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INVITED REVIEW

Male Endocrinology

Late-onset hypogonadism: current concepts and controversies of pathogenesis, diagnosis and treatment

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Although suppressed serum testosterone (T) is common in ageing men, only a small proportion of them develop the genuine syndrome of low T associated with diffuse sexual (e.g., erectile dysfunction), physical (e.g. loss of vigor and frailty) and psychological (e.g., depression) symptoms. This syndrome carries many names, including male menopause or climacterium, andropause and partial androgen deficiency of the ageing male (PADAM). Late-onset hypogonadism (LOH) describes it best and is therefore generally preferred. The decrease of T in LOH is often marginal, and hypogonadism can be either due to primary testicular failure (low T, high luteinizing hormone (LH)) or secondary to a hypothalamic-pituitary failure (low T, low or inappropriately normal LH). The latter form is more common and it is usually associated with overweight/obesity or chronic diseases (e.g., type 2 diabetes mellitus, the metabolic syndrome, cardiovascular and chronic obstructive pulmonary disease, and frailty). A problem with the diagnosis of LOH is that often the symptoms (in 20%–40% of unselected men) and low circulating T (in 20% of men >70 years of age) do not coincide in the same individual. The European Male Ageing Study (EMAS) has recently defined the strict diagnostic criteria for LOH to include the simultaneous presence of reproducibly low serum T (total T <11 nmol l^{-1} and free T <220 pmol l^{-1}) and three sexual symptoms (erectile dysfunction, and reduced frequency of sexual thoughts and morning erections). By these criteria, only 2% of 40- to 80-year-old men have LOH. In particular obesity, but also impaired general health, are more common causes of low T than chronological age *per se*. Evidence-based information whether, and how, LOH should be treated is sparse. The most logical approach is lifestyle modification, weight reduction and good treatment of comorbid diseases. T replacement is widely used for the treatment, but evidence-based information about its real benefits and short- and long-term risks, is not yet available. In this review, we will summarize the current concepts and controversies in the pathogenesis, diagnosis and treatment of LOH.
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INTRODUCTION

It is well-documented that testicular testosterone (T) production decreases in men with ageing, by 1%–2% per year after the age of 40 years. However, on average serum levels of T still remain within the normal range of young men.[1–4] The age-dependent reference range for T has not been defined and the criteria on cutoff levels for hypogonadism remain somewhat controversial. When only hormonal criteria are used (i.e., T below the lower limit of the reference range of young men (about 10 nmol l^{-1}), the prevalence of 'biochemical hypogonadism' is high: 23.3% in 40- to 79-year-old men of the European Male Ageing Study (EMAS).[5] In another study, the incidence of hypogonadal T levels increased to about 20% of men over 60, 30% over 70 and 50% over 80 years of age, and the prevalence of low free T in each age group was even higher,[3] due to the ageing-related increase of sex hormone binding globulin (SHBG) levels. This does not necessarily mean clinical hypogonadism, because most men with low T remain asymptomatic.[6] However, some ageing men do develop (usually mild) symptomatic T deficiency, which is associated with diffuse symptoms reminiscent of hypogonadism in young men, such as sexual dysfunction, muscle weakness, obesity, osteoporosis, hot flushes, insomnia, fatigue, poor concentration and depression. The combination of low T and an array of the above symptoms has been termed with many names, including male menopause or climacterium, partial androgen deficiency of the aging male (PADAM), andropause and late-onset hypogonadism (LOH). The last term describes best the nature of the syndrome. According to a recently formulated definition 'LOH is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum T levels (below the young healthy adult male reference range)'.[7]

Most of the studies on LOH have been carried out in Europe, USA and Australia, but there are also studies on the diagnosis, prevalence and treatment of LOH form numerous Asian countries (see e.g.[8–11]). Direct comparisons between the studies from different geographic regions are difficult to make because of heterogeneity of experimental approaches, but it is quite likely that the basic features of LOH are very similar in various geographic and cultural environments.

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Because the symptoms of LOH are similar to those of hypogonadism in young men, T replacement therapy has become a popular option for its therapy. Marketing of T treatments has been aggressive and effective, especially in the United States, where the sales volume of T preparations keeps rising, doubling between 2005 and 2010 (http://sorebuttcheeks.blogspot.co.uk/2010/12/growth-hormone-and-testosterone-sales.html), and following a similar trend in other parts of the world.[12] A worrying aspect of this trend is that it has occurred almost without any solid scientific evidence of the benefits and risks of the treatment. The diagnostics and evaluation of the effects of T therapy in LOH have largely been based on poorly controlled and underpowered treatment trials, on subjective opinions and experience of physicians and on data that might have been placebo effects.[13] The information targeting the health professionals and general public is biased in favor of T treatment, filled with statements from opinion leaders with ties to the pharmaceutical industry or to commercial medical practices (e.g.[14,15] and numerous web sites).

The uncertainty surrounding LOH means that there are now numerous recommendations for its diagnosis and treatment, which have been formulated by panels of experts.[7,16,17] Unfortunately, they too are, to some extent, based on insufficient scientific evidence and 'educated guesses'. An increase in reliable information about LOH has clarified the diagnostic criteria of LOH. However, the indications and contraindications for T treatment of LOH, including short- and long-term benefits and risks, still await evidence-based information. This review concerns the current facts and controversies in the pathogenesis, diagnosis and treatment of LOH.

PATHOGENESIS OF LOH, AGEING AND HYPOTHALAMIC-PITUITARY- TESTICULAR FUNCTION

Testicular function declines somewhat with advancing age,[18] but the purely age-dependent change is usually small and probably of the same magnitude as that of other organs of the body.[19] This is in clear contrast to the ovary, which undergoes a rapid functional involution at menopause. It is therefore counterintuitive to draw any parallels between the ageing-related changes in testicular and ovarian function. Spermatogenesis remains upon ageing sufficient to maintain a man's fertility throughout his entire postpubertal life. Testicular volume reflects closely the quantity of sperm production, and it decreases by about 15% between the ages of 25 and 80–90 years.[20] At the same time, the production of seminal fluid decreases, sperm become less motile and their structure deteriorates, although the sperm concentration in semen remains quite constant.[21] The time of unprotected intercourse needed to achieve fertilization, after correction for the woman's age, becomes longer with increasing age of the male partner.[22] The morphological changes in the testis upon ageing include degeneration of the germinal epithelium and increased proportion of connective tissue. Moreover, the total number of Sertoli and Leydig cells decreases to around half of that of the young testis.[23,24] The concomitant increase in pituitary gonadotrophin secretion indicates the primary testicular nature of these alterations, and this compensatory response is able to minimize the decline of testicular function in most ageing men.

The concentration of serum T reaches its maximum around 25–30 years of age and starts a slow steady decline thereafter at a rate of about 1% per year (**Figure 1**). A recent longitudinal study showed that serum total T decreases between 55 and 68 years of age by 1.4% per year, free T by 2.7%, while SHBG increased at the same time by 2.7%.[25] It is noteworthy that the aging-related decline of T shows great inter individual variability, with about 20% on men over 60 years having serum T in the upper normal range of young men, and about 20% being below the reference range, and even a larger proportion of men have their bioavailable T in the subnormal range.[2,26] About half of circulating T is bound to SHBG, and another half to albumin, and only 0.5%–3% of T remains in free, non-protein-bound form, representing the biologically active fraction.[27] The concentration of SHBG increases with ageing, which means that the proportion and absolute concentration of free T decrease (**Figure 1**). Hence the latter decreases more than total T, by about 2%–3% per year although the average free T level still remains within the normal range in most men (**Figure 1**). The decline of T purely due to biological ageing is primary, i.e., caused by testicular failure, and it is therefore accompanied by a reciprocal increase in luteinizing hormone (LH) secretion.

Another complexity to the age-related changes in T levels is brought about by the associated weight gain and deterioration of general health owing to chronic diseases-such as diabetes, hypertension, cardiac, hepatic or renal failure, chronic obstructive lung disease and inflammatory arthritis. Moreover, the medications associated with these disorders, such as opiates and glucocorticoids, are partially responsible for the decreased T through actions on LH secretory dynamics. T production can be considered a good indicator of a man's general health, which decreases in response to a variety of stressors. High body mass index (BMI) can be regarded to provide a read-out for metabolic stress, and its suppressive effect on T levels is much greater than that of chronological age (**Figure 1**). Serum T in a man with BMI >30 kg m^{-2} is, on average, 30% lower than that of a man with BMI <25 kg m^{-2}, at any age, which is more that the purely age-dependent decrease between 40 and 80 years. The mechanism of this effect is unknown, but it is apparently linked to the increased negative feedback inhibition of gonadotropin secretion by adipose tissue-derived estrogens, leptin and cytikones/adipokines.[28–30] A similar, though milder, suppression of T secretion is observed in men with chronic illnesses. Curiously, the decrease in T secretion associated with obesity and chronic illness is not associated with compensatory increase in gonadotropin levels, thus indicating a secondary central mechanism for the disturbance (**Figure 1**). Obesity as the cause of low T in ageing men is more common that chronological age; in the EMAS study, 73% of men fulfilling the criteria of LOH (see below) were obese or overweight.[6]

DIAGNOSIS OF LATE-ONSET HYPOGONADISM

How should T be measured in the diagnostics of late-onset hypogonadism

Immunoassays (IAs) have been the mainstay for measuring sex steroids since their inception in the late 1960s. They provide usually rapid, economical and reliable information about circulating hormone concentrations. However, the accuracy and precision of T IAs, especially at the low concentrations detected in children, women and hypogonadal men, remain a concern.[31–34] While most IAs measure high (adult male) T concentrations sufficiently well, they often overestimate low (e.g., female) concentrations,[35] thus reducing the specificity and sensitivity of diagnosis of female hyperadrogenism and male hypogonadism.

Whether IAs for T can reliably discriminate between eugonadal and hypogonadal men remains a contentious topic.[31,35,36] Therefore, there is a strong emphasis for the need of improved standardized methods, as well as traceability of the standards, to overcome the problems of, in fact, all steroid measurements.[16,33–38] Already during the era of the IA dominance, mass spectrometry (MS) was regarded as the 'gold standard' of steroid analysis. However, its technical complexity, cost and suboptimal sensitivity precluded it as a routine method in the clinical

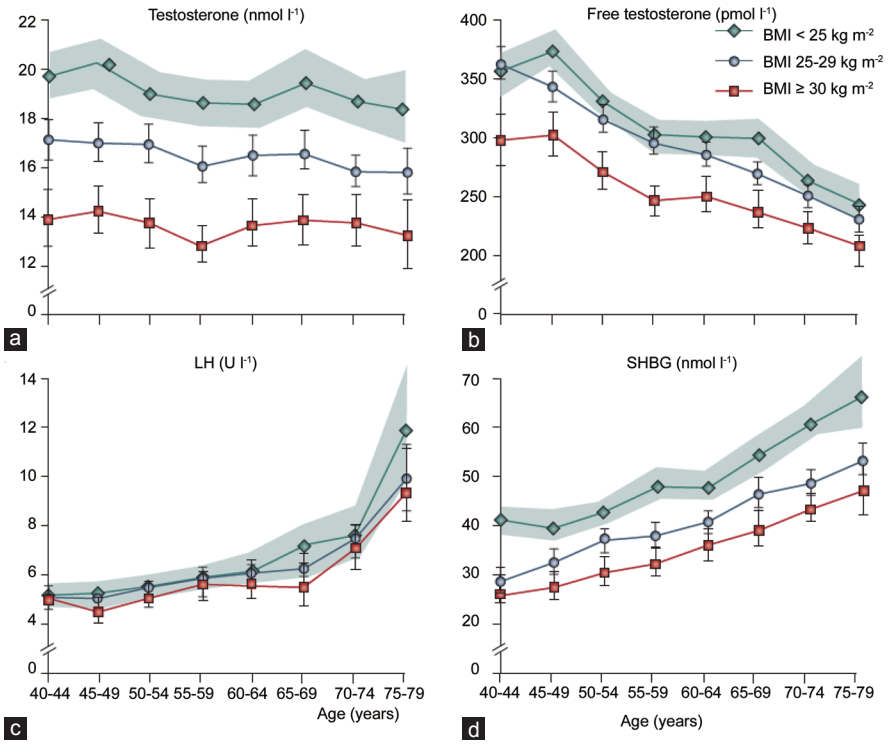

Figure 1: Relationship between age, BMI and reproductive hormones of 3220 men aged 40–79 years, from the EMAS study. The cohort was stratified according to BMI into nonobese (BMI < 25 kg m^{-2}), overweight (BMI 25–30 kg m^{-2}) and obese (BMI > 30 kg m^{-2}) men. The panels present mean (95% CI in shaded area and vertical lines) levels of (**a**) total and (**b**) free testosterone, (**c**) LH and (**d**) SHBG. Compared with nonobese men, total and free testosterone was significantly lower in the overweight and obese men at all ages. Total testosterone and SHBG age trends in the three BMI categories were similar (indicating no interaction between BMI and age). The free testosterone age trend in the obese group was less steep than in the other two groups (indicating an interaction between BMI and age). Mean LH was not significantly different among the three groups at the median age of 60 years. LH was higher in the older than 70 year nonobese men, compared with the overweight and obese groups, due to a negative BMI/age interaction. Male reference ranges for the measurements are: testosterone 10–35 nmol l^{-1}; free testosterone 250–700 pmol l^{-1}; LH 1.5–8.0 IU l^{-1}; SHBG 13–62 nmol l^{-1}. BMI: Body mass index; EMAS: European Male Ageing Study; LH: luteinizing hormone; SHBG: sex hormone binding globulin. This figure is reproduced from Wu *et al.*[1] with permission.

chemistry laboratory until very recently. The technical improvements in instrumentation and the wider availability due to falling cost of equipment have made MS now a competitive method with IA, having reached sufficient sensitivity yet maintaining its superior specificity.

Now opinions are being widely expressed to promote MS as the only acceptable method for clinical steroid hormone measurements.[36,38,39] However, MS still remains more expensive and labor intensive (requiring solvent extraction), shows similar lack of between-laboratory standardization as IA,[40,41] and it will take a long time before it becomes accessible to all practitioners. While it is clear that T measurements by IA are unreliable in children and women, it is uncertain whether MS or IA should be the method of choice for T quantitation in male hypogonadism.

Although MS is in general more specific with lower intra- and interassay variability than IA, it faces similar inter-laboratory variability issues as IA.[40,41] Even MS represents a heterogeneous group of methods with significantly differing performance, which makes referring MS as the 'gold standard' an overstatement. To what extent MS improves the clinical relevance of steroid measurements requires additional data and experience. A very recent study comparing total T assays in women concluded that the results obtained by IA and MS were comparable, and there is significant variability and poor precision also between various MS methods at low levels.[41] Hence, switching from IA to MS is not a guaranteed solution to improve the quality of sex steroid measurements at low concentrations. Improvements in performance and standardization in platform IAs are feasible alternatives that are already being implemented by some manufacturers. It is a major investment to abandon IA technology in favor of MS, and the reasons for this must be tangible and supported by evidence rather than conjecture.

The EMAS study research consortium[42] recently measured T concentrations in the serum samples of a large cohort (n = 3174) of 40- to 79-year-old men using both an established IA and MS method.[43] This provided a unique opportunity to compare the results with these two methods and to assess their applicability for clinical diagnostics and research. The conclusion from this comparison was that a validated platform IA is sufficient to detect subnormal T concentrations in the diagnosis of male hypogonadism (**Figure 2**). IA can be as good as MS in the clinically important discrimination between eugonadal and hypogonadal men, especially when combined with clinical signs of androgen deficiency. It seems prudent to conclude that the selection of an assay should be driven by the measurement performance in light of the clinical need and not by assay technology. Our findings do not support a mandatory requirement, on either analytical or clinical grounds, to switch from good-quality IAs to MS in the measurements of T in male subjects.

How to define low T in ageing men

The diagnosis of low T must be based on at least two measurements from morning blood samples taken in standardized conditions, i.e., before

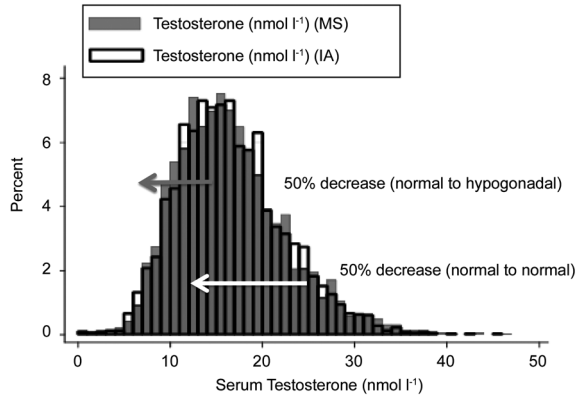

Figure 2: Distribution of testosterone (T) concentrations measured with established immunoassay (IA) and gas chromatograpyhy-mass spectrometry (GC-MS) methods in 3174 serum samples from the European Male Ageing Study (EMAS) population. The similar distribution of the concentrations measured indicates good agreement between the two methods. The two horizontal arrows demonstrate that a 50% decreased level of T from the upper part of the reference range (10–30 nmol l^{-1}) still remains normal (white arrow); whereas, a 50% decrease from the lower part becomes hypogonadal (grey arrow). This figure is modified from Huhtaniemi *et al.*[43] with permission.

10:00 hours. Proper age-dependent reference ranges for T do not exist. There are several consensus statements, based on existing information and expert opinions on limits of normal and hypogonadal T levels of ageing men. The International Society of Andrology and several other scientific societies recommend a cutoff-point of 12 nmol l^{-1}, above which men do not need T supplementation and 8 nmol l^{-1} below which supplementation might be beneficial.[7] The guidelines of The Endocrine Society set the cutoff level between normal and subnormal T to 9.8–10.4 nmol l^{-1}.[16] Bhasin *et al.*[44] recently proposed the 2.5th percentile of T in healthy men < 40-year-old, 12.1 nmol l^{-1}, as the limit. Sikaris *et al.*[36] using a panel of young sexually and reproductively healthy men, proposed a threshold of 10.4 nmol l^{-1}. A recent study examining a population-based cohort of 70- to 89-year-old men with perfect health came up with a threshold of 6.4 nmol l^{-1}.[45] Different symptoms appear at different T thresholds,[6] and therefore it may be impossible to define a strict limit between normal and low T. Furthermore, population-based cutoff points do not apply to individuals. As a rough guideline, the border between normal and low T runs somewhere around 10 nmol l^{-1}, but it is naturally dependent on laboratory-specific reference ranges.

Another problem in defining low T is caused by the individual variation of normal T levels. The mean ± 2 standard deviation (SD) reference range is usually about 10–30 nmol l^{-1}. This means by definition that 2.5% of normal men have their T levels below the lower limit of normal. Another so far hypothetical, but probably real 'misdiagnosed' group of men are those, whose T decreases within the reference range (**Figure 2**). Let us assume, for the sake of argument that a decrease of T of > 50% leads to clinically significant hypoandrogenism. This means that only men whose T is within the lower half of the reference range (10–20 nmol l^{-1}) can become 'biochemically hypogonadal' with a 50% decrease in T. In contrast, men with their T between 20 and 30 nmol l^{-1} still remain 'biochemically eugonadal' after a 50% suppression of T, and their apparent hypogonadism remains undiagnosed. The diagnosis of LOH should thus not be based solely on T measurements. Furthermore, low T levels have to be confirmed at least twice, because T levels near the lower limit of the reference range are often normal upon repeated measurement.[46]

One approach is to complement the total T measurement by assessment of free or bioavailable (i.e., non-SHBG-bound) T, which in some cases may be more accurate in defining hypogonadism. Recent guidelines recommend 'measurement of free or bioavailable T levels, using accurate and reliable assay, in some men in whom total T concentrations are near the lower limit of the normal range and in whom alterations of SHBG are suspected',[16] and 'particularly in obese men'.[7] How free T should be determined is at the moment somewhat contentious. Equilibrium dialysis is the best method, but it is expensive, labor-intensive and not generally available. Free T measurements based on analogue displacement are not reliable and should not be used.[47] Calculated free T, based on measurements of total T, SHBG and albumin[48] correlate well with measurements by equilibrium dialysis. However, the commonly used formulae have been recently criticized,[49] and it is possible that a simple reliable way to determine free T is not yet available. The EMAS study[6] observed that free T improved the LOH diagnosis especially at borderline levels of total T (see below). According to this study, a total T <8 nmol l^{-1} is sufficient for the diagnosis, but if it is in the gray zone of 8–11 nmol l^{-1} then free T <220 pmol l^{-1} strengthens the diagnosis.

Polymorphisms in genes of steroid metabolic enzymes, SHBG and androgen receptor induce variability in androgen action, but their clinical significance remain unclear.[50,51] Evidence is also mounting about different threshold levels causing deficiencies in the various androgen actions,[6,52,53] contributing to the variability in the occurrence of LOH symptoms.

A potentially useful parameter in the diagnosis of LOH is LH, which is elevated mainly in non-obese LOH men as a sign of primary age-dependent hypogonadism.[54] The cited study launched a new diagnostic entity, compensated hypogonadism, which entails men with low normal T (>10.4 nmol l^{-1}) and elevated LH (>9.4 IU l^{-1}). These men have mainly physical symptoms such as inability to do vigorous exercise, and with time a marked proportion of them seem to progress to genuine primary hypogonadism (EMAS, unpublished observation).

Clinical symptoms of late-onset hypogonadism

It is counterintuitive to base the diagnosis of LOH solely on hormone levels, and it has to be supported by clinical symptoms. Conversely, the diagnosis cannot be based only on symptoms, but it has to be supported by information on suppressed androgen levels. The array of symptoms associated with LOH is wide, covering many, and often nonspecific findings associated with aging, centering around declining bone mass, muscular mass and strength, physical function and frailty, metabolic changes including abdominal obesity, the metabolic syndrome and type 2 diabetes and sexual function. The key question is what, if any, of the wide array of LOH-related symptoms show correlation with low T levels. Various questionnaires have been constructed over the years to monitor the symptoms of LOH and their response to T treatment. These include the Ageing Male Symptom Score (AMS)[55] the Androgen Deficiency in Aging Men (ADAM)[56] and the Massachusetts Male Aging Study Questionnaire.[57] However, they are not recommended for the diagnosis of LOH because of their poor specificity.[7,16,58] There are also questionnaires specifically addressing the sexual symptoms of LOH.[59,60]

Combining T and the symptoms: the strict European male ageing study criteria for diagnosis of late-onset hypogonadism

A report from EMAS sought to determine the objective criteria for LOH diagnosis by identifying the symptoms that have a statistically significant inverse correlation with serum T, and to confirm the cut-off level of T, below which the frequency of these symptoms increases significantly.[6] The report investigated >3000 men between the ages of 40 and 79 years, from eight European centers. The men were asked about 32 symptoms that other studies have (often without scientific proof) suggested to be related to LOH, and that are being used in the LOH questionnaires mentioned above. In addition the

concentrations of total and free T were determined. Only nine out of the 32 symptoms demonstrated a significant correlation with either total or free T (**Table 1**). With a more strict statistical analysis, i.e. multiple correspondence analysis, only the correlation between sexual symptoms and T remained statistically significant showing a syndromic association. The other symptoms in the questionnaire (such as climbing stairs, light domestic tasks, nervousness, insomnia and weakened concentration) were unrelated or weakly related to low T.

The EMAS data made it possible to define the objective parsimonious criteria for LOH diagnosis. Accordingly, the patient must have three sexual symptoms (lessened sexual thoughts, weakened morning erections and erectile dysfunction), and either repeated (at least twice) serum total T level <8 nmol l^{-1}, or serum total T of 8–11 nmol l^{-1} and free T <220 pmol l^{-1}. This has enabled the creation of an algorithm, which could be helpful when assessing patients in whom LOH is suspected (**Figure 3**). When assessing patients according to such

Table 1: Definition and prevalence of symptoms and relationship to total and free testosterone in the European Male Ageing Study

Symptom	*Symptomatic men*	*Asymptomatic men*	*Symptom prevalence (%)*	*P value vs total testosterone*	*P value vs free testosterone*
Sexual					
Full morning erection	≤1 per month	≥2–3 times per month	39.9	0.007	<0.001
Erection sufficient for intercourse	Never or sometimes	Usually or always	30.03	0.34	<0.001
Occurrence of sexual thoughts	≤2–3 times in the past month	Once a week or more	27.5	0.048	<0.001
Physical					
Vigorous activity	Limited	Limited a little or not limited	24.7	0.03	<0.001
Capable of walking>1 km	Limited	Limited a little or not limited	6.7	0.01	<0.001
Ability to bend and kneel	Limited	Limited a little or not limited	6.2	0.26	0.001
Psychological					
Feeling of sadness or downheartedness	All or most of the time	Some time, little or none of the time	4.6	0.70	0.004
Loss of energy	Yes	No change	4.9	0.94	0.01
Fatigue	Yes	No change	5.5	0.30	<0.001

This Table is reproduced from Wu *et al.*[6] with permission.

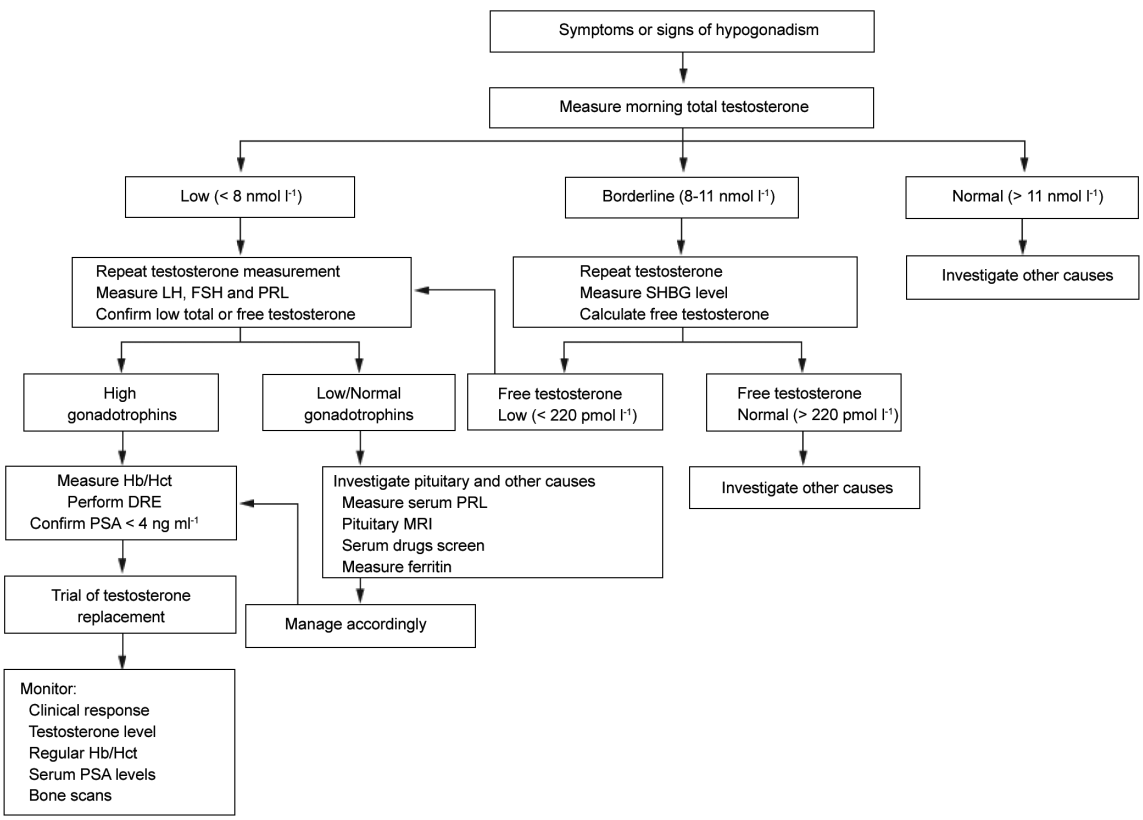

Figure 3: Algorithm for the diagnosis and treatment of LOH. If the clinician suspects the patient to have LOH, the diagnosis and choice of treatment can be obtained by following the flow chart from top to bottom, and choosing the next alternative on the basis of the findings. This figure is modified with permission from unpublished data provided by Prof. F. C. Wu (Manchester University, UK), and data previously published by Huhtaniemi and Forti[61] (reproduced with permission). BMD: bone mineral density; Calc: calculated; DRE: digital rectal examination; Eq. dial: equilibrium dialysis; FSH: follicle-stimulating hormone; Hct: hematocrit; LH: luteinizing hormone; LOH: late-onset hypogonadism; PRL: prolactin; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; T: testosterone. The numeric hormone levels presented are only suggestive, and in the diagnosis the clinician has to use local reference ranges for the assays.

an algorithm, it is important to note the combination of low T with high gonadotropins, which suggests the presence of primary and age-dependent testicular failure.[54] Obesity-related hypogonadism is not associated with increased gonadotropins (**Figure 1**). Suggestive to LOH is also a combination of the sexual symptoms with low-normal T and elevated LH (compensated hypogonadism).

According to the EMAS data, it is possible to state almost categorically that if a man does not have sexual symptoms he does not have LOH. However, it is noteworthy that even the sexual symptoms have a high background prevalence of 28%–40%, irrespective of T levels,[6] and that not all men who experience sexual dysfunction will report these symptoms to their doctor. The other LOH symptoms (**Table 1**) may support the LOH diagnosis, but are not sufficient without the presence of sexual symptoms. Even LOH fulfilling the strict EMAS criteria can be caused by something else than lack of T, which may explain the relatively modest outcome of T replacement therapy (see below). Another confounding factor is the reversibility of LOH. One longitudinal study demonstrated that LOH remission occurred in ~ 50% of men, either because the subnormal serum T level normalized or because the patient's symptoms subsided.[62]

When men participating in the EMAS were evaluated using the aforementioned criteria, LOH diagnosis was confirmed in only 2.1% of the participants aged 40–79 years. The prevalence increased gradually from 0.1% in 40- to 49-year-old men to 5.1% in men aged between 70 and 79 years. These results suggest that LOH is much less common than previously thought. Using more relaxed diagnostic criteria, the prevalence of symptomatic LOH has previously been found to be 5.6%–12% in similar cohorts of ageing men.[63,64] EMAS also confirmed the association between LOH, obesity and poor general health: LOH was diagnosed in 0.4% of men with normal weight, 1.6% of men with a BMI of 25–30 $kg\,m^{-2}$ and in 5.2% of men with a BMI > 30 $kg\,m^{-2}$. Overall, LOH was associated with high BMI in 73% of men. All 40- to 49-year-old men (0.1% of the age group) diagnosed with LOH were clinically overweight. The proportion of ageing-associated (primary) hypogonadism increased gradually to 40% in 70- to 79-year-old men. However, we have to remember that men seeking medical help for sexual problems do not represent the general population. A report from Italy detected a 15% prevalence of genuine LOH in men visiting andrology clinic.[65]

TREATMENT OF LATE-ONSET HYPOGONADISM

Who should be offered testosterone replacement?

T replacement is an effective therapy for the classic forms of male hypogonadism such as congenital hypogonadotropic hypogonadism, Klinefelter syndrome and anorchia. T treatment of LOH is a much more controversial issue because, as previously mentioned, the symptoms and signs are often unspecific and mild, the T levels are often borderline and low T and high symptom score often do not coincide. Furthermore, there is still no general consensus on the threshold of circulating T below which replacement therapy is recommended. The EMAS definition of LOH[6] supports the recommendations of several international societies.[16,66] However, the panelists for the Endocrine Society guideline failed to reach a consensus regarding the T threshold for older men, as some of them favored a threshold of 9.7–10.4 $nmol\,l^{-1}$; whereas, others felt that a threshold of 6.9 $nmol\,l^{-1}$ was more appropriate.

After the diagnosis of LOH is made, possible causes for low T such as obesity, metabolic syndrome and chronic diseases should be investigated, and if present, adequately treated. In overweight or obese men, lifestyle counseling to achieve sustained weight loss should be the mainstay of management, even if T treatment is likely to induce a small increase of the total lean body mass and a small decrease of total body fat (see also below). The recent EMAS data show that weight gain or loss have clear inverse correlation with circulating T (**Figure 4**).[67] Hence weight loss increases T levels, and *vice versa*. Moreover, the risk of experiencing adverse effects associated with T treatment was reported to increase in obese subjects.[68] T replacement should be offered to the LOH patient only after sufficient counseling, informing him that the long-term beneficial and adverse effects of this treatment for them are not known. We still lack randomized, placebo-controlled studies on T replacement in men aged ≥60 years, and the existing trials have low numbers of subjects, and are often of insufficient duration.[69] The published trials are also heterogeneous as some include asymptomatic men, different T thresholds are used for recruitment and the T formulations used, as well as dosing regimens, are variable.

Contraindications for T replacement

Absolute contraindications for T treatment include prostate and breast cancer.[7,16] Relative contraindications are a serum prostate specific antigen (PSA) level >4 $ng\,ml^{-1}$ (or 3 $ng\,ml^{-1}$ in men with increased risk for prostate cancer, such as those of African descent or with first degree relatives with a history of prostate cancer), a hematocrit >50%, severe lower urinary tract symptoms caused by benign prostatic hypertrophy (as defined by an International Prostate Symptom Score (IPSS) higher than 19), untreated or poorly controlled congestive heart failure and untreated sleep apnea.[16]

Beneficial effects of T replacement

The presence of sexual symptoms is crucial for the diagnosis of LOH, but the data on effect of T on sexual function in men with LOH are limited. Its main effect on sexual function is to increase sexual desire.[70] Several findings suggest that normal erections can be achieved in men with serum T below the normal range, and that higher levels of T do not improve them.[71,72] It is therefore not surprising, that mean serum T of men with different degrees of erectile dysfunction is generally in the normal range,[70] and there is no relationship between T level and the severity of erectile dysfunction.[73] A meta-analysis of 17 randomized, placebo-controlled trials showed that, in men with baseline T <12 $nmol\,l^{-1}$, T treatment moderately improved libido, nocturnal erections, erectile function scores and overall sexual satisfaction in comparison to placebo, but had no effect in eugonadal men. However, the evidence for a beneficial effect of T on erectile function was tempered by the progressively smaller effect with increasing baseline T levels and by the declining effect of the treatment over time.[74] These findings have been confirmed by another meta-analysis.[75] The earlier claims that T strengthens the effect of phosphodiesterase type 5 inhibitors in erectile dysfunction have not been reproduced in recent studies.[76]

T treatment has important effects on body composition, resulting in a significant increase in lean body mass, and a significant decrease in fat mass without a change in body weight.[16] The effects of T on muscle strength in older men are inconsistent. Some studies in healthy older men have reported improvements in grip strength, whereas others have not, and limited data are available on the beneficial effects of T on lower limb muscle strength.[77,78] Furthermore, only a few studies have reported statistically significant effects on physical function and performance.[77,79–81] Some cross-sectional and longitudinal studies have shown an inverse relationship between T levels and frailty – a composite measure of limitation of mobility and physical performance – in older

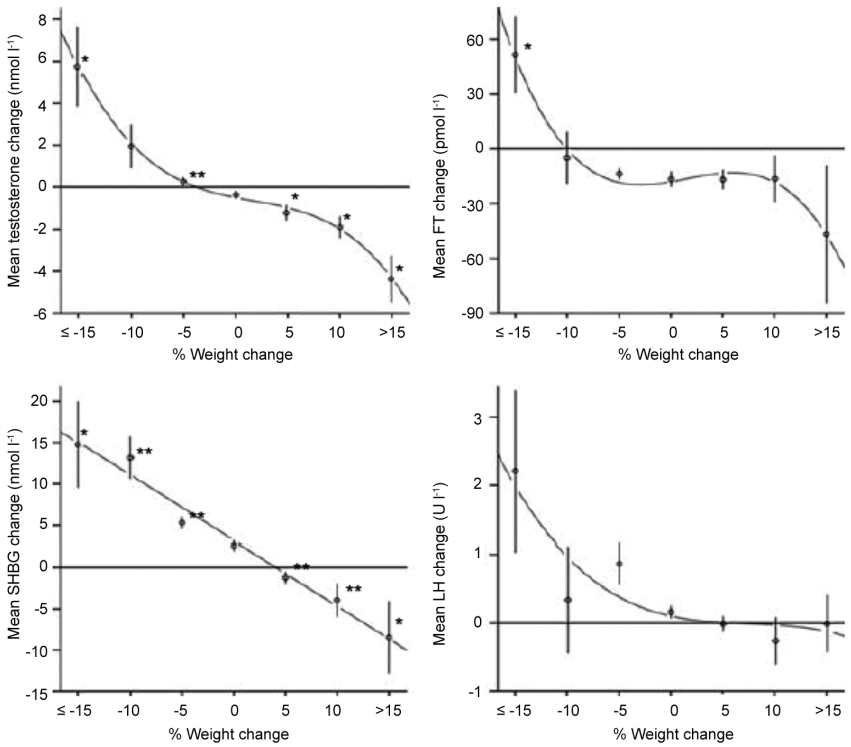

Figure 4: Mean changes in total testosterone, free testosterone, LH and SHBG by % weight change as a single categorical variable (loss of >15%, 10%–15% and 5%–10%, within 5%, gain of 5%–10%, 10%–15% and >15%) in the EMAS population upon an average of 4.4 year follow-up. This figure is modified from Camacho *et al.*[67] with permission. European male ageing study; LH: luteinizing hormone; SHBG: sex hormone binding globulin.

men.[82–84] A randomized, short-term, placebo-controlled trial on the effects of T treatment in frail older men with low or borderline serum T has shown some beneficial[77] though short-lived[85] effects. Altogether, there is still no convincing proof that these effects at safe doses would translate into clinically significant improvement in muscle performance and quality of life.[86,87]

The results of some controlled trials have also shown that T treatment in LOH men can have a modest beneficial effect on lumbar bone mineral density, which is inversely related to baseline T levels, but with no effect on femoral neck bone density.[79,88–90] The critical information whether T supplementation affects the occurrence of bone fractures, either in patients with the classic forms of hypogonadism or in men with LOH, is still missing.

Epidemiological studies have shown that low T predicts and is associated with type 2 diabetes mellitus and metabolic syndrome. Effects of T treatment in these conditions have been evaluated in a few controlled trials, and two meta-analyses[91,92] have reported some beneficial effects of T treatment on glycemic control and visceral obesity. However, the short duration of the trials and the limited number of enrolled subjects mean that firm conclusions cannot be drawn from these studies, and T treatment is not yet be recommended for these conditions.[93]

Concerning coronary artery disease (CAD), T is still generally considered atherogenic because of its adverse effects on the lipid profile. Androgenic-anabolic steroids are also associated with the coagulation cascade, hemostasis as well as damaged endothelial and myocardial function.[94] Conversely, also opinions are expressed that the normal physiological levels of T are beneficial for the male heart and low T is associated with adverse risk of coronary disease, and that T replacement therapy has positive effect on cardiovascular risk factors.[95] In accordance, T has been reported to function as a coronary vasodilator.[96] In men with stable CAD, transdermal T in addition to normal CAD medication seems to improve the angina threshold in treadmill exercise.[97] The higher prevalence of CAD in men suggests involvement of androgens, prompting caution in prescribing T replacement therapy for ageing men, especially if they have symptomatic CAD. However, numerous studies, albeit relatively small in size, on the association of androgens and CAD have found no adverse effect of T. Neither have significant beneficial effects of androgen treatment been reported in primary or secondary prevention. The key question is the causality; i.e., does low T promote CAD or does CAD decrease T levels? The answer to this question is crucial for the feasibility of T replacement in the prevention and therapy of CAD. It is probably bidirectional, therapeutic reduction of T in prostate cancer patients increased in an observational study on the CAD risk,[98] but also numerous comorbidities in ageing men reduce T levels.[1] Finally, a recent meta-analysis on circulating T and CAD concluded that an association was only found in men >70 years of age, and that finally low T in this group may be a sign of poor overall health.[99]

Approximately 25% of men with congestive heart failure have subnormal T levels, and low levels of T correlated with the progression of heart failure,[100] but the causality of these findings remains debatable. T replacement therapy decreases the symptoms of heart failure and improves the exercise capacity.[101] In a recent study, T therapy combined with the conventional treatment of heart failure improved muscle strength, exercise capacity, insulin sensitivity and baroreflex sensitivity, but did not improve myocardial function, suggesting that the effects are not mediated through improvement in cardiac function but merely through other associated mechanisms not entirely known.[102]

Some small, randomized, placebo-controlled studies have reported an improvement in cognition in men with LOH undergoing T treatment,[103] but this has not been supported in all studies.[104,105] Effects on quality of life and depression have also been reported, although these are inconsistent.[16]

In conclusion, the current information about benefits and risks of T replacement therapy still suffer from consisting mainly of studies that are insufficiently powered, poorly controlled and of short duration. An attempt to improve the situation is made by the Testosterone Trial in Older Men (ClinicalTrials.gov identifier NCT00799617), which aims to recruit 800 men, aged ≥65 years and having total T <10.4 nmol l^{-1}, from 12 sites in the United States. Their aim is to test the hypothesis that T treatment for one year compared to placebo will improve walking speed, sexual activity, vitality and verbal memory and correct anemia. The study is anticipated to be completed by the middle of 2015, and its results may provide for the first time solid evidence-based information about the real effects of T replacement therapy in LOH.

Potential adverse effects of treatment

Erythrocytosis (hematocrit >50%) is the most important and frequent risk of T treatment. Two recent meta-analysis have shown significant effects of T treatments over placebo on its appearance.[106,107] The risk is higher in older men as the dose-dependent, stimulatory response of their erythropoiesis to T is more pronounced than in young men.[108] This effect is not related to increased levels of erythropoietin,[108] but may be secondary to suppression of the master iron-regulatory-peptide, hepcidin.[109]

A potentially increased risk of clinical prostate cancer also exists, as the prostate is an androgen-responsive organ. A meta-analysis by Calof *et al.*[106] has shown that the total number of prostate events (including prostate biopsies, prostate cancers, serum PSA level >4 ng ml^{-1}, and increase in IPSS score) was significantly greater in T-treated men than in those who had received a placebo (odds ratio 1.90, (95% CI 1.11, 3.24; $P < 0.05$)). However, no difference was observed in the rates of any of these events between the two groups. The man-years of exposure in these trials were too small to allow reliable risk assessment. It has been estimated that randomization of approximately 6000 men aged 65–80 years with low T levels to placebo or T treatment for 5 years would be required to detect a 30% difference in prostate cancer incidence rates between T-treated and placebo-treated men.[110] It is unlikely that a study of this size will be funded, so it will remain uncertain whether long-term T replacement affects the incidence of clinically overt prostate cancer.

With respect to cardiovascular events, Calof *et al.*[106] showed that the rate of atrial fibrillation, myocardial infarction, coronary artery bypass or graft, vascular events and cerebrovascular accidents was not significantly different between the T and placebo-treated men. However, once again the short duration and the low number of subjects enrolled in most studies limits the final conclusions.

According to recent recommendations, men with untreated congestive heart failure should not be treated with T. Recently, a selected population of 106 elderly men (mean age 74 years) with low total T (between 3.5 and 12.1 nmol l^{-1}) or free T (<173 pmol l^{-1}), with limitations in mobility and a high prevalence of hypertension, obesity, diabetes, preexisting heart disease and hyperlipemia, was treated for 6 months with 1% T gel at daily doses ranging from 5 g to 15 g.[81] The treatment induced increased rate of adverse cardiovascular events in comparison to 103 placebo-treated men (23 *vs* 5 events, $P < 0.001$), and the trial was consequently terminated. Even if the cardiovascular events were not planned as primary or secondary outcome and the health conditions of the recruited men were rather poor in comparison to other trials, these findings suggest caution in T replacement of aged men with poor health, low mobility and multiple risk factors for cardiovascular events. Admittedly, pharmacological doses of T were used in this study, and we do not know whether the findings are applicable to a situation where low T levels are returned to the physiological range.

The effects of T on lipids in comparison to placebo have also been examined in a meta-analysis,[111] which showed that T decreased total cholesterol in men with lower T levels, and that it could reduce high density lipoprotein (HDL)-cholesterol, but only in men who had high baseline T levels. Another meta-analysis has reported a slight decrease in HDL-cholesterol (of 0.012 mmol l^{-1}) in T-treated men.[107]

Other potential, though infrequent, adverse effects of T include gynecomastia (although this condition occurs naturally in >50% of men older than 50 years)[112] and sleep apnea. The evidence that T replacement can cause sleep apnea is rather weak.

Finally, we do not know whether decreased T levels in ageing men, and especially in those with comorbidities, is a protective mechanism with beneficial effects of the homeostasis of the ageing organ systems with reduced functional capacity. This is a caveat that has to be kept in mind when considering the benefits and risks of T replacement therapy of LOH.

Duration and monitoring of T treatment

Improvement of symptoms should be assessed after a few months of T treatment. If no benefit is reported by the patient, treatment should be terminated and other causes of symptoms should be investigated.[7] If the treatment is effective, the patients should be monitored with regular checking of their hematocrit, hemoglobin and PSA levels and by doing digital rectal examination every 3–6 months.[7,16] The possibility of a spontaneous remission of LOH should also be considered,[62] and the treatment discontinued to permit assessment of the patient's symptoms and T level after an adequate time interval. It should also be kept in mind that the initial benefits of T could be a placebo effect, although such improvements are short-lived.[13] T therapy in men with classic forms of hypogonadism is usually life-long, meaning that long-term safety and follow-up studies of up to 10 years' duration have been reported;[113,114] whereas, the optimal duration of treatment for LOH men is currently uncertain, and controlled, long-term studies are needed to clarify this issue.

CONCLUSIONS

Using strict criteria, the prevalence of genuine LOH in the general population is much lower than previously reported (and generally assumed), as it occurs only in about 2% of 40- to 80-year-old men. However, it is likely to be much higher in the selected group of men who seek medical help for their LOH symptoms. When diagnosing LOH and choosing the most appropriate treatment, it is important to consider the general situation of the patient. Overweight or chronic illness might explain his symptoms and low T. In this situation, it would seem most logical to begin treatment with lifestyle modification and weight reduction, and to optimize the treatment of comorbidities, before T supplementation, which is expensive and of uncertain benefit.

If the clinician decides, after excluding contraindications, to initiate T treatment, the patient must be informed about the experimental nature of T therapy, as no evidence-based information is available regarding the long-term risks and benefits, and there are no specific guidelines for its use. When assessing the results of T treatment, it must be kept in mind that even placebo treatment of LOH can achieve statistically significant effects. T should not be prescribed for the treatment of symptoms that are not specific to LOH, and that can be caused by other conditions – such as obesity, metabolic syndrome,

depression, diabetes or other chronic diseases – even though low T is associated with these conditions. The information is unanimous that men with normal serum T do not benefit from T treatment.

In conclusion, if strict diagnostic criteria are used, genuine male LOH is a relatively infrequent condition; whereas, low level of T is common in elderly men with overweight and/or associated comorbidities. T replacement should be considered only for men with clear LOH diagnosis, but the beneficial effects of this treatment, as well as its potential risks are currently unknown. Only larger multicenter, long-term clinical trials will settle the current controversies surrounding the diagnosis and treatment of LOH.

COMPETING INTERESTS

Nothing to disclose.

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