Asian Journal of Andrology (2015) 17, 217–218

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INVITED RESEARCH HIGHLIGHT

Male Health

Effect of testosterone replacement treatment on constitutional and sexual symptoms in type 2 diabetic men: need for rules

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Asian Journal of Andrology (2015) **17**, 217–218; doi: 10.4103/1008-682X.140967; published online: 18 November 2014

In a recent publication, Gianatti and colleagues investigated the effect of testosterone treatment in obese, aging men with type 2 diabetes (T2D) with mild to moderate symptoms, a modest reduction in testosterone levels, mild to moderate aging male symptoms, and erectile dysfunction.[1] The authors could not show any significant improvement in constitutional or sexual symptoms in this group of men. This randomized double-blind, parallel, and placebo-controlled trial among other critically emphasizes the increased testosterone prescriptions worldwide and together with other corroborating or contradictory studies awakes the need for guidelines in the androgen replacement treatment.

Research investigational efforts into the endocrine correlates of aging and related diseases have raised an increasing interest in the use of androgens for a multitude of morbidities in aging men. Hypogonadism in men is a chronic and often irreversible severe decline in free and total testosterone levels, which fortunately, has a low prevalence. Nevertheless, in the aging male population the epidemiological data have revealed a substantial progressive androgen deficiency. In addition to chronological aging, chronic illnesses such as type 2 diabetes (T2D) among others and nutritional factors such as obesity contribute to the enhanced age-related diminution of serum testosterone levels. The significant inquiry being posed here is whether low levels of serum testosterone that are significantly associated with sexual symptoms in aging men with T2D are also severe enough to lead to constitutional symptoms and whether we should treat the reduction of male hormones in this group of aging men.

The trial in concern by Gianatti *et al.*[1] is based on a rigorous study design, employing a well-established testosterone administration way (i.e. intramuscular testosterone undecanoate) on the proper dosage and using an appropriate testosterone evaluation method by both electrochemiluminescence immunoassay and liquid chromatography-tandem mass spectroscopy. The headline results are not surprising and do not support the use of testosterone treatment to improve constitutional or sexual symptoms in the prevalent population of aging, obese men with T2D, who present with mild to moderate symptoms and modest reductions in circulating testosterone levels. However, other similar studies[2,3] and meta-analyses[4,5] furnish contradictory results encouraging the use of testosterone in men with T2D and low testosterone in order to increase sexual function and to ameliorate constitutional symptoms.

The testosterone replacement treatment (TRT) represents a hot topic and continues to be much discussion in the andrology community regarding the clinical significance of age-related declines in testosterone, and whether TRT is warranted in the context of other comorbidities such as T2D, depression and obesity or not. In order to justify the use of TRT, it is mandatory to reach a consensus of opinion on important issues of safety, efficacy and patients group targeting.

There has been a striking enhancement in TRT in older androgen-deficient men with nonspecific symptoms of low androgens. This therapeutical strategy includes significant overtreatment risk. Until now, interventional trials of TRT have been unable to fully delineate the risks and benefits of testosterone therapy due to methodological weaknesses including insufficient power and short treatment durations, even when examined under the form of meta-analysis.[6] Although, there are many supporting connections between treatment of testosterone deficiency and melioration in rates of morbidity and mortality, much continues to be obscure on the overall long-term benefits and risks of TRT. This has a significant impact on the decision for the duration of the therapeutical approach. In the study under concern Gianatti *et al.*[1] decided to cure their patients over a 40 week period. However, in the literature it is emphasized the direct association of the benefit and the duration of TRT. In TIMES2 study Jones *et al.*[7] observed a statistically significant improvement of TRT on overall sexual function and libido between the first observation at 6 months and the second observation at 12 months. This is confirmed in other studies as well[2,3] supporting the concept that testosterone-related benefits in T2D patients may take many months to reach maximum effect. Moreover, the form of the androgen preparation is also crucial for the outcome of the study in terms of efficacy. Some studies used oral testosterone undecanoate as a therapeutic agent, which did not increase or only slightly increased serum testosterone levels during follow-up.[8,9] It is, therefore, unlikely that this preparation was able to raise and maintain testosterone levels in the normal range over the full 24 h of the day. Other forms of testosterone such

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as patches, gels and especially injections[10] provide much more stable testosterone levels over days and weeks.

Another key point is the lack of an operational definition for "normal" testosterone values at different ages and in addition there is not yet a consensus on the identification of specific signs and symptoms to accurately discriminate between those who will benefit from the treatment and those who will not. There is, however, general agreement that the total testosterone level above 12 nmol l^{-1} (350 ng dl^{-1}) does not require substitution. Similarly, based on the data of younger men, there is unanimity that patients with serum total testosterone levels below 8 nmol l^{-1} (230 ng dl^{-1}) will usually benefit from testosterone treatment. Gianatti *et al.*[1] screened for patients with fasting morning total serum testosterone level < 12.0 nmol l^{-1} (346 ng dl^{-1}). However, when restricting the grey zone of testosterone level which is between 12 nmol l^{-1} or above (no need of TRT) and 8 nmol l^{-1} or less (need for TRT) the results become more apparent. For example, using the more stringent endocrinology society guidelines for male hypogonadism[11] with a cut-off of 10.4 (300 ng dl^{-1}) instead of 12.0 nmol l^{-1}, the effects of TRT *vs* placebo on the beck depression inventory (BDI-IA), aging males' symptoms (AMS) and International Index of Erectile Function (IIEF) turn stronger[12] and these results have been confirmed recently by others as well.[13] Hence, it appears that the effect of TRT is strongest in men with an overt hypogonadism, and the more severe the hypogonadism, the more significant or impressive are the results obtained with TRT.

Another issue relates to the age of hypogonadal diabetic men and their comorbidities. In a meta-analysis, Boloña *et al.*[5] investigated the possible role of aging as a possible moderator in evaluating the effect of TRT on sexual function. They reported a fairly large and significant effect of TRT on erectile function in the trials including young patients and a non-significant effect in those including older ones (mean age > 50 years). This can be explained by the fact that hypogonadism can be the main cause of erectile dysfunction in younger patients while it is generally only one more contributing factor of a multifactorial erectile dysfunction in older ones.[14]

Moreover, low testosterone is associated with many comorbidities, including obesity (in the context of metabolic syndrome or not), depression, and T2D mellitus, among others. Obesity predicts depressive symptoms in cross-sectional and longitudinal studies[15] and the decline in body mass index has been significantly associated with improvements in the BDI-IA, AMS, and IIEF-5 in men under TRT.[12] This emphasizes the importance of lifestyle changes in the management of hypogonadal men, whereas on the other the hand the expectations on sexual function after TRT cannot be the same among obese and nonobese hypogonadal T2D men. Depression, on the other hand is well-known to independently impact sexual function and to be associated with impaired diabetes control.[16] Furthermore, depressed mood is a symptom often associated with hypogonadism.[14] Although, the relationship between low testosterone levels and the incidence of clinical depression is still unclear, it is evident that in the presence of depression the therapeutic benefit of TRT will be seriously hampered when the primary end point of the treatment is the correction of the erectile dysfunction.

Thanks to the collective effort of researchers such as the authors of the current published work of Gianatti *et al.*[1] we now have a much clearer picture of androgen effects in this field. It becomes apparent that the administration of testosterone with the prospect to improve the sexual function should be expected in selected groups of hypogonadal T2D men. Under this prism, a general consensus should be reached proposing appropriate guidelines for the topic in concern. In the meantime, it is important to screen for hypogonadism in men with T2D and poor psychological and sexual well-being including depressive symptoms, low sense of vitality, and decreased libido and sexual function, because of the potential therapeutic benefits of androgen supplementation. This statement does not introduce any new indication for TRT. In the contrary, underlines the necessity to elucidate the role of androgens fully in pharmacologically manipulating a complex vascular-smooth muscle system such as that of the corpora cavernosa in the context of a multifactorial pathology such as erectile dysfunction which includes vascular, neurologic, psychogenic, and endocrinologic causes.

COMPETING INTERESTS

The authors declare no competing interests.

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