

## Is Total Testosterone a Convincing Indicator for the Need for Testosterone Supplementation? A Study of other Parameters: Nocturnal Penile Tumescence, Rigidity Monitoring and Questionnaires

Michael J Mathers<sup>1\*</sup>, Stephan Roth<sup>2</sup> and Frank Sommer<sup>3</sup>

<sup>1</sup>Department of Urology, Urological Ambulatory Remscheid, Klinikum Wuppertal, University Medical Center Wiiten/Herdecke, Germany

<sup>2</sup>Department of Urology, Helios Klinikum Wuppertal, University Medical Center Wiiten/Herdecke, Germany

<sup>3</sup>Department of Men's Health and Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

\*Correspondence author: Dr Michael J Mathers, Department of Urology, Urological Ambulatory Remscheid, Klinikum Wuppertal, University Medical Center Wiiten/Herdecke, Germany, Tel: + 0049-2191-291909; Fax: 0049-2191-291907; E-mail: irtima@t-online.de

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### Abstract

**Introduction and objective:** Every Andrologist knows numerous cases in which men with normal testosterone values present with clinical signs of testosterone deficiency. We present cases in which eugonadal men show a measureable objective improvement in functioning and symptoms after testosterone supplementation.

**Case report:** After testosterone supplementation two eugonadal men (total testosterone > 8.00 ng/ml) improved on nocturnal penile tumescence and rigidity monitoring (RigiScan®) with a 48.5 minutes increase (greater than 60% rigidity) at the base and 43.2 minutes at the tip compared to before supplementation. The second case an increase (greater than 60% rigidity) of 39.2 minutes at the base and 44.4 minutes at the tip. Furthermore International Index of Erectile Function (IIEF) and Aging Male's Symptom (AMS) scale improved after initiation of testosterone treatment.

**Discussion:** There seems to be a discrepancy between laboratory findings in eugonadal men and symptoms of hypogonadism such as objective nocturnal penile tumescence and rigidity, free testosterone and scores of questionnaires which address these symptoms. This inconsistency is discussed according to the literature.

**Conclusion:** Controlled studies are desirable to verify that eugonadal men with testosterone deficiency symptoms can objectively and subjectively benefit from testosterone supplementation.

**Keywords:** Testosterone supplementation; Hypogonadism

### Introduction and Objective

Total testosterone levels decline linearly with age, and the correlation between hypogonadism and sexual dysfunction is well documented [1]. Clinical trials confirm that the restoration of testosterone levels through testosterone replacement therapy (TRT) in hypogonadal men can improve overall sexual function and the symptoms of hypogonadism (e.g., decreased muscle mass and strength, increased body fat, dysphoria, fatigue and irritability, and depressed mood) [2]. However, when diagnosing hypogonadism there is controversy as to which serum parameters are necessary and which values mark the lower limits of normal total testosterone. In everyday practice it is well known that normal values of testosterone may vary individually, just as responses to the replacement of testosterone differ across individuals [3].

In order to more accurately interpret the level of bioactive testosterone, free testosterone and bioavailable testosterone are often calculated by using albumin and sex hormone-binding globulin (SHBG) [4,5]. However, men with normal serum total testosterone levels and elevated concentrations of SHBG can still suffer from symptoms of hypogonadism. This leads to a consensus that TRT

requires the presence of clinical signs and symptoms. To assess testosterone deficiency syndrome, the Aging Male's Symptom (AMS) scale is frequently used [6]. However, this questionnaire was developed on a normal aging population and does not specifically assess for low levels of testosterone. The International Index of Erectile Function (IIEF) is a common questionnaire for judging erectile function, but it has not been correlated with testosterone levels [7]. Although the limitations of these questionnaires are well known, the scales are commonly used to evaluate the efficacy of TRT. Offering an alternative to subjective measurement, sleep-related erections are regularly impaired when testosterone is below a certain threshold [8]. Nocturnal penile tumescence and rigidity monitoring (NPTRM) can be assessed by RigiScan® technology, a valid instrument to test nocturnal penile activity that can be used as a more objective tool to assess the influence of testosterone on sleep related erections [9].

In our practice we oversee numerous cases in which men with normal testosterone values present with clinical signs of testosterone deficiency and enjoy a measureable improvement in functioning and symptoms after testosterone supplementation. Here we report on two representative cases and discuss whether the current practice of diagnosing hypogonadism based on persistently low serum testosterone levels and the presence of symptoms should be generally accepted.

## Case Reports

### Case 1

For six years Mr. F., a 46 year-old athletic man, visited our outpatient clinic yearly for a precautionary physical check-up. His initial findings at age 40 were the following: total testosterone was 13.48 ng/ml (lab reference 2.80–8.00 ng/ml). Physical examination, SHBG, albumin, other hormones, PSA and all other standard blood work were within normal limits. His sexuality as assessed by the IIEF and AMS scale was within normal range and showed the following values: IIEF domain score: 27 points (regular good erections); AMS score: 21 points (no discomfort). His yearly check-ups showed the following. His total testosterone levels yearly decreased by 0.40 – 1.20 ng/ml. By his 46th birthday he had a value of 8.09 ng/ml, which was still above the normal lab reference of 8.00 ng/ml. However, at this point his AMS score had increased to 32, mainly due to a decrease in early morning erections, a reduction in erectile function, an increased need for sleep, a decrease in muscular strength, and irritability. Mr. F. then suffered erectile dysfunction, libido loss causing him psychological stress, and further decrease in early morning erections. He tested the PDE-5 inhibitor vardenafil 20 mg several times with only moderate success as documented in an IIEF domain score of 17. We began individual hormonal treatment with testosterone after assessing his condition with a SKAT and duplex-ultrasound examination. We performed intramuscular testosterone undecanoate injections, which pushed his testosterone value to a supraphysiological level. When his total testosterone fell under 10 ng/ml, we gave another testosterone injection. This seemed to be a good individual range for Mr. F.

To measure the effect of testosterone supplementation on Mr. F.'s erectile function, we performed RigiScan® measurements and administered the IIEF and AMS scale before and after initiation of the testosterone treatment. Compared to pre-treatment RigiScan® measurements, three RigiScan® measurements performed after six months of supplementation confirmed an improvement in erectile function (a 48.5 minutes increase (greater than 60% rigidity) at the base and 43.2 minutes at the tip compared to before supplementation). Furthermore, his AMS score improved to 25 after six months of treatment and to 19 after one year of supplementation. Mr. F. was able to experience spontaneous sexuality without PDE-5 inhibitors, and his IIEF domain score increased to 29.

### Case 2

Mr. M., a 64-year-old man, presented himself in our outpatient clinic and complained of libido loss and erectile dysfunction. A physical examination, SHBG, albumin, other hormones, PSA and all other standard blood work showed regular findings. Other than a significant loss of rigidity confirmed by SKAT and Doppler ultrasound, we found a normal total testosterone of 3.81 ng/ml and 4.10 ng/ml. Mr. M.'s AMS score was 36. This high value was attributed to the feeling that he had passed his peak, a decrease in libido, and the loss of early morning erections. While taking PDE-5 inhibitors, his IIEF domain score was 16. Five years earlier his AMS score was 24 and his IIEF domain score was 26 without taking PDE-5 inhibitors as his total testosterone was 8.61 ng/ml. We initiated intramuscular testosterone undecanoate injections and repeated them regularly. Blood samples at the time of the injections showed total testosterone values of 4.98–5.78 ng/ml. After the injections Mr. M. reported that he always felt vital and had good erections, but he noticed a general decline approximately two weeks before the end of the injection free interval. He expressed the

wish to shorten the injection free intervals. We performed three RigiScan® measurements to verify Mr. M.'s subjective decline in early morning erections. These measurements demonstrated reduced nocturnal erections while testosterone was 5.01 ng/ml. We then shortened the injection intervals to approximately eight weeks. His testosterone values are now 7.78–9.30 ng/ml at the time of injection. With this protocol he reports feeling better and his early morning erections have not decreased further. When Mr. M.'s testosterone level was 8.87 ng/ml, we performed another three RigiScan® measurements. We documented an increase (greater than 60% rigidity) of 39.2 minutes at the base and 44.4 minutes at the tip.

## Discussion

These two patients showed clinical signs of hypogonadism even though Case 1 had a "normal" total testosterone level without testosterone supplementation and Case 2's testosterone was within "normal" limits after testosterone treatment. Subjectively, their symptoms of hypogonadism were confirmed by an increased AMS score and a decreased IIEF domain value. Objectively, their symptoms were confirmed by low measurements of nocturnal penile tumescence and rigidity monitoring. After testosterone supplementation in a high range, both men felt vital and their erectile function and nocturnal erections improved, as confirmed by RigiScan® measurements.

The standard physiological range of total serum testosterone in healthy adult males is over 3.5 ng/ml. However, it is questionable whether age-adjusted testosterone values that were calculated in similarly-aged men who have also experienced a testosterone decline should be used as a reference, even though it is well known that testosterone values decline with age. Testosterone is largely bound to plasma proteins. A very small percentage is free, 40–50% is loosely bound to albumin, and 50–60% is specifically and strongly bound to the SHBG [10]. SHBG levels increase about 1–2% per year. Men with elevated SHBG may show symptoms of androgen deficiency due to a decline of bioavailable testosterone (the non-SHBG-bound free and albumin-bound testosterone), even though their total serum testosterone is within the normal range. Both the free and albumin-bound fractions are readily available for biological action because they diffuse passively through the cell membrane into the target cell and bind to the specific nuclear androgen receptor (AR) [11]. It has been suggested that normal testosterone values do not necessarily correlate with clinical signs and symptoms of hypogonadism [12]. Furthermore, research suggests that testosterone is not compulsory for sexually-induced erections and those nocturnal erections are androgen-dependent [13]. In our cases we were able to demonstrate that despite normal testosterone levels, both patients showed reduced nocturnal erections. With the assistance of RigiScan® measurements, an improvement in nocturnal erections was documented after supplementation in a high range. The importance of nocturnal erections for the maintenance of sexually-induced erections has been suggested in previous literature [6]. In an uncontrolled study of men with sexual dysfunction and low free testosterone, 73.6% of men with total serum testosterone considered to be within normal limits reported improved erections following TRT [14]. This suggests that eugonadal men can benefit from testosterone therapy. In other studies it has been shown that the use of testosterone supplementation in eugonadal men significantly increases spine bone mineral density [15]. The same seems to be true for cognition capabilities. An improvement in cognition has been shown after testosterone supplementation in eugonadal men [16]. These studies suggest that subjective well-being as

measured by AMS improves with testosterone supplementation even when testosterone levels before supplementation are within the normal range.

Differences in androgen sensitivity can be correlated with mutation in the AR and lead to variable phenotypes of androgen insensitivity. Other modulations of the transcriptional activity induced by the AR are assigned to a polyglutamine stretch of variable length within the N-terminal domain of the receptor protein [17]. This stretch is encoded by a variable number of (CAG)<sub>n</sub> in exon 1 of the AR gene which is located on the X-chromosome. Different androgen target tissues such as the prostate, bone, hair, metabolic parameters and psychological factors are influenced by polymorphism [18]. The CAG repeat length and the AR transactivation potential are inversely correlated. Elongated (CAG)<sub>n</sub> repeats have been found in patients showing hypoadrogenic traits, as well as disorders that are frequently associated with hypogonadism such as impaired cognitive function and obesity. Men presenting with symptoms of hypogonadism might exhibit normal testosterone levels but have CAG repeat lengths above the normal average. Indeed, in Europe the average length is 21 repeats, and although a CAG repeat length of more than 25 is still considered to be within the normal range, it is frequently associated with reduced androgen action and accompanying clinical symptoms [19]. Therefore, it may be appropriate to take CAG-repeats into account when evaluating a patient's testosterone levels.

## Conclusion

The literature and our study suggest that eugonadal men can experience symptoms of hypogonadism, which may be due to deficiencies in bioavailable testosterone or genetic effects on androgen sensitivity. Further controlled studies are needed to confirm that eugonadal men with testosterone deficiency symptoms can objectively and subjectively benefit from testosterone supplementation.

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