



## Letter to the Editor

**Reply to Anton Ponholzer and Stephan Madersbacher's Letter to the Editor re: Christina Wang, Eberhard Nieschlag, Ronald Swerdloff, et al. Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations. Eur Urol 2009;55:121–30**

We thank Drs. Ponholzer and Madersbacher for their comments on “Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations” [1]. Their comments included two questions. The first asked why, when low testosterone levels are significantly linked to specific symptoms, did we fail to provide valuable instruments to quantify this syndrome.

The recommendations writing group reviewed the characteristics of the available questionnaires suggested by Ponholzer and Madersbacher and did not feel that they had sufficient specificity to be used as stand-alone screening tools for late-onset hypogonadism (LOH). The problem with symptoms associated with low serum testosterone is that they may be found in other conditions, which become increasingly common as men age. While the questionnaires may be sensitive markers of the low testosterone state, they are not tightly correlated with low testosterone, particularly in the borderline low serum testosterone range (8.7–10.4 nmol/l [250–300 ng/dl]). In addition, responsiveness to testosterone is not only defined by serum testosterone levels but is also influenced by end organ responsiveness [2,3]. Furthermore, the thresholds for androgen actions and the dose response curves for various target organs may be different. For example, decreased libido and spontaneous erections are frequently reported in the older male population at testosterone levels <8–10 nmol/l; other symptoms such as physical fatigue may become apparent at higher testoster-

one concentrations ( $\geq 12$  nmol/l) (Wu et al, unpublished data).

The second question referred to the recent publication of two studies in which testosterone treatment showed no significant benefits in older men. The recommendations writing group was aware of the studies referenced by the writers of the letter to the editor but felt that they both had significant flaws in design and limitations in interpretation.

The study by Nair et al [4] included only 27 men who received testosterone compared with 39 men who received placebo; the Nair study, in our opinion, is underpowered to answer the critical questions. In addition, the selected men did not complain of hypogonadal symptoms, and the cut-off for inclusion was serum bioavailable levels at or below the 15th percentile of younger men (3.6 nmol/l [103 ng/dl]) with the median serum total testosterone concentration in the testosterone group at 12.3 nmol/l (357 ng/dl) and an interquartile range between 9.7 and 16.2 nmol/l (281 and 467 ng/dl), indicating that most of the men were not hypogonadal. In this study, after a testosterone transdermal patch (delivering about 5 mg of testosterone per day) was applied, serum bioavailable testosterone increased modestly and frequently remained substantially below the reference range of younger men. The serum total testosterone levels after treatment were not shown. Thus, in this study, the lack of responsiveness to testosterone may have been due to the following study design deficiencies: (1) many of the men were not hypogonadal before treatment, (2) testosterone treatment did not increase the serum bioavailable testosterone into the adult male reference range, (3) the numbers of subjects studied were small, (4) the study was underpowered, and (5) the subjects were not selected because they had symptoms. If the participants did not have symptoms, then they cannot improve on treatment.

The second study [5] consisted of a larger group of healthy older men ( $n = 237$ ) randomly selected from a population register on the basis of serum testosterone levels below the 50th percentile of men between 60 and 80 yr old (cut-off = 13.7 nmol/l [395 ng/dl]). Thus, many of the men were not hypogonadal by most if not all standards. The incorrect attribution of chemical hypogonadism was substantiated by data showing that many of these men did not have symptoms of testosterone deficiency. The participants were treated with 80 mg oral testosterone undecanoate twice per d or a placebo [5]; serum testosterone levels were unchanged after 6 mo of testosterone treatment. Thus, this study suffered from the same concerns as Nair et al [4]: Many of the men were not hypogonadal, they did not have symptoms of impaired cognitive function or poor quality of life, and their serum testosterone levels were not changed after treatment.

Though placebo-controlled studies of testosterone treatment are available, the subjects recruited were neither testosterone deficient nor symptomatic, and the testosterone treatment provided for these subjects failed to adequately elevate the participants' serum testosterone levels. Thus, the recommendations writing group, after thorough review of all the available studies to date, concluded that there are inadequate data to show patient-reported outcomes and functional benefits in response to testosterone treatment and that a larger study is required to definitively investigate these outcomes.

**Conflicts of interest:** Dr Wang is a temporary consultant for Indevus and receives research support from Acrux, Indevus, M et P, Clarus Therapeutics, and Besins Health Care. Dr Nieschlag has received honoraria for lectures on testosterone. Dr Swerdloff is a consultant for Pierre Fabre; a consultant and grant recipient for Acrux, Clarus, GlaxoSmithKline, Indevus, and Repros. Dr. Wu has nothing to disclose.

## References

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November 25, 2008

Published online on December 4, 2008