (DRE) followed by a transrectal ultrasound examination of the prostate are performed in each patient. TU (1000 mg) injection is administered in the clinic by slowly injecting the medication with a duration of at least 3 min, administered by use of a 20G needle into the relaxed gluteus medius muscle of the patient. The length of the needle is usually 40 mm; however, in very obese patients, we may select a needle with a 60 or 70 mm length. The patient can choose between receiving the injection in a recumbent position and in a standing position with the leg on the injection side slightly bent to relax the gluteal muscle. The injection area is then gently massaged for about 15 sec. There is a 100% adherence to TTh, as every single injection is applied in our office and documented accordingly. TTh was temporarily interrupted in patients diagnosed with prostate cancer, but it resumed between 1 and 3 years after radical prostatectomy. There were no dropouts during the entire observation time.

Only patients who completed 2 years of treatment are included in the registry. The dropout rate during the first 2 years is estimated in a magnitude of 5%. Reasons for discontinuation of TTh are that patients' expectations were not met by the treatment during this time, and there were a few men who withdrew their consent to use their data for analysis.

Patient educational support

As stated earlier, all patients with overweight and obesity are encouraged to modify their lifestyles and

Table 1. Laboratory Methods

Parameter	Device/manufacturer	Method	Kit	Intra assay variation (%)	Inter assay variation (%)	Description
Total Testosterone	Alinity i-Module/Abbott	CMIA	2nd Generation Testosterone Reagent Kit	2.8	3.1	Utilization of multi-angle polarized scatter separation technology, laser flow cytometry, integral reticulocyte analysis, and nuclear optical count.
Hemoglobin	CELL DYN RUBY/Abbott	Photometry		0.3	1.0	Utilization of multi-angle polarized scatter separation technology, laser flow cytometry, integral reticulocyte analysis, and nuclear optical count.
Leukocytes	CELL DYN RUBY/Abbott	Flow cytometry		1.3	1.6	Utilization of multi-angle polarized scatter separation technology, laser flow cytometry, integral reticulocyte analysis, and nuclear optical count.
Erythrocytes	CELL DYN RUBY/Abbott	Flow cytometry		0.8	0.9	Utilization of multi-angle polarized scatter separation technology, laser flow cytometry, integral reticulocyte analysis, and nuclear optical count.
Thrombocytes (Platelets)	CELL DYN RUBY/Abbott	Flow cytometry		1.3	2.6	Utilization of multi-angle polarized scatter separation technology, laser flow cytometry, integral reticulocyte analysis, and nuclear optical count.
MCV	CELL DYN RUBY/Abbott	Flow cytometry		0.5	0.3	Utilization of multi-angle polarized scatter separation technology, laser flow cytometry, integral reticulocyte analysis, and nuclear optical count.
Hematocrit	BC-3000Plus/Mindray	Calculated		0.5	1.5	The machine uses the impedance method to determine WBCs, RBCs, and PLTs. It does not directly measure the hematocrit, but rather calculates hematocrit from measurements of individual RBCs sizes and counts. The hematocrit of the original sample is calculated from the number of cells (rbc) by using the following equation: Hct = number of RBCs × MCV/10.
Hematocrit	PowerSpin™ BX Centrifuge/UNICO	Microhematocrit		1.0	1.0	12,000g, 5 min
ALT	Alinity c-Module/Abbott	Enzymatic (NADH)	Alinity c Activated Alanine Aminotransferase Reagent Kit	0.7	0.9	The reaction is monitored by measuring the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD.
AST	Alinity c-Module/Abbott	Enzymatic (NADH)	Alinity c Activated Aspartate Aminotransferase Reagent Kit	0.3	0.6	The reaction is monitored by measuring the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD.
GGT	Alinity c-Module/Abbott	Enzymatic	Alinity c Gamma-Glutamyl Transferase Reagent Kit	0.4	1.1	The rate of the absorbance increase at 412 nm is directly proportional to the GGT in the sample.
Bilirubin (Total)	Alinity c-Module/Abbott	Photometric color-test	Alinity c Total Bilirubin Reagent Kit	0.7	1.3	Total (conjugated and unconjugated) bilirubin couples with a diazo reagent in the presence of a surfactant to form azobilirubin. The increase in absorbance at 548 nm due to azobilirubin is directly proportional to the total bilirubin concentration.
LDL	Alinity c-Module/Abbott	Enzymatic color-test	Alinity c Direct LDL Reagent Kit	0.7	1.5	The Alinity c Processing Module uses photometric detection technology to measure sample absorbance for the quantification of analyte concentration after an enzymatically catalyzed reaction in a buffer solution.
HDL	Alinity c-Module/Abbott	Enzymatic color-test	Alinity c Ultra HDL Reagent Kit	0.6	1.1	The Alinity c Processing Module uses photometric detection technology to measure sample absorbance for the quantification of analyte concentration after an enzymatically catalyzed reaction in a buffer solution.
Cholesterol	Alinity c-Module/Abbott	Enzymatic color-test	Alinity c Cholesterol Reagent Kit	0.7	1.0	The Alinity c Processing Module uses photometric detection technology to measure sample absorbance for the quantification of analyte concentration after an enzymatically catalyzed reaction in a buffer solution.

(continued)

Table 1. (Continued)

Parameter	Device/manufacturer	Method	Kit	Intra assay variation (%)	Inter assay variation (%)	Description
Triglycerides	Alinity c-Module/Abbott	Enzymatic color-test	Alinity c Triglyceride Reagent Kit	0.5	0.8	The Alinity c Processing Module uses photometric detection technology to measure sample absorbance for the quantification of analyte concentration after an enzymatically catalyzed reaction in a buffer solution.
PSA	Alinity i-Module/Abbott	CMIA	Alinity I Total PSA Reagent Kit	3.1	3.3	
Creatinine	Alinity c-Module/Abbott	Enzymatic color-test	Alinity c Creatinine (Enzymatic) Reagent Kit	0.6	2.4	At an alkaline pH, creatinine in the sample reacts with picrate to form a creatinine-picrate complex. The rate of increase in absorbance at 500 nm due to the formation of this complex is directly proportional to the concentration of creatinine in the sample.
Insulin—C-Peptide HBA1c	Atellica® Solution/Siemens TOSOH (HLC-723 series)/ Bioscience	CLIA HPLC		1.12 0.33	6.5 0.50	HPLC, short for high-performance liquid chromatography, is a form of column chromatography (laboratory technique used to separate mixtures) used frequently in biochemistry and analytical chemistry. It involves passing a mixture that contains the and “analyte” through a column (stationary phase), by a liquid (mobile phase) at high pressure. Cation exchange chromatography is a process that allows the separation of the mixture based on the charge properties of the molecules in the mixture. Cation exchange chromatography retains analyte molecules based on coulombic (ionic) interactions. The stationary phase surface displays negatively charged functional groups that interact with positively charged cations in the mixture.
Glucose	Alinity c-Module/Abbott	Enzymatic (HK/G6PDH)	Alinity c Glucose Reagent Kit	0.65	1.51	Glucose is phosphorylated by HK in the presence of ATP and magnesium ions to produce G-6-P and ADP. G-6-PDH specifically oxidizes G-6-P to 6-phosphogluconate with the concurrent reduction of NAD to NADH. One micromole of NADH is produced for each micromole of glucose consumed. The NADH produced absorbs light at 340 nm and can be detected spectrophotometrically as an increased absorbance.
CRP	Alinity c-Module/Abbott	Immunoturbidimetric	Alinity c CRP Vario Reagent Kit	0.8	0.8	When an antigen-antibody reaction occurs between CRP in a sample and anti-CRP antibody, which has been adsorbed to latex particles, agglutination results. This agglutination is detected as an absorbance change (572 nm), with the rate of change being proportional to the quantity of CRP in the sample.

ADP, adenosine diphosphate; ALT, alanine transaminase (formerly GPT, glutamate pyruvate transaminase); AST, aspartate transaminase (formerly GOT, glutamate oxaloacetate transaminase); ATP, adenosine triphosphate; CLIA, chemiluminescent immunoassay; CMIA, chemiluminescent microparticle immunoassay; CRP, C-reactive protein; G-6-P, glucose-6-phosphate; G-6-PDH, glucose-6-phosphate dehydrogenase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HK, hexokinase; HPLC, high-performance liquid chromatography; LDL, low-density lipoprotein; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide reduced; PSA, prostate-specific antigen; RBC, red blood cell; WBC, white blood cell; PLT, platelet.

increase their physical activity to improve their quality of life. Patients are provided with an education pamphlet (Supplementary Appendix SA1) with exercise suggestions and nutritional recommendations. Patients with diabetes are encouraged to regularly check with their diabetologist. Patients with diabetes are treated in a local diabetes center and participate in a mandatory educational program for diabetes consisting of a certified educational course on diabetes, including information on lifestyle changes to prevent progression of diabetes. Patients who do not achieve the target HbA_{1c} after ~2–3 years are asked to attend the educational courses again. Whenever an adaptation of medication is necessary, educational material and support are provided to patients who undergo medication changes. Patients in whom a secondary disease or comorbidity occurs as a result of their diabetes are provided educational materials and support regarding such comorbidities.

Assessment and follow-up

Patients receiving TTh return every 3 months for their next injection. Patients who opted not to be treated with testosterone are encouraged to visit our office between two and four times each year, depending on their medical complaints (e.g., prostatic diseases or ED). At each follow-up visit, anthropometric parameters, BP, and blood chemistry measurements are repeated.

Questions are asked about change of medication prescribed by their GPs, visits to other specialists, etc. and the answers are entered into their patient records. All electronic patient records are transferred into the registry database. Data reported by the commercial clinical laboratory in conventional units are converted to SI units. All other calculations are listed in Table 2.^{19–23}

Statistical methods

Patients who opted to be treated with testosterone return quarterly for TU injections, whereas those who opted not to be treated return at least biannually for a routine visit. Data in both groups of patients are averaged across each year of patients participating in the study. The yearly data obtained are used to assess differences between patients treated with testosterone and those who were not treated, while adjusting for possible confounding.

Adjusted multivariable analyses

In adjusted multivariable analyses, changes from baseline in parameters (weight, WC, etc.) are analyzed by using a mixed model for repeated measures in terms of treatment, visit, and treatment-by-visit interaction as fixed factors and age, WC, weight, systolic and diastolic BP, TC, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), AMS,

Table 2. Calculated Parameters

Calculated parameter	Algorithm or method
BMI	Body mass in weight (kg) divided by the square of the body height (m)
Non-HDL cholesterol	Total cholesterol minus HDL cholesterol
Remnant cholesterol	Total cholesterol minus LDL cholesterol minus HDL cholesterol
HOMA-IR	Fasting insulin (U/L) × fasting glucose (mmol/L) / 22.5
HOMA-beta	$20 \times \text{Fasting insulin (U/L)} / \text{fasting glucose (mmol/L)} - 3.5$
HOMA2-IR	By use of the HOMA2 calculator provided by the Oxford University: www.dtu.ox.ac.uk/homacalculator/download.php
HOMA2_%S	By use of the HOMA2 calculator provided by the Oxford University: www.dtu.ox.ac.uk/homacalculator/download.php
HOMA2_%B	By use of the HOMA2 calculator provided by the Oxford University: www.dtu.ox.ac.uk/homacalculator/download.php
Matsuda index (ISI)	By use of the web calculator for Matsuda index: http://mmatsuda.diabetes-smc.jp/MIndex.html
Increment AUC glucose	By use of the web calculator for Matsuda index: http://mmatsuda.diabetes-smc.jp/MIndex.html
Increment AUC C-peptide	By use of the web calculator for Matsuda index: http://mmatsuda.diabetes-smc.jp/MIndex.html
IGI	By use of the web calculator for Matsuda index: http://mmatsuda.diabetes-smc.jp/MIndex.html
Disposition index	By use of the web calculator for Matsuda index: http://mmatsuda.diabetes-smc.jp/MIndex.html
MCH	(hemoglobin/erythrocytes) × 10
MCHC	(Hemoglobin/hematocrit) × 100
Pulse pressure	Systolic BP minus diastolic BP
RPP	Systolic BP × heart rate / 100
VAI	According to the equation published by Amato et al. ¹⁹
ABSI	According to the equation published by Krakauer and Krakauer ²⁰
LAP	According to the equation published by Kahn ²¹
FLI	According to the equation published by Bedogni et al. ²²
eGFR	According to the equation published by the Modification of Diet in Renal Disease Study Group ²³

ABSI, A Body Shape Index; eGFR, estimated glomerular filtration rate; FLI, Fatty Liver Index; HOMA-IR, homeostasis model assessment of insulin resistance; IGI, insulinogenic index; ISI, insulin sensitivity index; LAP, lipid accumulation product; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RPP, rate pressure product; VAI, visceral adiposity index.

glucose, and baseline values of the analysis parameter as covariates. Baseline parameter values are the values recorded before the first TU injection. A random effect is included in the model for the intercept. Adjusted mean differences between treatment groups at each time point and across time within each treatment group are estimated by using estimate statements in SAS PROC MIXED, Version 9.3 (2011) provided by SAS Institute, Inc., Cary, North Carolina.

Propensity matching analyses

For some analyses, we used propensity matching. Our general strategy for propensity matching of those on active treatment to those who remained untreated included calculating propensity score based on logistic regression model and selecting matching pairs (or one to many) based on the score. The matching was performed by “nearest neighbor” selection with caliper set to a fraction of standard deviation (SD) of the propensity score. Several scenarios were considered. We first attempted to create propensity score based on the following variables: age, WC, weight, SBP and DBP, TC, HDL, LDL, TG, AMS, and glucose. That model discriminated between active drugs and those who remained untreated too well, resulting in a very small overlap of propensity score distributions. We then created propensity score based on the following variables: age, BMI, and WC. The 1:1 matching was done by choosing the nearest neighbor match with the caliper set to 0.2 SD of the propensity score. In addition, we explored a 1:1 matching setting caliper to 0.5 SD and 1:2 matching with 0.2 SD and 0.5 SD calipers. These additional scenarios did not result in noticeable gain of the matched sample. Analyses were performed by using SAS 9.3 software (SAS Institute, Cary, North Carolina).

Results

Table 3 describes the baseline characteristics, comorbidities, and concomitant medications of all patients (T-treated or -untreated), categorized into patients with functional hypogonadism and those with primary hypogonadism. Men with primary hypogonadism were younger than men with functional hypogonadism. Forty-seven (61.8%) of men with primary hypogonadism had Klinefelter’s syndrome. Most of these patients had been referred by orthopedists with a suspicion of hypogonadism, because they had presented with back pain and osteoporosis at a young age, with the youngest of these patients being 33 years old.

Results from this registry study were published since 2007, partly pooled with a parallel registry of a similar design.^{24–28} Table 4 shows the bibliography of papers published from this registry. So far, six papers were published in journals of Endocrinology, five in Urology, four in Andrology, four in Obesity, three in General Medicine, three in Diabetes, and two in Cardiology.

Of note, the benefits of long-term effects of TTh in hypogonadal patients were exemplified by reduced body weight (Fig. 1A), WC (Fig. 1B), and BMI (Fig. 1C).²⁸ More importantly, the impact of long-term TTh on obesity in comparison with untreated controls is shown in Figure 2.²⁹ These findings were not observed in prior studies, because there were no long-term studies with TTh before this registry. Moreover, our recent publication that one third of men with TD and type 2 diabetes experience remission of diabetes is of great clinical importance (Fig. 3).³⁰

The findings from this registry study have contributed important clinical knowledge regarding treatment of TD and the beneficial health effects that were not seen in short-term studies. In terms of safety of TTh, reductions in mortality, myocardial infarctions, strokes, and prostate cancer became apparent after less than 8 years of follow-up,^{31,32} and those early results were confirmed and became more robust with continued observation time (Fig. 4).³³

Discussion

Our registry is the first observational study carried out over more than 15 years in a single urological practice. Since the initiation of the study in 2004, all patients have been under the care of the same urologist (A.H.) so that investigator bias can be excluded. Because there are no randomized, placebo-controlled studies exceeding 3 years’ duration, the registry revealed new insights that had been unpredictable in the field of androgen therapy.

One unexpected finding was that men with hypogonadism undergoing TTh lose weight. This became apparent for the first time when 5-year data were analyzed.³⁴ The weight loss is slow but progressive and usually remains below 5% in the first year of TTh.³⁴ Also, men who are obese lose more weight than men who are overweight who lose more weight than men of normal weight.²⁹ In almost all RCTs, obesity was not an inclusion criterion and populations were mixed regarding their baseline BMI, which may explain why weight loss was not described in

Table 3. Baseline Characteristics, Comorbidities, and Concomitant Medication at Baseline in Men with Functional Hypogonadism and in Men with Primary Hypogonadism

	All functional hypogonadism (n=773)	Functional hypogonadism treated (n=380)	Functional hypogonadism untreated (n=393)	p-Value between groups	All primary hypogonadism (n=85)	Primary hypogonadism treated (n=76)	Primary hypogonadism untreated (n=9)	p-Value between groups
Mean baseline age (years)	61.5±6.1	59.1±6.3	63.8±4.8	<0.0001	52.3±96.1	51.0±8.8	63.0±3.0	0.0001
Mean follow-up (years)	9.0±2.5	8.7±2.7	9.4±2.3		7.8±1.9	8.0±1.8	6.8±2.2	
Median follow-up (years)	10	10	10		9	9	7	
Testosterone								
Total testosterone (nmol/L)	9.6±1.4	9.6±1.5	9.7±1.1	0.1580	9.3±1.7	9.3±1.7	9.5±1.1	0.7288
Anthropometric parameters								
Weight (kg)	100.7±16.4	106.3±17.1	95.2±13.5	<0.0001	97.8±14.7	97.0±14.2	104.3±18.4	0.1606
Waist circumference (cm)	110.4±12.5	110.1±13.1	110.8±11.8	0.4078	105.4±12.1	102.7±7.7	128.3±18.3	<0.0001
BMI (kg/m ²)	32.5±5.7	34.2±5.4	30.8±5.5	<0.0001	30.0±5.1	29.4±4.5	34.5±7.2	0.0040
Height (cm)	176.6±3.3	176.3±3.0	176.9±3.7	0.0177	181.2±4.7	181.8±4.5	176.4±4.4	0.0010
Waistheight ratio	0.63±0.07	0.62±0.07	0.63±0.07	0.6295	0.58±0.08	0.57±0.05	0.73±0.12	<0.0001
VAI	4.6±2.4	5.0±2.5	4.2±2.2	<0.0001	4.5±1.4	4.5±1.3	4.3±2.1	0.6531
Normal weight (proportion), n (%)	56 (7.2)	19 (5.0)	37 (9.4)	<0.0001	8 (9.4)	8 (10.5)	0 (0.0)	0.1110
Overweight (proportion), n (%)	246 (31.8)	85 (22.4)	161 (41.0)	<0.0001	42 (49.4)	38 (50.0)	4 (44.4)	0.1110
Obesity (proportion), n (%)	471 (60.9)	276 (72.7)	195 (49.6)	<0.0001	35 (41.2)	30 (39.5)	5 (55.5)	0.1110
Obesity class I (proportion), n (%)	0	99 (26.1)	132 (33.6)	<0.0001	22 (25.9)	21 (27.6)	1 (11.1)	0.1110
Obesity class II (proportion), n (%)	164 (21.2)	118 (31.1)	46 (11.7)	<0.0001	7 (8.2)	5 (6.6)	2 (22.2)	0.1110
Obesity class III (proportion), n (%)	76 (9.8)	59 (15.5)	17 (4.3)	<0.0001	6 (7.1)	4 (5.3)	2 (22.2)	0.1110
Glycemic control								
Fasting glucose (mmol/L)	6.2±1.2	6.5±1.4	5.8±0.7	<0.0001	5.7±0.9	5.6±0.9	6.4±0.8	0.0161
HbA1c (%)	7.0±1.9	8.0±2.1	6.3±1.4	<0.0001	6.2±1.6	6.0±1.5	7.2±1.7	0.0288
Fasting insulin (μU/mL)	25.9±6.6	26.4±8.4	25.3±2.9	0.1468	27.9±3.8	29.8±3.6	26.3±3.4	0.1361
HOMA-IR	8.7±2.3	10.1±2.1	7.2±1.3	<0.0001	9.6±2.7	11.5±2.9	8.1±1.5	0.0350
BP and hemodynamic parameters								
Systolic BP (mmHg)	148.8±16.7	155.7±16.4	142.2±14.0	<0.0001	137.3±14.2	136.6±13.9	143.1±16.3	0.1918
Diastolic BP (mmHg)	87.1±11.9	92.9±11.8	81.6±9.0	<0.0001	81.7±10.1	81.4±9.5	84.8±14.4	0.3392
Heart rate (bpm)	77.5±4.5	78.3±3.9	76.8±4.8	<0.0001	76.9±3.9	76.5±3.8	80.2±3.9	0.0065
Pulse pressure (mmHg)	61.6±8.1	62.7±8.4	60.6±7.8	0.0004	55.5±6.8	55.2±6.9	58.3±4.9	0.1945
RPP	11537±1658	12172±1741	10923±1309	<0.0001	10577±1444	10467±1393	11503±1620	0.0412
Lipids								
Total cholesterol (mmol/L)	7.3±1.4	8.0±1.1	6.6±1.3	<0.0001	7.1±0.9	7.1±0.8	7.1±1.3	0.8395
HDL cholesterol (mmol/L)	1.1±0.4	1.0±0.3	1.2±0.5	<0.0001	1.0±0.3	0.9±0.3	1.2±0.4	0.0014
LDL cholesterol (mmol/L)	3.9±1.2	4.3±0.9	3.5±1.4	<0.0001	4.0±0.9	4.1±0.9	3.3±0.6	0.0094
Triglyceride (mmol/L)	3.1±0.6	3.2±0.6	3.0±0.5	<0.0001	2.8±0.4	2.8±0.4	3.0±0.6	0.2977
Non-HDL cholesterol (mmol/L)	6.1±1.5	6.9±1.1	5.4±1.4	<0.0001	6.2±0.9	6.2±0.8	5.9±1.6	0.02404
Remnant cholesterol (mmol/L)	2.2±1.0	2.6±1.0	1.9±0.9	<0.0001	2.2±0.8	2.1±0.7	2.5±1.3	0.1302
LAP (cm×mmol/L)	143.7±60.3	149.6±67.4	138.0±51.9	0.0075	115.6±46.0	107.0±34.4	188.1±67.4	<0.0001
Questionnaires								
AMS	46.5±10.0	53.0±9.5	40.3±5.6	<0.0001	47.8±9.6	49.1±9.3	36.6±2.8	0.0001
IPSS	5.9±3.1	7.1±3.6	4.8±1.9	<0.0001	3.4±3.0	3.1±3.0	5.9±0.8	0.0084
IIEF-EF	18.6±4.9	17.4±5.8	19.8±3.4	<0.0001	18.7±5.8	18.7±6.0	18.0±3.6	0.7249
Prostate parameters								
Prostate volume (mL)	33.7±8.0	32.2±9.3	35.2±6.1	<0.0001	22.8±10.5	20.9±9.3	39.1±4.6	<0.0001
PSA (ng/mL)	2.3±1.2	2.1±1.0	2.5±1.3	<0.0001	1.2±1.3	0.9±0.9	3.7±1.5	<0.0001

(continued)

Table 3. (Continued)

	All functional hypogonadism (n = 773)	Functional hypogonadism treated (n = 380)	Functional hypogonadism untreated (n = 393)	p-Value between groups	All primary hypogonadism (n = 85)	Primary hypogonadism treated (n = 76)	Primary hypogonadism untreated (n = 9)	p-Value between groups
Erythropoiesis								
Hemoglobin (g/dL)	14.6±0.6	14.4±0.7	14.7±0.5	<0.0001	14.7±0.5	14.7±0.5	14.9±0.7	0.1605
Hematocrit (%)	45.0±2.0	44.1±2.2	45.8±1.3	<0.0001	44.9±1.9	44.8±1.9	46.4±1.1	0.0101
Inflammatory markers								
CRP (mg/dL)	3.5±5.4	5.7±6.9	1.4±1.3	<0.0001	3.4±5.0	3.4±5.2	2.6±2.7	0.6370
Liver function								
AST (U/L)	33.2±13.9	40.0±15.2	26.6±8.1	<0.0001	34.1±12.2	33.2±12.3	42.3±7.1	0.0314
ALT (U/L)	38.8±13.6	42.9±15.1	30.8±8.5	<0.0001	36.1±13.0	34.9±13.1	46.2±6.6	0.0127
AST:ALT ratio	0.90±0.12	0.93±0.15	0.86±0.05	<0.0001	0.96±0.16	0.96±0.17	0.91±0.04	0.3881
FLI	86.8±13.0	89.4±11.9	84.1±13.5	<0.0001	80.7±13.4	79.1±13.1	94.6±5.2	0.0007
Renal function								
Creatinine	0.96±0.15	0.92±0.15	1.00±0.14	<0.0001	0.90±0.09	0.88±0.07	1.02±0.16	<0.0001
eGFR	81.4±12.6	85.7±11.8	77.3±12.0	<0.0001	90.1±10.2	91.7±8.4	76.1±13.8	<0.0001
Comorbidities at baseline, n (%)								
Type 2 diabetes	345 (44.6)	173 (45.5)	172 (43.8)	0.6226	11 (12.9)	5 (6.6)	6 (66.7)	<0.0001
Type 1 diabetes	21 (2.7)	21 (5.5)	0 (0.0)	<0.0001	0 (0.0)	0 (0.0)	0 (0.0)	1.0
Hypertension	664 (85.9)	362 (95.3)	302 (76.8)	<0.0001	56 (65.9)	52 (68.4)	4 (44.4)	0.0014
Prior cardiovascular disease ^a	217 (28.1)	99 (26.1)	118 (30.0)	0.2191	9 (10.6)	4 (5.3)	5 (55.6)	<0.0001
Prior myocardial infarction	105 (13.6)	64 (16.8)	41 (10.4)	0.0093	6 (7.1)	3 (3.9)	3 (33.3)	0.0011
Prior stroke	55 (7.1)	24 (6.3)	31 (7.9)	0.3953	0 (0.0)	0 (0.0)	0 (0.0)	1.0
Prior coronary artery disease	143 (18.5)	53 (13.9)	90 (22.9)	0.0014	6 (7.1)	3 (3.9)	3 (33.3)	0.0011
ED	744 (96.3)	354 (93.2)	390 (99.2)	<0.0001	72 (84.7)	63 (82.9)	9 (100.1)	0.0411
Osteoporosis	59 (7.6)	26 (6.8)	33 (8.4)	0.4157	46 (54.1)	46 (60.5)	0 (0.0)	0.0006
Concomitant medication, n (%)								
Antidiabetic medication	362 (46.8)	190 (50.0)	172 (43.8)	0.0825	11 (12.9)	5 (6.6)	6 (66.7)	<0.0001
Antihypertensive medication	364 (47.1)	223 (58.7)	141 (35.9)	<0.0001	14 (16.5)	10 (13.2)	4 (44.4)	0.0013
Statins	414 (53.6)	189 (49.7)	225 (57.3)	0.0362	15 (17.6)	10 (13.2)	5 (55.6)	0.0016
PDE5 inhibitors	184 (23.8)	97 (25.5)	87 (22.1)	<0.01	15 (17.6)	12 (15.8)	3 (33.3)	0.1917
Alpha-blockers	366 (47.3)	168 (44.2)	197 (50.1)	0.1498	13 (15.3)	5 (6.6)	8 (88.9)	<0.0001
5- α -reductase inhibitors	43 (5.6)	10 (2.6)	33 (8.4)	0.0005	3 (3.5)	0 (0.0)	3 (33.3)	<0.0001
Klinefelter's syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1.0	47 (55.3)	47 (61.8)	0 (0.0)	0.0004
Smoking	289 (37.4)	15 (38.3)	144 (36.6)	0.6425	42 (49.4)	37 (48.7)	5 (55.6)	0.6966

p-values in bold are statistically significant.

Data are shown as means±SD.

^aCardiovascular disease was defined as prior myocardial infarction, stroke, or diagnosis of coronary artery disease.

AMS, Aging Males' Symptoms; ED, erectile dysfunction; IIEF-EF, International Index of Erectile Function—Erectile Function Domain; IPSS, International Prostate Symptom Score; SD, standard deviation.

Table 4. Bibliography

Papers published on registry study until July 8, 2020

1. F Saad, L Gooren, A Haider, A Yassin
An exploratory study of the effects of 12 month administration of the novel long-acting testosterone undecanoate on measures of sexual function and the metabolic syndrome
Arch Androl. 2007;53(6):353–357.^a
2. A Haider, LJ Gooren, P Padungtod, F Saad
Concurrent improvement of the metabolic syndrome and lower urinary tract symptoms upon normalisation of plasma testosterone levels in hypogonadal elderly men
Andrologia. 2009;41(1):7–13.
3. A Haider, LJ Gooren, P Padungtod, F Saad
Beneficial effects of 2 years of administration of parenteral testosterone undecanoate on the metabolic syndrome and on non-alcoholic liver steatosis and C-reactive protein
Horm Mol Biol Clin Invest. 2010;1(1):27–33.
4. A Haider, LJ Gooren, P Padungtod, F Saad
A safety study of administration of parenteral testosterone undecanoate to elderly men over minimally 24 months
Andrologia. 2010;42(6):349–355.
5. A Haider, W Kurtz, EJ Giltay, LJ Gooren, F Saad
Administration of testosterone to elderly hypogonadal men with Crohn's disease improves their Crohn's Disease Activity Index: A pilot study
Horm Mol Biol Clin Invest. 2010;2(3):287–292.
6. A Haider, LJ Gooren, P Padungtod, F Saad
Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate
Exp Clin Endocrinol Diabetes. 2010;118(3):167–171.
7. F Saad, A Haider, EJ Giltay, LJ Gooren
Age, obesity and inflammation at baseline predict the effects of testosterone administration on the metabolic syndrome
Horm Mol Biol Clin Invest. 2011;6(1):193–199.
8. F Saad, A Haider, G Doros, A Traish
Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss
Obes 2013;21(10):1975–1981.
9. A Haider, A Yassin, G Doros, F Saad
Effects of long-term testosterone therapy on patients with "diabesity": Results of observational studies of pooled analyses in obese hypogonadal men with type 2 diabetes
Int J Endocrinol. 2014;2014:683515.^a
10. A Haider, F Saad, G Doros, L Gooren
Hypogonadal obese men with and without diabetes mellitus type 2 lose weight and show improvement in cardiovascular risk factors when treated with testosterone: An observational study
Obes Res Clin Pract. 2014;8(4):e339–e349.
11. A Haider, U Meergans, A Traish, F Saad, G Doros, P Lips, L Gooren
Progressive improvement of T-scores in men with osteoporosis and subnormal serum testosterone levels upon treatment with testosterone over six years
Int J Endocrinol. 2014;2014:496948.
12. AM Traish, A Haider, G Doros, F Saad
Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: An observational, long-term registry study
Int J Clin Pract. 2014;68(3):314–329.
13. A Haider, M Zitzmann, G Doros, H Isbarn, P Hammerer, A Yassin
Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: Observations from 5-year median followup of 3 registries
J Urol. 2015;193(1):80–86.^a
14. F Saad, A Yassin, A Haider, G Doros, L Gooren
Elderly men over 65 years of age with late-onset hypogonadism benefit as much from testosterone treatment as do younger men
Korean J Urol. 2015;56(4):310–317.^a

(continued)

Table 4. (Continued)

Papers published on registry study until July 8, 2020

15. M Nasser, A Haider, F Saad, W Kurtz, G Doros, M Fijak, L Vignozzi, L Gooren
Testosterone therapy in men with Crohn's disease improves the clinical course of the disease: Data from long-term observational registry study
Horm Mol Biol Clin Invest. 2015;22(3):111–117.
16. A Haider, A Yassin, KS Haider, G Doros, F Saad, G Rosano
Men with testosterone deficiency and a history of cardiovascular diseases benefit from long-term testosterone therapy: Observational, real-life data from a registry study
Vasc Health Risk Manag. 2016;12(6):251–261.^a
17. F Saad, A Yassin, G Doros, A Haider
Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: Observational data from two registry studies
Int J Obes. 2016;40(1):162–170.^a
18. F Saad, A Haider, L Gooren
Hypogonadal men with psoriasis benefit from long-term testosterone replacement therapy—A series of 15 case reports
Andrologia. 2016;48(3):341–346.
19. AM Traish, A Haider, KS Haider, G Doros, F Saad
Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism: A real-life observational registry study setting comparing treated and untreated (control) groups
J Cardiovasc Pharmacol Therap. 2017;22(5):414–433.
20. KS Haider, A Haider, G Doros, A Traish
Long-term testosterone therapy improves urinary and sexual function, and quality of life in men with hypogonadism: Results from a propensity matched subgroup of a controlled registry study
J Urol. 2018;199(1):257–265.
21. M Hanefeld, A Haider, M Zitzmann, F Saad
Remission of type 2 diabetes after long-term testosterone therapy
Diabetes, Stoffwechsel und Herz. 2018;27(1):33–37
22. F Saad, G Doros, KS Haider, A Haider
Hypogonadal men with moderate-to-severe lower urinary tract symptoms have a more severe cardiometabolic risk profile and benefit more from testosterone therapy than men with mild lower urinary tract symptoms
Investig Clin Urol. 2018;59(6):399–409.
23. X Zhang, Y Zhong, F Saad, K Haider, A Haider, X Xu
Clinically occult prostate cancer cases may distort the effect of testosterone replacement therapy on risk of PCa
World J Urol. 2019;37(10):2091–2097.
24. F Saad, M Caliber, G Doros, KS Haider, A Haider
Long-term treatment with testosterone undecanoate injections in men with hypogonadism alleviates erectile dysfunction and reduces risk of major adverse cardiovascular events, prostate cancer, and mortality
Aging Male. 2020;23(1):81–92.
25. X Zhang, Y Zhong, F Saad, KS Haider, A Haider, A Clendenin, X Xu
Testosterone therapy may reduce prostate cancer risk due to testosterone deficiency at a young age via stabilizing serum testosterone levels
Aging Male. 2020;23(2):112–118.
26. F Saad, G Doros, KS Haider, A Haider
Differential effects of 11 years of long-term injectable testosterone undecanoate therapy on anthropometric and metabolic parameters in hypogonadal men with normal weight, overweight and obesity in comparison with untreated controls: Real-world data from a controlled registry study
Int J Obes. 2020;44(6):1264–1278.
27. KS Haider, A Haider, F Saad, G Doros, M Hanefeld, S Dhindsa, P Dandona, A Traish
Remission of type 2 diabetes following long-term treatment with injectable testosterone undecanoate in patients with hypogonadism and type 2 diabetes: 11-year data from a real-world registry study
Diabetes Obes Metab. 2020;22(11):2055–2068.

Papers published on registry study until July 22, 2020.

^aPapers reporting pooled analyses from the current registry study in combination with parallel registry studies

FIG. 1. Reductions of (A) weight, (B) waist circumference, and (C) BMI in 411 hypogonadal men receiving long-term testosterone treatment. All values are shown as mean $\pm$ SE. From: Saad et al.²⁸ BMI, body mass index; SE, standard error.

FIG. 2. Changes of (A) weight (kg), (B) weight (%), (C) BMI, and (D) waist circumference in men with testosterone deficiency and normal weight, overweight, and obesity after treatment with testosterone undecanoate injections, compared with untreated men (Control). Data from: Saad et al.²⁹

those trials. However, more recently, our results were confirmed in a small RCT with 2 years' duration in men with obesity and type 2 diabetes.³⁵ Another controlled study in mostly obese men treated with testosterone after an ischemic stroke also resulted in profound weight loss after 2 years, of which most was maintained over 5 years whereas patients who discontinued TTh after 2 years regained all the weight they had previously lost at 5 years.³⁶ Francomano demonstrated progressive reductions in weight and WC over 5 years in obese men with metabolic syndrome compared with an untreated control group.⁶ Hackett et al. could show that a reduction in WC was progressive over 5 years in the follow-up of a study in men with type 2 diabetes mellitus (T2DM) that had started as an RCT.³⁷ The magnitude of weight loss is clearly a function of treatment duration³⁸ but may also depend on formulation and the route of administration with testosterone injections having a greater effect than topical preparations.³⁹

Because the majority of our patients were overweight or obese, it was not surprising to see a substantial proportion of men with T2DM. Although some studies had shown benefits of treating men with TD and T2DM with testosterone, the fact that long-term TTh could lead to remission of T2DM in one third of the patients after a mean treatment duration of more than 8 years did come unexpectedly.³⁰ These profound improvements resulted in more referrals from diabetologists to our urological office for assessing TD and treating men with T2DM with TTh if indicated.

Another unexpected result was the improvement noted in patients with inflammatory bowel disease (IBD). After the local hospital had realized that a few men with Crohn's disease receiving TTh were benefiting from this treatment, they started assessing TD in these patients and referring men with TD to the urologist for TTh. Over time, 74 patients with Crohn's disease and two with ulcerative colitis were included in the

Fig. 2. (Continued).

FIG. 3. Proportion of patients achieving remission, NGR, or HbA_{1c} targets of 6.5% and 7.0%, respectively, in patients with testosterone deficiency and type 2 diabetes with ($n=178$) and without ($n=178$) testosterone therapy. From: Haider et al.³⁰ NGR, normal glucose regulation.

FIG. 4. Adverse events (%) in patients with testosterone deficiency following up to 8 years with ($n = 360$) and without ($n = 296$) testosterone therapy (left) and following up to 12 years with ($n = 412$) and without ($n = 393$) testosterone therapy (right). Data from: (left) Traish et al.³¹; Haider et al.³² (right); Saad et al.³³ CTRL, control group; T-group, testosterone-treated group.

registry, and without exception all improved on TTh.⁴⁰ Suspecting that this effect could be of a more general nature in autoimmune diseases, we looked for other autoimmune diseases and identified 17 men with psoriasis whose response to TTh was very similar to that seen in IBD patients.⁴¹ The anti-inflammatory effects of testosterone have recently been discussed in a comprehensive review,⁴² however testosterone is rarely used to clinically treat inflammatory diseases. As more evidence becomes available, we expect that this clinical area will be the new front of TTh.

Because considerable concerns arose suggesting that TTh may cause prostate cancer or activate occult prostate cancer, much attention was paid to prostate examinations. Patients' prostate-specific antigen (PSA) levels were measured up to four times per year, and transrectal ultrasound and DREs were performed at least twice a year. Decisions about prostate biopsies were always made by the same clinician (A.H.) so that investigator bias can be excluded. With the long-term follow-up, a better understanding of the relationship between TTh and prostate cancer became available. Not only was it reassuring to demonstrate that there was no increased risk of prostate can-

cer in men receiving TTh,²⁵ but we also noted that prostate cancer always occurred during the first 18 months of TTh⁴³ and the hypothesis was supported that maintaining stable testosterone levels could be protective.⁴⁴

It should be noted that the UK Androgen Study reported the 25 years' experience with TTh of a single center in the United Kingdom with various androgen preparations, also concluding that long-term TTh was safe with regard to prostate and cardiovascular function.⁴⁵

We firmly believe that the use of the three-monthly TU injections is essential in our registry, as it allows for complete control of medication adherence. Every single injection is administered in our office and documented. This level of adherence cannot be achieved with any preparation that is self-administered by the patient. Moreover, the intramuscular route of administration excludes any potential problems with absorption that may be experienced with transdermal application, particularly in patients with obesity.⁴⁶ The superior effectiveness of intramuscular compared with transdermal TTh has been demonstrated by Skinner et al. and is consistent with our own clinical

experience.³⁹ Therefore, it may not be possible to extrapolate results from our registry study to the use of other testosterone preparations.

An interesting development in the field was that TTh affects many medical specialties. Originally, testosterone was believed to primarily play a role in sexual function and used in endocrinology, urology, andrology, and sexual medicine to treat patients with sexual dysfunction and infertility. TTh has now made its way into diabetology, cardiology, gastroenterology, dermatology, psychology, and the emerging field of obesity, which, in turn, affects almost all medical disciplines.

It is rewarding to note that other researchers have expressed an interest in using our data for their own analyses, and collaborations have been established with Texas A&M University in College Station, TX, USA, and University Hospitals Birmingham NHS Foundation Trust, Good Hope Hospital, Birmingham, United Kingdom.

Limitations and strengths

As with all observational studies and registries, randomization of patients is neither expected nor feasible, in particular in an office setting where patients expect to be treated. We must note that a substantial proportion of patients opted against TTh. By adjusting for baseline differences between groups or performing propensity matching, the best possible measures have been taken to achieve robust results. A limitation of our study is that we do not have information on adherence to concomitant medication or to the lifestyle changes recommended to our patients. Other limitations of the study are the lack of untreated patients in IBD, psoriasis, type 1 diabetes, and Klinefelter's syndrome for ethical considerations. We have not attempted to include a trial registration, because duration and clinical significance of the study exceeded expectations by far.

The strengths of the study are its long duration, the real-life patient population that was only selected for the presence of symptomatic TD, and the fact that there is no investigator bias in our setting, which was managed exclusively by a single urologist (A.H.). This has resulted in trustful patient–physician relationships, in many cases developed over decades. Another strength of this registry study is the large number of patients recruited concomitant with the highest possible level of medication adherence. Because injections of TU have to be applied in the physician's office, every single administration is documented.

Outlook

As the study is ongoing, we will continue to perform further analyses. These may include studying additional subgroups as well as other aspects such as the impact of concomitant medications, for instance in patients with T2DM, hypertension, and dyslipidemia.

In summary, our registry study has provided new insights in the field of TTh, particularly in regard to the time course of treatment and patients' and physicians' expectations. Beyond confirming the safety of TTh, we provided further evidence that TTh can reduce mortality and major adverse cardiovascular events. The registry is ongoing and will continue to deliver long-term real-world data.

Acknowledgments

The authors thank all patients who participated in the study. The work described in this article received partial financial support for data entry and statistical analyses from Bayer AG, Berlin, Germany, manufacturer of the testosterone preparation used in this study.

Author Contributions

K.S.H. and A.H. treated the patients and performed the data entry. A.H. and F.S. designed the study and collected the data. GD performed the statistical analyses. K.S.H., A.H., and F.S. interpreted the data and wrote and reviewed the article.

Author Disclosure Statement

K.S.H. and A.H. have received partial financial compensation for data entry, travel grants and speaker honoraria from Bayer AG. G.D. received payment for statistical analyses from Bayer AG. F.S. is a consultant to Bayer AG.

Funding Information

Initially, the study was unfunded. After ~4 years, Bayer AG (then Schering AG) contributed partial funding for statistical analyses and data entry, as well as travel grants for presentations of results (A.H., K.S.H.).

Supplementary Material

Supplementary Appendix SA1

References

1. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: Results from a meta-analysis study. *Eur J Endocrinol.* 2016;174(3):R99–R116.

2. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab.* 1999;84(6):1966–1972.
3. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab.* 2004;89(2): 503–510.
4. Basaria S, Harman SM, Travison TG, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels. *J Am Med Assoc.* 2015; 314(6):570–581.
5. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab.* 2004;9(5):2085–2098.
6. Francomano D, Ilacqua A, Bruzziches R, Lenzi A, Aversa A. Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome. *Urology* 2014;83(1):167–174.
7. Kaptechuk TJ. The double-blind, randomized, placebo-controlled trial: Gold standard or golden calf? *J Clin Epidemiol.* 2001;54(6): 541–549.
8. Cohen AT, Goto S, Schreiber K, Torp-Pedersen C. Why do we need observational studies of everyday patients in the real-life setting? *Eur Heart J Suppl.* 2015;17(Suppl. D):D2–D8.
9. Seidell JC, Björntorp P, Sjöström L, Kvist H, Sannerstedt R. Visceral fat accumulation in men is positively associated with insulin, glucose and C-peptide levels, but negatively with testosterone levels. *Metabolism.* 1990;39(9):897–901.
10. Zhao B, Hong Z, Wei Y, Yu D, Xu J, Zhang W. Erectile dysfunction predicts cardiovascular events as an independent risk factor: A systematic review and meta-analysis. *J Sex Med.* 2019;16(7):1005–1017.
11. Heinemann LAJ, Saad F, Heinemann K, Thai DM. Can results of the Aging Males' Symptoms (AMS) scale predict those of screening scales for androgen deficiency? *Aging Male.* 2004;7(3):211–218.
12. Yeap BB, Wu FCW. Clinical practice update on testosterone therapy for male hypogonadism: Contrasting perspectives to optimize care. *Clin Endocrinol.* 2019(1);90:56–65.
13. Jais A, Brüning JC. Hypothalamic inflammation in obesity and metabolic disease. *J Clin Invest.* 2017;127(1):24–32.
14. Morelli A, Sarchielli E, Comeglio P, et al. Metabolic syndrome induces inflammation and impairs gonadotropin-releasing hormone neurons in the preoptic area of the hypothalamus in rabbits. *Mol Cell Endocrinol.* 2014;382(1):107–119.
15. Zitzmann M, Nieschlag E, Traish A, Kliesch S. Testosterone treatment in men with classical vs. functional hypogonadism: A 9-year registry. *J Endocr Soc.* 2019;3(Suppl. 1):SUN-222.
16. Heinemann LAJ, Zimmermann T, Vermeulen A, Thiel C, Hummel W. A new 'aging males' symptoms' rating scale. *Aging Male.* 1999;2:105–114.
17. Barry MJ, Fowler Jr FJ, O'Leary MP, et al. The American Urological Association Symptom Index for Benign Prostatic Hyperplasia. The Measurement Committee of the American Urological Association. *J Urol.* 1992; 148(5):1549–1557.
18. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urol.* 1999;54:346–351.
19. Amato MC, Giordano C, Galia M, et al. Visceral Adiposity Index. A reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care.* 2010;33(4):920–922.
20. Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. *PLoS ONE.* 2012;7(7): e39504.
21. Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: A population-based comparison. *BMC Cardiovasc Disorders.* 2005;5:26.
22. Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: A simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol.* 2006;6:33.
23. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann Int Med.* 1999;130(6):461–470.
24. Haider A, Yassin A, Doros G, Saad F. Effects of long-term testosterone therapy on patients with "diabesity": Results of observational studies of pooled analyses in obese hypogonadal men with type 2 diabetes. *Int J Endocrinol.* 2014;2014:683515.
25. Haider A, Zitzmann M, Doros G, Isbarn H, Hammerer P, Yassin A. Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: Observations from 5-year median followup of 3 registries. *J Urol.* 2015; 193(1):80–86.
26. Saad F, Yassin A, Haider A, Doros G, Gooren L. Elderly men over 65 years of age with late-onset hypogonadism benefit as much from testosterone treatment as do younger men. *Korean J Urol.* 2015;56(4): 310–317.
27. Haider A, Yassin A, Haider KS, Doros G, Saad F, Rosano G. Men with testosterone deficiency and a history of cardiovascular diseases benefit from long-term testosterone therapy: Observational, real-life data from a registry study. *Vasc Health Risk Manag.* 2016;12(6): 251–261.
28. Saad F, Yassin A, Doros G, Haider A. Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: Observational data from two registry studies. *Int J Obes.* 2016;40(1):162–170.
29. Saad F, Doros G, Haider KS, Haider A. Differential effects of 11 years of long-term injectable testosterone undecanoate therapy on anthropometric and metabolic parameters in hypogonadal men with normal weight, overweight and obesity in comparison with untreated controls: Real-world data from a controlled registry study. *Int J Obes.* 2020;44(6): 1264–1278.
30. Haider KS, Haider A, Saad F, et al. Remission of type 2 diabetes following long-term treatment with injectable testosterone undecanoate in patients with hypogonadism and type 2 diabetes: 11-year data from a real-world registry study. *Diabetes Obes Metab.* 2020;22(11):2055–2068.
31. Traish AM, Haider A, Haider KS, Doros G, Saad F. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism: A real-life observational registry study setting comparing treated and untreated (control) groups. *J Cardiovasc Pharmacol Therap.* 2017;22(5):414–433.
32. Haider KS, Haider A, Doros G, Traish A. Long-term testosterone therapy improves urinary and sexual function, and quality of life in men with hypogonadism: Results from a propensity matched subgroup of a controlled registry study. *J Urol.* 2018;199(1):257–265.
33. Saad F, Caliber M, Doros G, Haider KS, Haider A. Long-term treatment with testosterone undecanoate injections in men with hypogonadism alleviates erectile dysfunction and reduces risk of major adverse cardiovascular events, prostate cancer, and mortality. *Aging Male.* 2020; 23(1):81–92.
34. Saad F, Haider A, Doros G, Traish A. Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. *Obesity.* 2013;21(10):1975–1981.
35. Groti Antičić K, Antičić B, Žuran I, Pfeifer M. Continuation of testosterone treatment beyond one year results in more profound benefits—Glycemic efficacy and metabolic profile in obese hypogonadal males with type 2 diabetes in a two-year clinical trial. *Aging Male.* 2020. DOI: 10.1080/13685538.2020.1793132.
36. Morgunov LY, Denisova A, Rozhkova TI, Stakhovskaya LV, Skvortsova VI. Hypogonadism and its treatment following ischaemic stroke in men with type 2 diabetes mellitus. *Aging Male.* 2020;23(1):71–80.
37. Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S. Long-term testosterone therapy in type 2 diabetes is associated with decreasing waist circumference and improving erectile function. *World J Men's Health.* 2020;38(1):68–77.
38. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: Results from a meta-analysis of observational studies. *J Endocrinol Invest.* 2016;39(9):967–981.

39. Skinner JW, Otzel DM, Bowser A, et al. Muscular responses to testosterone replacement vary by administration route: A systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 2018;9(3):465–481.
40. Nasser M, Haider A, Saad F, et al. Testosterone therapy in men with Crohn's disease improves the clinical course of the disease: Data from long-term observational registry study. *Horm Mol Biol Clin Invest*. 2015; 22(3):111–117.
41. Saad F, Haider A, Gooren L. Hypogonadal men with psoriasis benefit from long-term testosterone replacement therapy—A series of 15 case reports. *Andrologia*. 2016; 48(3):341–346.
42. Traish A, Bolanos J, Nair S, Saad F, Morgentaler A. Do androgens modulate the pathophysiological pathways of inflammation? Appraising the contemporary evidence. *J Clin Med*. 2018;7:549.
43. Zhang X, Zhong Y, Saad F, Haider K, Haider A, Xu X. Clinically occult prostate cancer cases may distort the effect of testosterone replacement therapy on risk of PCa. *World J Urol*. 2019;37(10):2091–2097.
44. Zhang X, Zhong Y, Saad F, et al. Testosterone therapy may reduce prostate cancer risk due to testosterone deficiency at a young age via stabilizing serum testosterone levels. *Aging Male*. 2020;23(2): 112–118.
45. Carruthers M, Cathcart P, Fennelly MR. Evolution of testosterone treatment over 25 years: Symptom responses, endocrine profiles and cardiovascular changes. *Aging Male*. 2015;18(4):217–227.
46. Winter A, Marte A, Kelly M, Funaro M, Schlegel P, Paduch D. Predictors of poor response to transdermal testosterone therapy in men with metabolic syndrome. *J Urol*. 2014;45(Suppl.):e528.

Cite this article as: Haider KS, Haider A, Doros G, Saad F (2020) Design and conduct of a real-world single center registry study on testosterone therapy of men with hypogonadism, *Androgens: Clinical Research and Therapeutics* 2.1, 1–17, DOI: 10.1089/andro.2020.0011.

Abbreviations Used

AMS = Aging Males' Symptoms
BMI = body mass index
DRE = digital rectal examination
ED = erectile dysfunction
GP = general practitioner
HDL = high-density lipoprotein
IBD = inflammatory bowel disease
LDL = low-density lipoprotein
RCTs = randomized controlled trials
T2DM = type 2 diabetes mellitus
TD = testosterone deficiency
TG = triglyceride
TTh = testosterone therapy
TU = testosterone undecanoate
WC = waist circumference

Publish in *Androgens: Clinical Research and Therapeutics*

Androgens

Clinical Research and Therapeutics

liebertpub.com/andro