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Research Highlight

Testosterone deficiency and treatment in older men: definition, treatment, pitfalls

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Two manuscripts were recently published in the *New England Journal of Medicine* [1, 2] that relate to testosterone deficiency and treatment in older men. To many readers, both these studies will seem to be dealing with the same topic in a complementary manner: the first [1] looks at how to define an illness and the second [2] looks at how to treat it (or maybe not treat it). If perceived as having stringent logical (and clinical) progression, these papers could have a major impact not only on andrology but on medicine in general.

The first article is by Frederick Wu and his co-authors [1], using data from the European Male Aging Study. The authors recognize that the association between an age-related decline in testosterone concentration and a clinically relevant entity of (late-onset) hypogonadism in men remains a controversial concept. They sought evidence-based criteria to identify an illness named late-onset hypogonadism in a general male population using associations between symptoms and low testosterone levels. To this end, the authors used questionnaires to survey a random population-based sample of 3 369 men between the ages of 40 and 79 years from eight European locations about their general, sexual, physical, and psychological health as well as their testosterone levels [1].

The second article is from a research group led by Shalender Bhasin [2], reporting results from the Testosterone in Older Men with Mobility Limitations (TOM) trial. The TOM trial was a placebo-controlled, randomized study designed to determine the effects of testosterone administration on strength and physical function in older men with limitations in mobility and low serum concentrations of testosterone. Participants were 65 years or older, with a mean age of 74 years, and lived in Massachusetts. The trial, originally designed to last for 6 months for each individual, was discontinued by the data and safety monitoring board because they received a high rate of adverse cardiovascular events in the testosterone group compared to the placebo group [2].

Taken together, the two studies suggest a logical connection regarding the diagnosis and treatment of a particular disease, namely late-onset hypogonadism in men, and the likely cardiovascular hazards that are related to therapy by testosterone substitution. However, the principles and populations involved in these studies differ markedly; so this pair of papers does not in fact promote such conclusions. In addition, each study by itself has limitations regarding generelisability

The study by Wu *et al*. [1], which is based on various general populations, not patients, across Europe, arrives at the conclusion that late-onset hypogonadism is rare in men (overall 2.1% of the study population). Although paucity of morning erections, low sexual desire, erectile dysfunction, inability to perform vigorous activity, depression and fatigue were significantly related to low testosterone levels and increased probabilities of the three sexual symptoms, and limited physical vigor was related to decreased total testosterone (tT) levels, only the three sexual symptoms had, in this specific analysis, a syndromic association with decreased testosterone levels. Therefore, the authors concluded that late-onset hypogonadism should be

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defined by the presence of at least three sexual symptoms associated with a tT level of less than 11 nmol per liter.

These are not the first results published from the European Male Aging Study. Previous publications from this research take a wider approach to the problem of low testosterone levels in aging men [3, 4]. It is acknowledged that the prevalence of low testosterone in men is more likely when increases in body-mass index (BMI) and numbers of coexisting illnesses are taken into account during modelling, which is a clinically reasonable approach: age itself is compatible with the likelihood of a multifactorial complex in which obesity and deterioration of general health are involved. The authors report a tT rate of 17.0% less than 11 nmol per liter and a syndromic association between low testosterone concentrations and obesity and comorbidities in their general population: men with a higher BMI were more likely to be diagnosed with hypogonadism with a relative risk ratio of 3.30 ($P < 0.001$) and 8.74 ($P < 0.001$) for a BMI of 25 to 30 kg m^{-2} or a BMI of greater than 30 kg m^{-2}, respectively. Those who reported more than one comorbid condition had a relative risk ratio for hypogonadism of up to 2.25 ($P < 0.05$). Interestingly, older men were more likely, with a relative risk ratio of 3.04 ($P < 0.001$) per decade, to have hypogonadism, but this was also linked to both obesity and comorbidities [3, 4].

This corroborates a previous approach focused on patients, rather than subjects from a general population, which shows that in men with chronic illnesses, such as obesity, diabetes mellitus or metabolic syndromes, the prevalence of hypogonadism is about 40% [5]. This is in agreement with current concepts regarding mutual and self-perpetuating disturbances of the hypothalamic-pituitary-gonadal axis and metabolic disorders in men [6]. While all these approaches do not conclusively describe causalities for the disorder but rather describe associations, they provide a useful and holistic view of the aging male patient. The definition of a detached testosterone deficiency syndrome that is related to sexuality alone dose not appear to reflect accurately either the experience of the clinical realm or of the whole patient. Nevertheless, the paper by Wu and colleagues corroborates previous findings [7, 8] that different symptoms related to decreasing testosterone concentrations may have different thresholds (a range of 8 to 13 nmol L^{-1} is reported), which is clinically useful.

In the TOM study by Bhasin and colleagues [2], the selection of subjects for treatment was based on measurements of testosterone alone, rather than in combination with defined clinical symptoms such as the restriction to sexuality taken by Wu *et al*. [1], or the complete range of psychological and somatic properties or deficiencies related to hypogonadism that are given in the current clinical recommendations and guidelines [9, 10].

The TOM study is an experimental clinical trial resembling a phase III study, as it is a dose seeking procedure and neither making a diagnosis of testosterone deficiency nor pursueing the application of its usual treatment (the dosage chosen in the TOM study starts at the highest recommended levels of 10 g of testosterone gel per day, titrating the dose up to 15 g per day in some subjects). Augmentation of physical strength and ability was the primary goal. Using such high doses of testosterone to reach a significant effect in strength-related parameters has previously been shown to be helpful [11], but is not unproblematic due to the increase of hematocrit in older men [12]. The usual procedure for testosterone substitution by gel would be to start at 5 g and titrate up to 10 g per day, which is also consistent with the official international guideline for the use of this preparation [9, 10].

Taking this information into consideration, a total of 209 men were enrolled at the time the TOM trial was terminated. At baseline, there was a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity among the participants. During the course of the study, the authors described higher rates of cardiac events in the testosterone group compared with the placebo group. A total of 23 subjects in the testosterone group, as compared with 5 in the placebo group, recorded cardiovascular events [2].

However, monitoring these events was not the target endpoint of this study and reporting was partly done by telephone interviews of subjects or by reviewing external medical records. Thus, subjective feelings of tachycardia, syncopes of unknown origin, arterial hypertension, and myocardial infarctions were all summarized as cardiovascular events.

Therefore, the authors themselves warn against generalizing their findings: “However, caution is warranted in interpreting this finding, because of the small numbers

of events and because of limitations with respect to the ascertainment of adverse events. Caution is also warranted in extrapolating these findings to other doses and formulations of testosterone or to other populations, particularly young men who have hypogonadism without cardiovascular disease or limitations in mobility" [2].

Such a statement is strengthened by an earlier meta-analysis of placebo-controlled trials in older men receiving testosterone substitution (involving 651 men who were treated with testosterone and 433 who were given placebo): no effect regarding cardiovascular endpoints was described [13]. In addition, a similar placebo-controlled trial involving 274 men of a comparable age-range and setting, using a labelled dose of testosterone gel (5 g per day), described no adverse effect regarding cardiovascular endpoints (three events in each group) [14]. Cross-sectional epidemiological approaches usually demonstrate a higher cardiovascular risk in those men with low testosterone concentrations [15, 16]; however, a putative cause-effect relationship cannot be elucidated by such investigations. Interestingly, both trials involving older men with reduced mobility and application of testosterone gel [2, 14] describe a favorable effect regarding the intended endpoint, namely muscle strength.

In summary, important lessons can be learned from these two publications: a) the definition of a disease must include a holistic assessment of the patient, reviewing all information about the patient's medical history, including somatic properties; b) late-onset hypogonadism occurs within a complex of metabolic disorders and co-morbidities, the likelihood of which increases with age but is not restricted to the process of aging itself; c) sexual symptoms are probably the most important properties that are related to low testosterone levels in older men but are not the only ones; and d) it remains unclear whether cardiovascular endpoints are influenced by testosterone substitution, but caution is advised when using higher testosterone doses than recommended, not only in older men with co-morbidities, but also in men of any age.

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