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Research Highlight

Diagnosis and treatment of hypogonadism in older men: proceed with caution

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Male hypogonadism, defined as clinical features of androgen deficiency combined with confirmed unequivocally low testosterone levels [1], is a straightforward diagnosis in younger men with underlying testicular and pituitary pathology. The diagnosis of hypogonadism in older men is challenging, because of the non-specificity of symptoms and the age-related decline in testosterone levels which is accelerated by chronic disease and obesity. Two recent publications in the *New England Journal of Medicine* (Table 1) suggest that "Late Onset Hypogonadism (LOH)", a controversial entity, is at best an uncommon, over-diagnosed condition [2], and raise the possibility that supra-physiological testosterone therapy in frail elderly men may increase the risk of adverse cardiovascular events [3].

In contrast to women, whose oestrogen levels fall precipitously at menopause, men of all ethnicities experience a more gradual fall in testosterone levels, averaging 0.5%–2% per year, from early middle age onwards. Up to 30% of men older than 60 years have testosterone levels below the normal range for young men, usually in the absence of pituitary or testicular pathology. Observational studies have associated this age-related fall in testosterone to phenotypic features of ageing, such as loss of sexual vigour, decreased energy, loss of muscle mass and bone density, and weight gain, features that are reminiscent of pathological hypogonadism (due to pituitary or testicular disease) in younger men. Association studies however, do not prove causation, which can only be addressed in appropriately powered, randomized placebo-controlled trials (RCTs). The most consistent effects of testosterone therapy in RCTs of older men are modest increases in muscle mass and bone mineral density, and small decreases in fat mass. To date, trials were neither powered to inform about patient-important endpoints, such as quality of life, physical function, or fracture rates, nor about the potential risks of testosterone therapy, especially regarding prostate and cardiovascular disease, conditions that are highly prevalent in older men.

In this context, Wu *et al*. [2] aimed to identify diagnostic criteria for "LOH", using a questionnaire-based approach in relatively healthy men participating in the European Male Aging Study (EMAS) (Table 1). Of the 32 candidate symptoms of hypogonadism interrogated, only three sexual symptoms consistently clustered with a low testosterone level: erectile dysfunction, decreased sexual thoughts, and decreased frequency of morning erections, with testosterone threshold levels of 8.0 nmol L^{-1}, 8.5 nmol L^{-1} and 11 nmol L^{-1}, respectively. Therefore Wu and colleagues propose to define "LOH" by the presence of at least these three symptoms, and a total testosterone level of less than 8 nmol L^{-1} (or less than 11 nmol L^{-1} if the free testosterone level was less than 220 pmol L^{-1}). The overall prevalence of "LOH" according to this definition was only 2.1%.

However, even for these sexual symptoms, differences in testosterone

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Table 1. The summary of Wu *et al*. [2] and Basaria *et al.* [3].

	Wu *et al*. [2]	Basaria *et al*. [3]
Study design	Questionnaire-based approach with multiple statistical analyses involving a training and validation set to identify threshold levels of testosterone below which symptoms occurred, and to assess for syndromic clustering of symptoms with low testosterone.	Randomized placebo-controlled six month intervention trial of testosterone gel therapy
Study population	3369 community-dwelling men at eight European centres	209 community-dwelling men from the Greater Boston area
	Mean age (range): 60 (40–79) years	Mean age (range): 74 (65 or older) years
	Mean total testosterone: 16.5 nmol L^{-1}	Mean total testosterone: 8.4 nmol L^{-1}
	Population characteristics:	Population characteristics:
	75% good to excellent general health	Significant mobility limitations
	50% free of coexisting illness	Requiring 30 seconds to walk 50 meters
	Prevalence of diabetes < 10%, heart disease < 20%	Prevalence of diabetes 25%, heart disease 50%, obesity 50%
Main findings	Only nine of 32 candidate symptoms for hypogonadism were associated with low testosterone	Cardiovascular-related adverse events (suspected or confirmed evidence myocardial ischemia, arrhythmia, syncope, peripheral oedema, cardiac failure or hypertension):
	Only three sexual symptoms clustered with low testosterone but not independently of comorbidities	23 /106 subjects in the testosterone group (5 serious events)
		5 / 103 subjects in the placebo group (0 serious events)

levels between symptomatic and asymptomatic men were minimal, and more than 25% of men with unequivocally normal testosterone levels also experienced them. Psychological symptoms, such as sadness, loss of energy or fatigue had little or no association with testosterone level.

This study [2] shows that even the most specific symptoms of androgen deficiency are highly prevalent in the general population of ageing men. Thus, such symptoms are suggestive of androgen deficiency only if total testosterone levels are clearly subnormal (less than 8 nmol L^{-1}). This study also shows that "LOH" by this definition is uncommon. As this was a cross-sectional study, whether low testosterone is causally related to these symptoms remains unknown. Indeed, the finding that the association of low testosterone and symptoms was attenuated after adjustment for age, body mass index and comorbidies leaves open the possibility that poor general health contributes to both symptoms and low testosterone levels. Given that this study was not an intervention trial, the operational definition of "LOH" proposed by Wu *et al*. should not be misinterpreted as an indication for initiation of testosterone therapy. Rather, these criteria could be considered for enrolment in clinical trials to determine the benefits and risks of testosterone treatment.

The second study in the same issue of the *New England Journal of Medicine* by Basaria *et al*. [3] was a randomized, placebo-controlled, six month trial designed to assess the effects of testosterone therapy on muscle strength and functional mobility in frail elderly men. The trial was terminated early because of significantly increased cardiovascular events in the testosterone-treated group. Twenty-three of the 106 subjects in the testosterone group, compared to 5 of the 103 subjects in the placebo group, had cardiovascular-related adverse events. Five serious cardiac events (three myocardial infarctions, one stroke and one death due to suspected myocardial infarction) occurred in the testosterone group, with no such events in the placebo group. Thus these data suggest that testosterone therapy may increase the risk of cardiac events. However, the trial was small, with only a small number of cardiovascular events which lacked a consistent pattern. Therefore, differences between the testosterone and placebo groups may have been

due to chance. Indeed, previous similar trials and a recent meta-analysis did not show an increased risk of adverse cardiovascular events with testosterone therapy [4]. A recent trial by Srinivas-Shankar *et al.* [5], which was very similar in subjects, design and methods to Basaria's trial, showed a very low incidence of adverse cardiac events which was not different between the testosterone- and placebo-treated groups. However, Srinivas-Shankar *et al.* [5] used a lower testosterone treatment dose, half of that used by Basaria *et al.* [3]. Given that achieved mean testosterone level in the testosterone-treated group in Basaria's study was 19.9 nmol L^{-1}, men received pharmacological rather than replacement testosterone therapy [3]. Further, cardiovascular events were not a planned outcome in Basaria's study [3], which may have introduced an ascertainment bias. Early termination of the trial may overestimate treatment differences.

Assuming that the increased adverse rate was not due to chance, what are potential mechanisms by which testosterone may increase cardiovascular events? Given that adverse events appeared within weeks, they are not explained by effects of testosterone on changes in lipid levels or atherosclerosis. The increased rate of oedema is consistent with the salt and water retaining effects of supra-physiological doses of testosterone. Acute effects of testosterone on thrombosis and vascular reactivity are ill-defined, and invoking such mechanisms remains speculative.

In the limited efficacy analysis, testosterone therapy improved leg-press, chest-press strength and stair climbing, but not walking speed or grip strength. However, inferences were limited because of loss of statistical power owing to early termination of the trial, and the clinical significance of these findings remains uncertain. Given the absence of difference in walking speed, it appears unlikely that cardiovascular events were triggered by increased activity in the testosterone-treated group. In contrast to Basaria, Srinivas-Shankar *et al.* [5] did complete their study and showed a significant improvement in lower limb muscle strength in the testosterone-treated group.

What are the implications of these two studies for future clinical trials? Future RCTs of testosterone therapy should select the patient population with the most potential for benefit and least potential for harm, such as men with multiple symptoms consistent with androgen deficiency and a total testosterone level of less than 8 nmol L^{-1}. Cardiovascular events should be included as a planned outcome measure and prospectively adjudicated by an independent data and safety monitoring board. Ideally, such trials should be powered to inform about endpoints such as physical function and fracture rate, and lifestyle measures (weight reduction and exercise) should be incorporated. A conceptual distinction should be made between physiological (replacement) and pharmacological testosterone therapy, given the differences in trial design and risk-benefit ratio. Trials should be coordinately designed to allow aggregate data analysis in the form of meta-analyses, as individual trials are unlikely to provide conclusive information about risk.

What are the implications of these studies for clinical practice? Clearly, they are not relevant for men with pathological hypogonadism due to testicular or pituitary disease, in whom testosterone therapy dramatically improves the features of androgen deficiency. Application of Wu's criteria should guard against excessive diagnosis of hypogonadism in ageing men. In the recently updated US Endocrine Society testosterone therapy guidelines [1] there was substantial disagreement among the expert panel as to whether, in older men with symptoms compatible with hypogonadism, testosterone therapy should be recommended at total testosterone levels of less than 6.9 nmol L^{-1} or less than 10.4 nmol L^{-1}. The two studies in the *New England Journal of Medicine* lend strong support to the more conservative cut-off of less than 6.9 nmol L^{-1} (confirmed by a validated assay), although it must be emphasized that even in such men the risk-benefit ratio of testosterone therapy remains uncertain. Clearly, the EMAS study suggests that "LOH" is uncommon, and that symptoms attributed to testosterone deficiency may be a consequence of poor health. Thus, low testosterone may be a marker of poor health leading to non-specific symptoms, rather that a direct cause of the reported symptoms. If this is true, lifestyle measures such as maintaining a healthy weight and regular exercise, as well as prevention and treatment of comorbidities may be more effective (and safer) than testosterone therapy in preventing, or even treating "LOH", although this hypothesis will need to be tested in prospective trials. Moreover, although the findings may be due

to chance, the increased rate of adverse cardiovascular events in the Basaria study [3] should further dampen the enthusiasm for testosterone therapy in older men. Given the current knowledge gap, until new evidence is available, heeding Hippocrates' adage "first do no harm" may be the most prudent course of (in) action.

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