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CLINICAL

Have the Testosterone Trials demonstrated the effectiveness of testosterone therapy in older men without classical hypogonadism?

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TITLE Effects of testosterone treatment in older men

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SUMMARY

The 'Testosterone Trials' (TTT) are an interlinked and coordinated series of seven US National Institutes of Health (NIH)-sponsored, double-blinded, placebo-controlled studies examining the potential benefits of testosterone therapy in a hyper-selected cohort of older men.[1] TTT aimed to evaluate the impact of testosterone therapy on symptoms commonly associated with male ageing and also postulated to relate to testosterone deficiency, but were not powered to detect adverse outcomes. Findings from the three lead studies, focusing on vitality, sexual and physical function, were recently published.[1]

These three lead studies comprised 790 men (having screened 51,085 applicants) aged 65 years and older, with an average serum total testosterone concentration less than 275 ng/dl (9.5 nmol/l), from morning venepuncture on two separate days. Participants received either testosterone or placebo gel for 1 year. Each man could participate in one or more of the three trials, depending on their reported symptoms in relation to impairment of sexual function, physical function and/or vitality.

In order to evaluate efficacy, assessments were made every three months from baseline to end-of-study at 12 months. Testogel (Androgel® 1%) was initiated at 5 g daily and the dose titrated so as to achieve serum total testosterone concentrations in what would be the mid-normal range for men aged between 19 and 40. A statistically significant improvement in sexual activity from baseline was observed in the treatment arm, as ascertained by the Psychosexual Daily Questionnaire score; this emerged from the Sexual Function Trial itself and also when data from all three trials were combined: OR 0.58 ($p < 0.001$) and 0.62 ($p < 0.001$), respectively. A better response was associated with a greater increase in testosterone level. Sexual desire and erectile function also improved with a treatment effect of 2.93 ($p < 0.001$) and 2.64 ($p < 0.001$), respectively. However, the magnitude of these responses began to decline in a linear manner from 9 months until observations ceased at the study end-point of 12 months.

The Physical Function Trial examined the percentage of men whose 6-min walking distance increased by at least 50 m over the course of the study, and failed to identify any benefit from testosterone therapy, although a small but significant improvement was noted when data from all three studies were pooled (20.5% in T arm vs 12.6% receiving placebo: OR 1.75; $p = 0.003$). The Vitality Trial likewise failed to identify any significant improvements in this domain for the testosterone arm, although there was a statistically significant difference in PANAS (positive and negative affect schedule) scores compared with the placebo arm when data from all three studies were pooled, suggesting slightly better mood and lower severity of depressive symptoms with testosterone treatment.

Overall, testosterone therapy increased levels of free testosterone, estradiol and dihydrotestosterone, but unsurprisingly did not increase levels of sex hormone binding globulin. No significant adverse effects were observed in the treatment arms and no significant between-group differences were observed in cardiac adverse events in the 12-month study period. However, the study was a priori underpowered for evaluation of safety.

CLINICAL OPINION

Despite the accompanying media fanfare, TTT data are largely irrelevant to mainstream clinicians treating men with organic hypogonadism of all ages. This includes true late-onset hypogonadism in the ageing male as defined by the European Male Ageing Study (EMAS), for whom testosterone replacement therapy is already well established. However, clinicians and researchers with an interest in 'anti-ageing' treatment strategies may be more enthused by a better definition of the potential benefits, at least initially. TTT aimed to inform decisions about the benefits of testosterone treatment for men aged 65 years and older whose levels are low for no apparent reason other than age, albeit without statistical power to detect adverse outcomes, particular cardiovascular outcomes. TTT comprised seven studies conducted with some shared measures and participants, thus maximising the overall study power.

However, such stringent exclusion criteria were applied that only 1.5% of the screened population was identified as being eligible for the study, which is both a major strength (in terms of eliminating at least some confounding factors) and a major limitation (with respect to the applicability of the study findings to a broader population of older men).

Crucially, TTT did not recruit men with late-onset hypogonadism. EMAS had previously demonstrated that the overwhelming contribution to age-related decline in serum testosterone levels relates to physiological inhibition of gonadotrophin secretion with obesity and/or accumulating disease burden, rather than being a directly age-related effect.[2] EMAS did, however, identify a small (around 2%) number of men with true late-onset hypogonadism, characterised by testicular insufficiency and modestly elevated serum gonadotrophin concentrations.[2] Given that elevated gonadotrophins were a key exclusion criterion, TTT could not recruit older men with true late-onset hypogonadism. TTT likewise did not recruit men with frailty of old age, even though proponents of testosterone therapy beyond the classical envelope have criticised the only study in this area,[3] which was terminated early due to an excess of adverse cardiovascular outcomes, on the basis that the testosterone dosing schedule was inappropriately aggressive.

Ultimately, the majority of the eligible participants were older men with comorbidities associated with low circulating testosterone.[4,5] More than half of the participants (63.5%) were obese (mean BMI 31 ± 3.5 kg/m^2) and over a quarter of them (37.5%) had type 2 diabetes. In such men with metabolic syndrome, total testosterone typically underestimates true androgenicity, due to suppression of hepatic sex-hormone binding globulin synthesis by hyperinsulinaemia, making free testosterone (either calculated by mass action equation or well-validated assay) a key tool in avoiding misdiagnosis of hypogonadism.

Thus, to characterise TTT as examining the potential benefits of testosterone therapy in older men is only true in the narrowest sense of the word. In reality, these were studies of men with predominantly obesity/metabolic syndrome-related perturbation of hypothalamic-pituitary-gonadal (HPG) axis function,[2] who just happened to be aged 65 years and over. This phenotype has already been studied in a randomised-controlled trial, albeit one directed more at investigating metabolic and glycaemic outcomes.[6] Whether the TTT's findings would have been any different in a cohort of younger men, matched for BMI and comorbidities, remains an intriguing point of speculation. Overall, the headline description of TTT as examining a potential role of testosterone therapy in ageing males owes more to 'brand-recognition' than reference to a distinct disease phenotype. Moreover, clinicians should be aware that the HPG axis will invariably recover once the modifiable risk factors are removed, and that it remains unclear whether ill health-related HPG axis suppression is an adaptive or maladaptive phenomenon.[7] Further confounding issues with the trial include the lack of fasting bloods to assess testosterone status and a lack of information on medications (e.g. thiazolidinediones) that might affect testosterone levels.

TTT demonstrated relatively modest improvements in sexual function that were not fully sustained during the latter half of the 12-month study period. Overall, these short-term benefits were less than previously reported for non-endocrine intervention with oral phosphodiesterase inhibitors. Moreover, extrapolating these gradients beyond the available 12 month data suggest that, around 18 months after study initiation, they intersect the line of 'zero net benefit'.

In respect of physical and mental functions, benefits were even more uncertain. The Physical Function Trial found no significant improvement in the 6-minute walking distance for the active treatment arm, although significance was reached (OR: 1.76; $p = 0.003$) when participants from all three lead trials were combined (even though the overall effect size differed little between the physical function trial alone and combined trial data (1.42 vs 1.76). The authors themselves concluded that no benefit was seen with respect to vitality or walking distance, which we interpret as indicating that potential improvements were not clinically significant, even if they reached statistical significance.

It was also unclear how a modest improvement in the score used to assess mood and mental function might translate into discernible clinical benefits, e.g. mean difference of -0.49; ($p < 0.001$) in PANAS negative

affective score, where total score ranges between 10–50. Hence, the small to modest improvement in the scoring systems used to assess physical function; mood and depressive symptoms should not be over-emphasised.
Although no major adverse effects were observed, TTT was never powered to achieve statistical significance in this area. Larger studies with longer follow up durations would be required to examine long-term safety but the equivocal benefits recorded in these three lead studies probably would not justify such investment by any major grant-giving body. Although testosterone therapy in patients with classical hypogonadism is safe, and cardiovascular risk does not appear to increase in middle-aged men on testosterone therapy,[8] the long-term effects of testosterone treatment on cardiovascular disease susceptibility and mortality in older men with comorbidities are currently unclear. Some recent publications suggested potential cardiovascular disease risks with testosterone therapy,[3,9] whereas other evidence suggested protective effects of therapy to keep testosterone within the normal range in older people.[10] Interestingly, a recent large population-based observation study found that long term exposure to testosterone therapy in older men aged 65 years and older was associated with reduced risks of mortality and cardiovascular events, although short duration of therapy was associated with increased mortality.[11]

A recent meta-analysis of randomised controlled trials also highlighted significant concerns and, worryingly, identified a major source of discrepancy between studies that raised concerns about cardiovascular safety and those purporting to show benefit, based on whether these were independent and industry-supported[12] Several publications have also drawn our attention to the potential deleterious effects of keeping testosterone levels at the high end of normal for older men.[13,14] These findings have drawn the attention of the US Food and Drug Administration and resulted in exclusion of age-related and idiopathic hypogonadism from the list of indications for testosterone therapy (BRUDAC).[15]

In summary, the first paper to emerge from TTT confirmed limited, short-term efficacy of testosterone therapy in sexual function among a hyper-selected cohort of older men without either classical, or late-onset (by EMAS criteria) hypogonadism, and with a participant phenotype dominated by general comorbidities and obesity. These findings are in keeping with those of previous observational studies and a smaller scale randomised trial, demonstrating short-term improvement in sexual function and quality of life in older men receiving testosterone therapy.[16–18] TTT was not powered to answer the obvious question of whether testosterone therapy is safe and effective in older men outside the traditional diagnostic envelope for male hypogonadism.
We diverge from the TTT authors' view that data on benefits presented therein are sufficiently informative and compelling to justify future funding for the larger randomised controlled trials that would be required to generate conclusive cardiovascular safety data. Hence, consideration should be given to developing trials that, unlike TTT, are more inclusive of old age in respect of recruitment and less inclusive of obesity and comorbidity, seeking thus to properly evaluate potential benefits for testosterone therapy in old age. Randomised controlled trials examining a role for testosterone therapy in men with obesity/metabolic syndrome have already been performed[6] and in this era of tightened research funding, do not necessarily require duplication.

In the context of so much persisting uncertainty, clinicians can refer to the Society for Endocrinology's pragmatic and measured position statement for advice in this area.

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