Mortality Associated to Late-Onset Hypogonadism: 
Reasons Not to Treat With Testosterone?

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ge-related decline of serum T and its clinical implications remain the subject of controversies. These are unlikely to be settled soon due to the lack of appropriate randomized trials. It nevertheless is important to keep adjusting clinical practice advice to current knowledge.

Population means of serum T decline and SHBG increases with age, but there is considerable between-subject variation in prevalent (free) T in apparently healthy older men (1, 2). Genetic and lifestyle-related factors account for only part of T variation (1), which suggests that health-related factors contribute. Indeed, to define a “healthy state” for populations of elderly men with a high prevalence of (subclinical) comorbidities is not straightforward. Recently, serum T was reported as stable across age strata among men self-reporting very good health (3).

Signs and symptoms of “normal aging” are reminiscent of those in young hypogonadal men (1, 4), which raised expectations that T substitution in (borderline) low T might help reverse or limit progression of some consequences of aging, if not improve general health and longevity. In apparent support of the concept of late-onset hypogonadism (LOH), observational studies have reported associations of serum (free) T below the reference for young men with symptoms that are part of the clinical picture of hypogonadism, ie, in particular sexual symptoms besides others such as fatigue, decreased muscle mass and physical vigor, or osteopenia (1, 2, 4–8). According to practice guidelines (4, 8), the diagnosis of androgen deficiency in the elderly or LOH, for which T treatment might be considered, should be based on the concurrent presence of consistent symptoms of hypogonadism and unequivocally low serum (free) T. However, symptoms and low T both become more prevalent and less specific with age, so that the likelihood of LOH diagnosis increases (5), whereas a causal link between clinical and hormonal findings becomes more evasive. A close look at the data shows that a majority of symptomatic men do not have low T, whereas a substantial part of those with low T are asymptomatic (5). Among men with LOH, clinicians thus have limited ability to distinguish those in whom low T is the cause of symptoms from those in whom low T is unrelated to their health problem or rather its consequence. As an epiphenomenon of comorbidity, low T can be irrelevant to the patient’s health state, or of clinical relevance by contributing to further deterioration of health, or a beneficial adaptive response to the present status (9).

Beyond classical symptoms of hypogonadism, low T and LOH have been associated in observational studies with prevalent and/or incident obesity, metabolic syndrome, type 2 diabetes, dyslipidemia, and other cardiovascular risk factors (10, 11). The relation between serum T and metabolic disturbances is likely bidirectional, but a major component of reverse causality is apparent from effective restoration of serum T with lifestyle measures and weight loss (10). Systematic review and meta-analysis of community-based observational studies indicate a mostly modest association in elderly men of low endogenous T with incident cardiovascular disease and risk of cardiovascular and all-cause death. This might imply protective effects of T, but authors generally concur to consider residual confounding with low T a marker of poor health status as a plausible interpretation of the data (11–13). Marked between-study heterogeneity, partly accounted for by characteristics of the subjects and study methods, tend to support the latter view (12). Yeap et al (14) reported a U-shaped association between T (and calculated free T) and all-cause mortality in older commu-
nity-dwelling Australian men; whereas the highest mortality was in the lowest T quartile, mortality was not significantly lower in the highest quartile, although men with midrange T had the lowest mortality. As for all observational studies, an effect of residual confounding cannot be excluded, but if confirmed, these findings are compatible with neither a direct causal relation between T deficiency and mortality nor interpretation of low T as a simple biomarker of ill health.

In an attempt to improve specificity of the LOH diagnosis, Wu et al (6) proposed minimal diagnostic criteria, derived from elegant cluster analysis of data from the European Male Aging Study (EMAS) and consisting of the “syndromic” simultaneous presence of three sexual symptoms (ie, poor morning erections, decreased sexual interest, and erectile dysfunction), together with a serum total T < 11 nmol/L (320 ng/dL) and free T < 220 pmol/L (6.4 ng/dL); men fulfilling these criteria with serum total T < 8 nmol/L (230 ng/dL) are considered as having severe LOH (6, 7). Prevalence of such defined LOH in the EMAS population increased with age, body mass index, and number of coexisting illnesses and was 5.1% in men 70–79 years old (6). The men with LOH had a lower hemoglobin, muscle- and bone mass and poorer physical performance and general health compared to their peers; men with low T only, irrespective of sexual symptoms, showed lesser magnitude of associations with the same end-points (7).

In this issue of the JCEM, Pye et al (15) report prospective data on mortality in 2599 community-dwelling men from EMAS, aged 40–79 years and followed for a median of 4.3 years. Global mortality was 5.7%, whereas mortality was 30.9% in 55 men with LOH. After adjusting for age, center, current smoking, body mass index, and poor general health, 29 men with severe LOH had a 5-fold risk of all-cause mortality compared to men without LOH; mortality was 2-fold in men with T < 8 nmol/L (<230 ng/dL) compared to eugonadal men, irrespective of sexual symptoms, and was 3-fold higher in men with three sexual symptoms compared to asymptomatic men, irrespective of serum T. Risks were similar for cardiovascular death. Although based on a small number of events, these observations fit expectations. Indeed, besides reports of association of low T with mortality, meta-analysis of 12 prospective cohort studies involving 36,744 participants confirmed individual reports of association of erectile dysfunction with increased risk of cardiovascular disease, stroke, and all-cause mortality (16). Although possibly independent of “classical” cardiovascular risk factors (16), these associations most likely reflect common pathophysiological mechanisms between erectile dysfunction and cardiovascular disease and/or a role of erectile dysfunction as a marker of more generalized vascular alterations. Anyway, sexual function and poor health do not match well, and considering the relatively short follow-up in EMAS, observed associations between sexual symptoms and mortality most likely reflected pre-existing cardiovascular disease or more generalized health problems. In this regard, two aspects of the EMAS findings in severe LOH are noteworthy: first, no statistical interaction was observed between associations of low T and sexual symptoms with mortality; and second, a broadly similar pattern was observed for cardiovascular- and cancer-related mortality (15). The characteristics of men with LOH reflecting poorer general health status (7), the apparently independent associations of low T and sexual symptoms with adverse outcome, and the association with multiple causes of mortality all suggest that severe LOH is in essence a non-specific marker of poor health and frailty in older men, rather than revealing a causative role of low T in the deterioration of health and risk of death.

In any case, as concluded by the EMAS authors, severe LOH identifies a small group of men at high risk of death in need of medical attention. This raises the question whether this should include considering T therapy. Presently, the risk-benefit profile of T therapy is not established due to the lack of appropriate randomized trials (11). Moreover, reported T trials are heterogeneous in their inclusion criteria, going from healthy men with a variety of baseline T levels to men with specific disease (eg, liver cirrhosis, AIDS, type 2 diabetes, etc), and in their treatment modalities. Applied dosages often were supra-physiological, either manifestly (eg, many regimens with injections of short-acting T esters) or more subtly with regimens aiming at stable “midphysiological” levels for the young without taking into account diurnal variation of T levels. If there is indeed a U-shaped relation between serum T and mortality (14), that might explain inconsistencies among study results. Review of the literature shows that T treatments have not been proven to be beneficial with respect to cardiovascular disease, but neither have they definitely shown specific adverse cardiovascular effects (11). It is nevertheless important to pay attention to recent data suggesting that T treatment might carry a cardiovascular risk. Xu et al (17) concluded from a meta-analysis of placebo-controlled, randomized trials that exogenous T overall, but in particular in trials not funded by industry, increased the risk of cardiovascular-related events. Results should be interpreted with caution in view of severe limitations of included studies. Basaria et al (18) reported early termination of a randomized trial with transdermal T in elderly men with low T, limitations in mobility, and high prevalence of cardiovascular risk factors because of increased incidence of (diverse) cardiovas-
cular-related adverse events. Shore et al (19) reported, in an observational study in 1031 veterans with low T (<250 ng/dL), lower mortality in 398 T-treated men compared to untreated men. In contrast, Vigen et al (20) found, in 8709 men in the VA health care who underwent coronary angiography and had low T (<300 ng/dL), that 1223 T-treated men had a higher risk of adverse outcome (myocardial infarction, stroke, death). These data, although not conclusive, indicate the possibility that T treatment in LOH carries a risk of cardiovascular-related adverse events, and that frail elderly men and men with prevalent cardiovascular disease might be more at risk. These warnings emphasize the appropriateness of a cautious, restrained approach to T treatment in elderly men while we await more robust evidence from randomized trials. A paradox hereby is that among elderly men meeting suggested criteria for diagnosis of symptomatic androgen deficiency or LOH (4, 6, 8), in the present state of knowledge treatment should be discouraged in those most severely affected because low T is less likely to substantially contribute to their health problems and they might be at higher risk of adverse treatment effects.

In conclusion, the finding of a severe LOH should be taken by clinicians as a warning of a potentially high-risk health status of their patient and should prompt them to take appropriate action, which in the present state of the art should not include T treatment. Whether screening for severe LOH as a marker of poor health has a role in clinical practice has not been studied, but it seems highly unlikely considering the low prevalence of severe LOH and clinically obvious poor health in at least part of this small number of subjects.

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References