

Journal für

# Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik  
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### Report

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Behre HM

*J. Reproduktionsmed. Endokrinol 2008; 5 (2), 70-75*

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Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz

# New Developments In Testosterone Therapy – a Congress Report\*

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*This congress report summarizes the presentations on the association of metabolic syndrome, testosterone deficiency, erectile dysfunction and the options of therapy with intramuscular testosterone undecanoate given at the Educational Symposium, "Testosterone Therapy: New Developments in Sexual Medicine", held at the 9<sup>th</sup> Congress of the European Society for Sexual Medicine.*

*Men presenting with erectile dysfunction might have evidence of the metabolic syndrome and of insulin resistance. One of the consequences of obesity and type 2 diabetes is the promotion of a hypogonadal state also featuring hepatic, skeletal muscle insulin resistance, and visceral fat deposition. Intramuscular testosterone undecanoate fulfills the criteria for a favorable parenteral system: improved pharmacokinetics allowing injections four times a year without clinically significant non-physiological peaks or troughs of serum testosterone levels in hypogonadal men.*

*Identification and treatment of hypogonadism and metabolic syndrome are certainly beneficial for the overall health of the male patient, and may also benefit erectile dysfunction. **J Reproduktionsmed Endokrinol 2008; 5 (2): 70–5.***

**Key words:** metabolic syndrome, erectile dysfunction, hypogonadism, testosterone therapy, intramuscular testosterone undecanoate

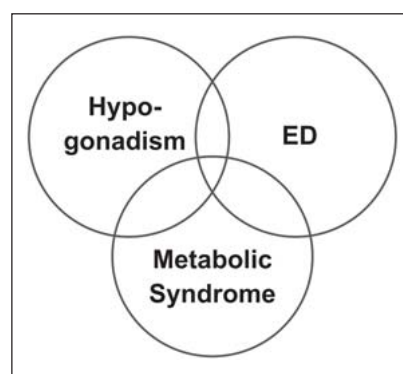
Sometimes, progress of the pharmacotherapy for a given indication appears to have come to a halt. The reason for a certain standstill in testosterone therapy was the fact that, for a long time, clinically useful dosage forms were not available. Oral formulations were insufficiently active or hepatotoxic while parenteral formulations had sub-optimal pharmacokinetics. Now, the situation is changing and several suitable testosterone preparations such as oral, transdermal, intramuscular or buccal systems are on the market or in the pipeline.

Due to the delayed launch of modern testosterone preparations, there is a lot of catching up to be done as regards clinical experience and communication of the findings to physicians. What we know now is not yet enough [1–3]. Therefore, it would very much welcome if, in the context of a high-level congress, scientific educational symposia were organized to communicate the latest findings on testosterone therapy. The main topics of the symposium in Vienna cited below were the relationships between testosterone and the metabolic syndrome (MetS) and between testosterone and erectile dysfunction (ED) in hypogonadal ED patients. It is estimated that more

than 300 million men worldwide will experience ED along with its psychological and clinical sequelae [4] in 2025. This indicates the great importance of curative or preventive strategies to effectively treat this disorder or prevent its development.

## Development of Metabolic Syndrome in Relation to Male Hypogonadism

As is well known, e.g. from the Massachusetts Male Aging Study, obesity in men is associated with decreased levels of total and free testosterone [5, 6] and total testosterone negatively correlates with the Body Mass Index (BMI) and insulin resistance [7]. Consequently, the correlations between late-onset hypogonadism (LOH) and the pre-stages of diabetes mellitus, obesity, and the metabolic syndrome are of interest (Fig. 1). The symptoms of LOH are a reduction in strength, increase in fat mass and other changes of body composition, lack of concentration and fatigue, sleep disorders, dysphoria/depression, sweating, osteoporosis, lack of libido, and ED. A total of 353 physicians interviewed in Germany, Spain, the UK, Brazil, Korea, and Saudi Arabia cited the following main symptoms of testosterone defi-



**Figure 1.** Schematic representation of the interrelations between hypogonadism, erectile dysfunction, and metabolic syndrome.

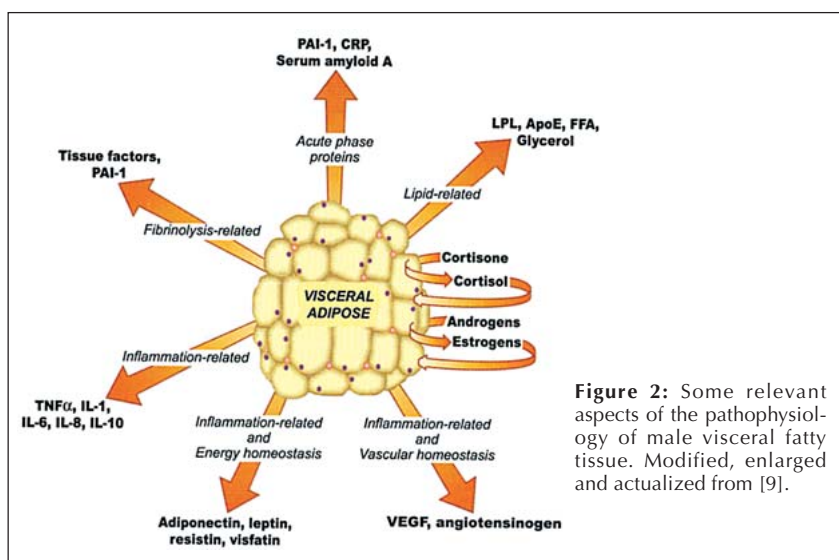
ciency: lack of libido/low sexual desire (71 %), ED (51 %), fatigue (39 %), loss of energy (17 %), depression (14 %), loss of muscle mass (9 %), and of body hair (9 %) [8]. It is obvious that these symptoms are related to disturbances of lipid and carbohydrate metabolism such as obesity, metabolic syndrome (MetS) and, finally, diabetes mellitus type 2.

Some relevant aspects of the pathophysiology of male visceral fatty tissue are shown in Figure 2. The obese patient is trapped in a vicious cycle: obesity and diabetes mellitus type 2 promote a high-insulin, high-leptin, and high-estrogen state which down-regulates the hypothalamic GnRH

\* Presented at the Educational Symposium, "Testosterone Therapy: New Developments in Sexual Medicine", held at the 9<sup>th</sup> Congress of the European Society for Sexual Medicine (ESSM), December 3–6, 2006, in Vienna, Austria, sponsored by an unrestricted educational grant from Bayer Schering Pharma AG.

Received: June 12, 2007; accepted after revision: October 4, 2007.

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**Figure 2:** Some relevant aspects of the pathophysiology of male visceral fatty tissue. Modified, enlarged and actualized from [9].

pulsatility. One of the consequences is a hypogonadal state featuring hepatic and skeletal muscle insulin resistance and visceral fat deposition. Low testosterone availability completes the vicious circle by increasing waist circumference, waist-to-hip ratio (WHR), leptin and HbA<sub>1c</sub> levels and by impairment of visceral lipolysis and skeletal muscle building. Hypogonadism appears to be a common feature of the metabolic syndrome [10]. Whether hypogonadism develops as a consequence of the metabolic syndrome or whether hypogonadism is involved in its pathogenesis is, at present, unclear. However, there is epidemiological evidence suggesting that hypogonadism might predict the subsequent development of the metabolic syndrome [11]. Whether impairment of carbohydrate and lipid metabolism causes hypogonadism or vice versa, for therapeutic interventions and based on our current knowledge, the question of the causality might be more or less unimportant for today's medical practice.

A. Heufelder presented his so-called DIMALITE study (DIabetes MANagement by Lifestyle and TEstosterone). The objective of this study was to test the potential therapeutic effects of testosterone administration in addition to exercise and diet in men with MetS and newly diagnosed diabetes mellitus type 2 with lower-than-normal free testosterone levels. A total of 32 men aged between 35 and 70 with MetS and diabetes mellitus type 2 were included, and they followed a moderate exercise program and mediterranean diet. Sixteen patients

received additional treatment with transdermal testosterone (Testogel® 50 mg/day). The exercise and diet showed the following beneficial effects (mean): waist circumference decreased from 107.4 to 102.6 cm ( $p < 0.05$ ), HbA<sub>1c</sub> from 7.6 to 6.8 % ( $p < 0.05$ ), triglycerides from 271 to 168 mg/dl ( $p < 0.05$ ), HDL increased from 38.6 to 43.7 mg/dl ( $p < 0.05$ ). In men who received testosterone in addition to exercise and diet, the effects were significantly greater: waist circumference decreased from 106.8 to 95.7 cm ( $p < 0.05$ ), HbA<sub>1c</sub> from 7.5 to 6.3 % ( $p < 0.05$ ), triglycerides from 286 to 149 mg/dl ( $p < 0.05$ ), HDL increased from 38.2 to 46.5 mg/dl ( $p < 0.05$ ). In summary: normalizing testosterone levels in men with MetS and diabetes mellitus type 2 has additional beneficial effects compared with the basic therapeutic program of exercise and diet.

### Is there a Link between ED, Hypogonadism, and Risk Factors for the Metabolic Syndrome?

ED is a common medical disorder that has a negative impact on the quality of life of millions of men worldwide. Because penile erection is a vascular process, risk factors for ED can be grouped into those that affect the vascular system and those that do not. Causes of vasculogenic ED include diabetes mellitus, among other things. There is increasing evidence that this disease is associated with endothelial dysfunction, which

is believed to be one of the earliest stages of vascular pathologies. It is correlated with subclinical cardiovascular disease and prospectively associated with an increased risk for ED [12]. Central obesity, assessed by several anthropometric indicators, is associated with the presence of ED in men > 60 years. Sagittal abdominal diameter, sagittal abdominal diameter-height index, maximum abdominal circumference, waist circumference, and waist-hip index are useful independent indicators for predicting the presence of ED [13]. In a study with 864 men (mean age 52 years), Kaplan et al [14] demonstrated that aging men with obesity and the MetS have a significant decrease in total serum testosterone levels compared to aging, metabolically healthy men. These recent data suggest that the well-established association between ED and pre-diabetes/diabetes (particularly in obese pre-diabetic/diabetic patients) may involve a hormonal component.

I. Eardley summarized the current knowledge about the link between ED, hypogonadism, and risk factors for the MetS. Men presenting with ED might have evidence of the MetS and of insulin resistance. Furthermore, men with the MetS have a higher prevalence of ED than controls [15–17]. Finally, it has recently been suggested that ED might be predictive of the subsequent development of the MetS, especially in men with BMI < 25 [18]. All three conditions are frequently seen in aging men. Therapeutically, there is evidence that weight reduction (and obesity is perhaps the major risk factor for the MetS) can result in improved erectile function.

Concerning hypogonadism and erectile dysfunction, it has been known for many years that hypogonadism is one of the causes of ED. In many cases, the pathophysiology has been unclear and has been confused by the concurrent effects of hypogonadism on sexual desire. However, there is a suggestion from animal models that androgens regulate both NOS (eNOS and nNOS) and PDE5 expression and the number of adipocytes in the penis [19–23]. In hypogonadal ED patients, the therapeutic efficiency of PDE5 inhibitors can be improved by concomitant testosterone administration [24, 25]. There is also

evidence that, in hypogonadal patients presenting with ED, testosterone-only treatment may restore normal erectile function [26]. Vice versa, the restoration of sexual activity by PDE5 inhibitors in ED patients increases endogenous testosterone as demonstrated in uncontrolled clinical studies [27].

Taking these lines of evidence together, the nature of the association between hypogonadism, MetS, and ED becomes clearer. Men present with the symptom of ED, which may be a feature of both hypogonadism and/or of the MetS. Identification of hypogonadism and the MetS is certainly beneficial for the overall health of the patient, and may also be beneficial for ED.

### Co-therapy with Testosterone and PDE5 Inhibitors in Hypogonadal ED Patients: Rationale and Perspectives

Interviews of 353 physicians in different regions and countries revealed that 12 % of ED patients can be treated with testosterone alone and that 13 % of ED patients could benefit from a combination therapy of testosterone plus PDE5 inhibitors [8] (Fig. 3). What is the scientific background for these therapeutic options?

J. Buvat gave a review of co-therapy with testosterone and PDE5 inhibitors in hypogonadal ED patients. ED and hypoactive sexual desire are key symptoms of severe organic hypogonadism in young patients, and

testosterone therapy consistently restores erectile function and libido in such cases. On the other hand, the prevalence of hypogonadism is substantial in men consulting for ED (serum testosterone level < 3 ng/ml or 10.4 nmol/l in 12 %, including 14.7 % beyond the age of 50). A recent meta-analysis by Isidori et al [29] combined 17 randomized controlled trials on the effects of testosterone therapy on sexual function of hypogonadal men of any age. A significant improvement of all aspects, including erectile function and sexual desire, was found in men with low normal testosterone levels (< 3.46 ng/ml or 12 nmol/l). Although these data suggest a significant benefit of testosterone therapy on erectile function of men with marked or moderate hypogonadism, the effects of this treatment have often been disappointing in middle-aged and elderly patients consulting for ED, who were subsequently diagnosed with hypogonadism following routine testosterone determination. A compilation of eight observational studies totaling 259 patients (serum testosterone < 3 ng/ml) concluded that testosterone therapy definitely improved erectile function in only 36 % of cases.

There are several possible explanations for these relatively disappointing results. The most relevant is the frequent multifactoriality of ED. Significant vascular factors such as obstruction of the penile arteries or veno-occlusive dysfunction have been found in up to 42 % of hypogonadal ED patients [30]. More subtle vascular alterations such as endo-

thelial dysfunction may be present in many other cases, as shown by the frequent association of both ED and hypogonadism with vascular risk factors such as obesity and diabetes [31]. In a study of diabetic ED patients, hypogonadism was associated with a greater deterioration of penile arterial function as shown by penile duplex ultrasound (PDU). These vascular co-morbidities are likely to hamper the effects of testosterone therapy in hypogonadal patients consulting for ED [32, 33].

Due to the failure of testosterone therapy in certain hypogonadal ED patients, phosphodiesterase type V (PDE5) inhibitors were tried in those patients not responding to testosterone alone and they proved to be successful. These drugs were also investigated in hypogonadal ED patients, but proved to be unsuccessful in a substantial proportion. Several observational studies reported low and low-to-normal testosterone levels in 30–40 % of ED patients not responding to sildenafil, which appears to be a higher prevalence than in unselected ED patients. This led to the hypothesis that a minimum serum testosterone level may be required for a full effect of PDE5 inhibitors in ED patients. Several uncontrolled studies of hypogonadal ED patients who were previous non-responders to sildenafil or tadalafil, and who reported improved response in 52–92 % following a combination with testosterone supplementation, support this hypothesis to some extent [34, 35]. Guay et al [36, 37] found that the success rate of sildenafil was inversely related to free testosterone levels. In diabetic men, the serum testosterone levels of non-responders were lower than those of responders (6.9 vs 18.6 nmol/l). 70 % of non-responders improved on additional treatment with testosterone undecanoate [38]. Rosenthal [39] showed that in 27 % of non-responders to sildenafil, the serum testosterone level was < 4 ng/ml. 92 % of these patients improved following combination with testosterone (T) gel. The therapeutic efficiency of PDE5 inhibition in non-responders to tadalafil was improved after combination with T gel. The combination was more effective than testosterone gel alone [40].

However, more convincing arguments may be found in the results of

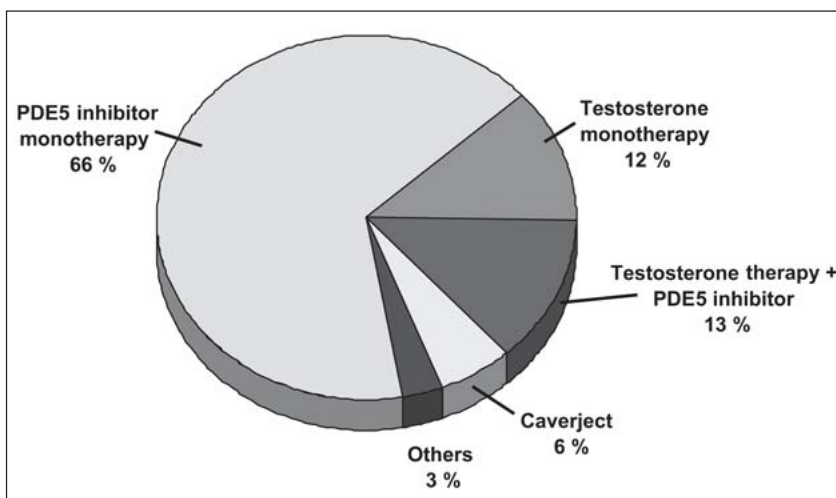


Figure 3. Therapeutic Options for ED patients; 353 physicians interviewed in Germany, Spain, the UK, Brazil, Korea, and Saudi Arabia. Reprint with permission from [28].

basic experiments in animals, and in some better designed clinical trials in men. Studies in rodents show indeed that, besides its well-known effects on the brain centers of sexual function, testosterone plays a key role in the peripheral modulation of erectile function. It is first required for maintenance of penile structure and functional integrity [41]. In addition, testosterone modulates both endothelial and neuronal nitric oxide synthase expression in erectile tissue, and, therefore, the capacity for NO production and cGMP formation which are testosterone-dependent [42, 43]. Testosterone relaxes pre-contracted smooth muscles via an endothelium- and NO-mediated pathway. This effect is mediated via a non-genomic pathway [44]. Moreover, testosterone also modulates the expression of the PDE5 enzyme in the corpora cavernosa. Castration reduces the activity of PDE5 while testosterone treatment up-regulates it [45]. Castration results in veno-occlusive dysfunction and ED [46] and decreases erectile response to electrostimulation [47]. Hence, medical or surgical castration prevents the enhancing effect of PDE5 inhibitors on erections induced by electrostimulation of the cavernous nerves, and re-administration of testosterone restores it [22, 26, 43]. Taken together, in animal models, normal androgen levels appear to be a prerequisite for proper functioning of PDE5 inhibitors.

Until now, there has been no definitive demonstration of such a critical impact on the mechanisms of erection in human males. However, there are androgen receptors in the human corpora cavernosa [48] and some recent studies suggest that androgens may modulate the vascular mechanisms of erection in men as well. Testosterone also modulates PDE5 in human penile tissue [22]. Peak systolic velocity (PSV) measured at the level of the cavernosal arteries following intracavernosal injection of PGE1 in ED patients with severe hypogonadism (serum testosterone < 2 ng/ml) and no other co-morbidity, especially vascular, was found to be significantly lower than in a control group of psychogenic ED patients and increased to the range of the latter group following testosterone therapy for 6 months [49]. Aversa et al [50] found a highly sig-

nificant correlation between the resistive index and the serum value of free testosterone based on PDU of the cavernosal arteries. In another study of 20 arteriogenic ED patients with low normal testosterone not responding to sildenafil, testosterone supplementation significantly enhanced the acceleration effect of sildenafil on PSV measured in the cavernosal arteries [51]. Lastly, Morelli et al [22] have shown that the expression of PDE5 may be at least partly testosterone-dependent in humans.

As regards clinical studies testing the hypothesis that a minimum level of serum testosterone is required for a complete restorative effect of PDE5 inhibitors in ED patients, it is first clear that PDE5 inhibition therapy may improve erections in certain ED patients. Rochira et al [52] demonstrated that sildenafil may normalize sleep-related erections of men with very low levels of testosterone. Prior to that report, there was consent that sleep-related erections are solely androgen-dependent (for review see [53]). Nevertheless, combining testosterone therapy with sildenafil resulted in an even greater enhancing effect on the erections. Conversely, PDE5 inhibitors fail in other hypogonadal ED patients. In a study of men with severe hypogonadism and no apparent cause for ED, sildenafil failed to improve the erectile response to visual sexual stimulation as it did in psychogenic and eugonadal ED patients. Its enhancing effect on erectile response was restored following testosterone substitution.

The responsibility of hypogonadism for the failure of PDE5 inhibition therapy in certain cases is also made more plausible by two randomized placebo-controlled trials. Aversa et al [51] studied 20 ED patients with low normal testosterone who did not respond to sildenafil. Testosterone co-medication significantly increased arterial inflow to the cavernous bodies in response to sildenafil, as well as the scores for the erectile function, intercourse satisfaction, and overall satisfaction domains of the International Index of Erectile Function (IIEF) in these patients versus placebo. On the other hand, Shabsigh et al [24] investigated 75 ED patients with total testosterone  $\leq 4$  ng/ml

who were also non-responders to sildenafil. After 4 weeks of combined treatment with sildenafil plus testosterone gel, the scores for the IIEF domains erectile function, orgasmic function, and overall satisfaction, as well as the number of patients reporting that the gel improved their response to sildenafil, were significantly higher than in the sildenafil plus placebo group. However, the differences between the two groups lost statistical significance at 8 and 12 weeks. These studies tend to support the possibility that a minimum threshold of serum testosterone is required for a complete effect of PDE5 inhibitors in certain patients, but this hypothesis still needs confirmation in larger studies such as the one completed in June 2007.

In conclusion, hypogonadism is a potential etiological factor often present in ED patients, at least those older than 50. It is often associated with vascular factors likely to hamper the effect of testosterone therapy. Nevertheless, there are important benefits to routine screening for testosterone deficiency. Achieving physiologic levels of testosterone is one of the rare opportunities for restoring spontaneous erections and preventing patients from having to meticulously plan sexual activity. In addition, providing testosterone therapy may restore sexual desire and improve other symptoms associated with hypogonadism, including lack of energy and mood disturbances. Lastly, a threshold level of serum testosterone may be required for a full efficacy of PDE5 inhibitors. Therefore, serum testosterone should be assayed if an ED patient does not respond satisfactorily to PDE5 inhibitors. If the level is low or low normal ( $\leq 4$  ng/ml or 14 nmol/l), combining testosterone therapy with PDE5 inhibition for at least 2 months is recommended. But if a low testosterone level is found and confirmed at initial assessment, it is more logical to start with a trial of testosterone therapy alone for 2 or better 3 months, and to add a PDE5 inhibitor only if testosterone treatment alone fails. In the final instance, combined therapy with testosterone and PDE5 inhibitors is often indicated in middle-aged and elderly ED patients and is clearly a big step forward in the treatment of their condition.

## Safety, Efficacy, and Sexual Benefits of Long-acting, Injectible Testosterone Undecanoate in Men with Low Testosterone Levels

The progress in the development of modern testosterone formulations is illustrated by the example of intramuscular testosterone undecanoate (TU, Nebido®). It was found that the terminal elimination half-lives (d) for the different intramuscular testosterone esters are 0.8 for testosterone propionate, 4.5 for testosterone enanthate, 20.9 for testosterone undecanoate dissolved in tea seed oil, and 33.9 for testosterone undecanoate dissolved in castor oil [54]. Under the leadership auspices of H. Behre, an open-label, prospective, multicenter, one-arm study was performed to evaluate intramuscular TU for treatment of hypogonadal men under conditions resembling real-life situations as closely as possible (e.g. variable injection intervals, minimum selection of patients). Men with hypogonadism aged 18–75 years with total testosterone serum levels < 10 nmol/l and no contraindications for testosterone therapy were included. A total of 161 patients were screened and 96 included. A group of 87 patients (90.6 %) received all 6 injections. An amount of 1000 mg TU was given at individually adjustable loading intervals of 6–10 weeks between the first 2 injections and maintenance intervals of 10–14 weeks (total: 6 TU injections). The mean injection interval (weeks  $\pm$  SEM) between the 1<sup>st</sup> and 2<sup>nd</sup> injection was  $7.7 \pm 0.3$ , and between the 5<sup>th</sup> and 6<sup>th</sup> injection  $11.3 \pm 0.2$ . The study included 96 men (age  $48.6 \pm 12.7$  years [mean  $\pm$  SD]; height  $178.85 \pm 7.84$  cm; body weight  $93.33 \pm 15.71$  kg; BMI  $29.22 \pm 4.80$  kg/m<sup>2</sup>). Trough concentrations of total testosterone (regarded as an indicator of the adequacy of substitution) increased from  $5.60 \pm 3.30$  at baseline to  $13.9 \pm 0.5$  nmol/l at the end of the study. Median values for trough testosterone after the 2<sup>nd</sup> TU injection were 12–13.25 nmol/l. The mean serum PSA concentration of  $0.82 \pm 0.08$  ng/ml at screening increased moderately to  $1.23 \pm 0.14$  ng/ml after the 6<sup>th</sup> TU injection. At the time of the 5<sup>th</sup> TU injection, 75 % of the patients had PSA values  $\leq 1.40$  ng/ml (3<sup>rd</sup> quartile). At the

time of the final examination, the 3<sup>rd</sup> quartile was 1.5 ng/ml. The total prostate volume (ml  $\pm$  SEM) assessed by transrectal sonography increased slightly from  $20.7 \pm 1.2$  at baseline to  $22.6 \pm 1.4$  at the end of the study. The proportion of patients with elevated HbA<sub>1c</sub> (normal range: 4.3–6.1 %) dropped from 23.5 to 12.5 %. All physical examinations and standard safety laboratory tests confirmed the safety of TU. Assessment of the intensity of androgen-deficiency symptoms by means of the AMS (Aging Males' Symptoms rating scale) revealed an improvement of the score for sexual symptoms from  $13.2 \pm 5.0$  before treatment to  $8.2 \pm 3.3$  at the end of the study. 92.5 % (n = 87) of the patients were satisfied, 2.1 % (n = 2) were neither satisfied or dissatisfied, and 3.2 % (n = 3) were dissatisfied. In conclusion, intramuscular testosterone undecanoate fulfills the criteria for a favorable parenteral system: improved pharmacokinetics allowing injections 4 times a year without clinically significant non-physiological peaks or troughs of serum testosterone levels in hypogonadal men. The formulation appears to be a safe and efficient drug for the treatment of male hypogonadism under real-life conditions.

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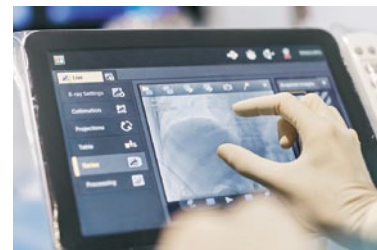
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