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Research Article

Improvement of Sexual Function in Men with Late onset Hypogonadism Treated with Testosterone

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Abstract

Aim: Late onset hypogonadism is associated with relatively mild testosterone deficiencies. This study investigated the effects of restoring testosterone levels to normal in men with complaints of low sexual desire and erectile dysfunction Main outcome measures: Sexual function was assessed with International Index of Erectile Function (IIEF) at baseline and after 24 weeks of testosterone administration.

Methods: 22 hypogonadal men (mean age: 58 years) with erectile dysfunction were studied. 15 patients had serum testosterone below 6.9 nmol/L) and 7 between 7.2- 11.7 nmol/L. (N >12.0 nmol/L); there were considerable co-morbidities. The duration of sexual complaints was on average 3.8 years. Patients received i. m. long-acting testosterone undecanoate.

Results: In all patients' serum testosterone levels were restored to normal within 6-8 weeks. Twelve patients reported significant improvement in the sexual desire domain (from 4.5 to 8.4) and experienced an improvement in the erectile function domain (from 12 to 25 (Qs 1-5 plus 15), following treatment with this long-acting testosterone, in 9 of 12 patients this occurred only after at least 12 to 24 weeks. The remaining 10 patients reported an improvement of sexual desire (from 4.5 to 7.5) but no significant improvement in erectile function domain (from 12 to 14). No changes in serum PSA or prostate volume were noticed while receiving this long-acting testosterone preparation.

Conclusion: restoring testosterone levels to normal in men with proven subnormal testosterone levels, improves libido in most subjects and erectile function

Keywords: Late-Onset-Hypogonadism; Sexual Function; Testosterone

Introduction

Functional or Late-onset-hypogonadism is associated with mild degrees of testosterone deficiency. Restoring testosterone levels to normal improved libido in most subjects and erectile function in more than 50% of these men, be it sometimes with a delay up to 12-24 weeks. New research has presented convincing evidence that testosterone has profound effects on tissues of the penis involved in the mechanism of erection and that testosterone deficiency impairs the anatomical and physiological substrate of erectile capacity. in more than 50% of these men. It may take 12-24 weeks before the effects of testosterone become manifest.

The introduction of the Phosphodiesterase type 5 inhibitors (PDE 5-inhibitors) has been a step forward in the treatment of erectile dysfunction. These efficacious and relatively safe compounds have had a profound impact on diagnosis and treatment of Erectile Dysfunction (ED). The success of the PDE 5- inhibitors rendered androgens as treatment for erectile problems in the average patient as something of the past, which seemed rational in view of the then prevailing assumption that the effects of testosterone were primarily on libido, and much less so on erectile mechanisms [1]. Over the last 15 years the age-related decline of circulating testosterone in men has received abundant attention, though its clinical significance is still hotly debated. Recently consensus on its diagnosis/treatment has been reached by a few professional bodies [2]. Moreover, new research has presented convincing evidence that testosterone has profound effects on tissues of the penis involved in the mechanism of erection and that testosterone deficiency impairs the anatomical and physiological substrate of erectile capacity, at least in part reversible upon androgen replacement. There are androgen receptors in the human corpus cavernosum [3] the expression of Nitric Oxide (NO) synthesis [4, 5] is regulated by androgens. Several studies show that Androgen plays A critical role in restoring and maintaining the penile trabecular smooth muscle structure and function [6-8] as well as regulating the cell apoptosis [9]. Testosterone deficiency induces both biological and structural/functional changes in the trabecular cavernosal tissues. Adipocyte accumulation in penile subtunical area of the corpus cavernosum emphasized the potential mechanism for Veno occlusive dysfunction in androgen deficiency [10] (for review: [11]. These novel insights prompted us to investigate the merits of testosterone treatment in a cohort of elderly men who had complaints of erectile dysfunction and whose plasma testosterone levels were found to lie below the lower limit of reference values of our laboratory (12.0 nmol/L). Over the last 15 years the age-related decline of circulating testosterone in men has received abundant attention, though its clinical significance is still hotly debated. Recently consensus on its diagnosis/treatment has been reached by a few professional bodies.

Subjects and Methods

A total of 22 hypogonadal men (mean age: 58 years, range 37-73 years) presenting with sexual dysfunction (low sexual desire and Erectile Dysfunction (ED) were prospectively evaluated. Laboratory tests included measurement of total testosterone, 5-Dihydrotestosterone (DHT), lipid profile, blood glucose and HbA1c as well as prostate specific antigen. It appeared that 15 patients had serum testosterone levels below 6.9 nmol/L) and 7 between 7.2 – 11.7 nmol/L. The lower limit of reference values in our laboratory is 12.0 nmol/L. As indicated in table1, there were considerable co-morbidities. The duration of ED was on average 3.8 years. The criteria to label the etiology of ED as organic, psychogenic or mixed were as follows: earlier in law actions and the presence of demonstrable somatic factors explaining the etiology of ED in the absence of exaggerated psychological response to the emergence of ED. Psychogenic ED was present if there were no plausible attributable somatic etiological factors for ED. Mixed etiology was assumed when somatic etiological factors could be identified which could not reasonably account for ED. Sexual function assessment was performed using the International Index of Erectile Function (IIEF) at baseline and again after 24 weeks. Patients received i.m. long-acting testosterone undecanoate (Nebido®) on day 1, after six weeks and thereafter approximately every 12 weeks and were followed for a mean of 24 weeks under this long-acting testosterone preparation. Before each new injection with testosterone undecanoate plasma testosterone was determined. The therapeutic profile of this relatively new long-acting testosterone preparation has been extensively reviewed. [12, 13]. Physical and sonographic examination of the prostate were performed. Total prostate volume and volume of the Transitional Zone (TZ) were measured each three months, as well as serum PSA levels. All patients gave their informed consent to be included in this study which was approved by the institute's review board for investigations on human subjects.

Results

No patient needed to be excluded from study or discontinued treatment in this study period. No patient reported local irritation or pain in the gluteal injection site (injection performed very slowly using a 22-gauge syringe) or any other adverse events. In all patients' serum testosterone levels were restored to normal within 6-8 weeks after the first injection. Twelve patients reported significant improvement in the sexual desire domain (from 4.5 to 8.4) and experienced an improvement in the erectile function domain (from 12 to 25 (Qs 1-5 plus 15), following treatment with this long-acting testosterone, which took longer than 6 weeks, up to 12 to 24 weeks for 9 of the 12 patients. The remaining 10 patients reported an improvement in sexual desire (from 4.5 to 7.5) but no significant improvement in erectile function domain (from 12 to 14). These men are still under follow-up. No significant changes in serum PSA or prostate volume were noticed while receiving this long-acting testosterone preparation. Serum PSA was 1.02 ± 0.07 before treatment and 1.33 ± 0.11 ng/mL after 12 months of testosterone administration (not significant). Total prostate volume was 39.5 ± 1.0 mL before treatment and 41.5 ± 1.4 mL after 12 months (n.s.) The volume of the transitional zone was 14.2 ± 0.5 mL before treatment and 16.0 ± 1.2 mL after 12 months testosterone administration (n.s.)

Discussion

This study investigated the effects of testosterone administration on sexual functioning of a cohort of men of advanced age with

relatively mild testosterone deficiency as found in late onset hypogonadism (15 patients had serum testosterone levels below 6.9 nmol/L) and 7 between 7.2 – 11.7 nmol/L). All patients experienced an improvement in the domain of sexual desire as assessed with the IIEF. A significant improvement in erectile function was noted in 12/22 (54%) of patients while the remaining 10 patients did not observe an improvement in erectile function. An important observation of our study was that after six weeks of testosterone administration, only 13% of patients had noted an improvement in erectile functions while this increased to 54% after 24 weeks. The well-known effects of testosterone on libido reportedly occurred much earlier than 24 weeks, rather than within 4-5 weeks [1]. The explanation for the delay in improvement of erectile function up to 24 weeks might lie in the direct effects testosterone has on the anatomical and physiological substrate of the erectile tissue/ mechanism (for review: [11]. Recent studies provide convincing evidence that there is powerful effect of testosterone on anatomical and physiological substrate of penile erection. Furthermore, it has become clear that testosterone is not simply one of the many factors playing a role in erectile (dys)function. Circulating levels of testosterones are closely related to manifestations of other etiological factors in ED, such as atherosclerotic disease and diabetes mellitus. The latter are correlated with lower-than-normal testosterone levels. Therefore, the role of testosterone in erectile (dys)function is increasingly recognized. Over the last 5 years new insights have been gained into the important role of testosterone in male sexual functioning and male health in general [11]. Long-term testosterone deficiency impairs the anatomical and physiological substrate of erection, and its potential restoration may require the presence of normal testosterone for longer periods, up to 24 weeks [14].

Obviously, the etiology of erectile dysfunction is multifactorial, and largely identical with aging process of the vascular and nervous system. Not all damage will be reversed by restoring plasma testosterone to normal. There was no evidence that the co-morbidities of the 10 patients who showed no improvement of ED upon testosterone administration, were more severe than of the others with greater success of treatment. But these 10 patients were on average 8 years older and had suffered ED for more than six years, so age and the duration of erectile dysfunction might be a prognosticator of the success of testosterone administration to men with late onset hypogonadism. The results of this study add to the body of evidence that restoration of testosterone to its normal levels in elderly men with testosterone levels typical of late onset hypogonadism, improves erectile function [15-19], be it, as in our study, that not 100% of the men will experience an improvement, and are maybe served with the prescription of a PDE 5-inhibitor [17, 18]. There are also fewer positive findings [20]. The fact that all subjects experienced an improvement sexual appetite is probably significant in the sense that it will contribute to continuation and compliance with the treatment. Lack of sexual desire appeared to be one of the reasons to discontinue treatment with sildenafil [21-24]. This study used a rather novel injectable testosterone preparation, long-acting testosterone undecanoate (Nebido®), which, in contrast to the more traditional injectable testosterone preparations, provide the patient with plasma levels of testosterone in the reference range [12]. No changes in prostate volume and/or serum PSA were noted while receiving treatment with this preparation. Obviously, the safety aspects of long-term effects of testosterone administration to elderly men are not yet clear, but in the short term there were no safety concerns.

Conclusion

Restoration of testosterone levels to the reference range in elderly men with relatively benign testosterone deficiencies as occurring in late onset hypogonadism, is in more than 50% of cases successful with testosterone replacement only. Unlike effects on libido, effects on erection may have a latency of up to 24 weeks to become manifest. In the short term there are no safety concerns.

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