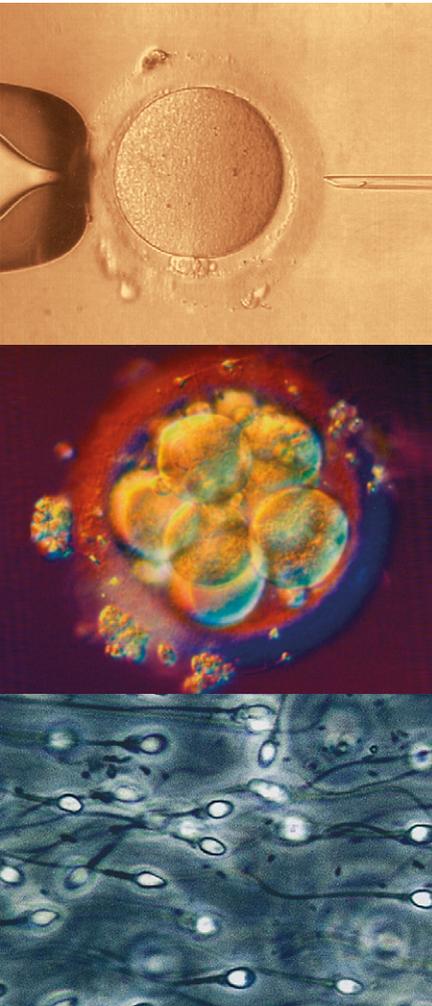


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Huhtaniemi IT

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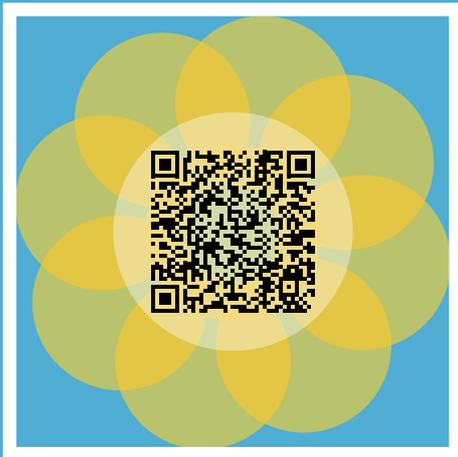
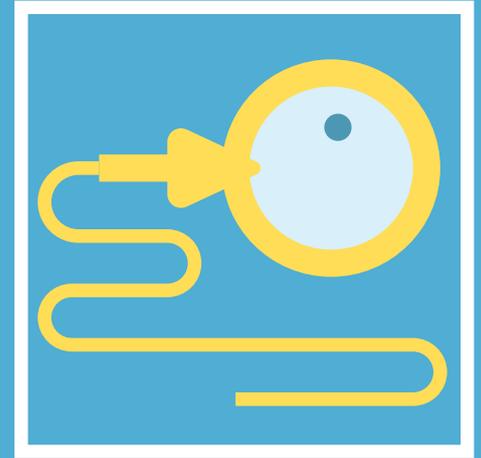
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BACK TO THE FUTURE

Male Late-Onset Hypogonadism (LOH) – Current Concepts and Controversies

I. T. Huhtaniemi

Late-onset hypogonadism (LOH), also called andropause, or by the misnomer ‘male menopause’, is a situation where a middle-aged or older man has lowered serum testosterone (T) concentration in conjunction with diffuse symptoms, reminiscent of those of genuine male hypogonadism (e.g. reduced sexual function, loss of vigor, muscle weakness, depression). Similar symptoms are common in ageing men with no other specific reason. There is considerable uncertainty about the diagnostic criteria, prevalence and treatment options of LOH even amongst experts. We review here some salient findings on the prevalence, diagnostic criteria, impact on health, and treatment options of LOH, as well as the current controversies concerning T replacement therapy of LOH. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 388–91.**

Key words: ageing, andropause, sexual function, serum testosterone (T), testosterone replacement therapy (TRT), late-onset hypogonadism (LOH)

■ Introduction

It is a well-documented fact that there is a slow gradual decline in testicular testosterone (T) production as the man ages [1, 2]. This is mainly due to obesity as well as the deteriorating health upon ageing, because men in perfect health do not show any decline in circulating T levels [3]. When the decrease of T is associated with symptoms of androgen deficiency the condition is usually termed “andropause” or “late-onset hypogonadism” (LOH). The decline of T is in general small, 0.5–2% per year, and the T level remains within the reference range of young men in the majority of old men. However, in some men the decrease is more profound and may lead to biochemical (T < 10.4 nmol/L) or even clinical, i.e. symptomatic hypogonadism. LOH is currently receiving much attention both in professional and lay circles, not the least because T replacement therapy (TRT) is aggressively marketed for its treatment, both for medical professionals and public at large, especially in the United States [4]. The most debated controversy around LOH is currently whether TRT or ageing men is associated with increases risk of cardiovascular disease (CVD) [5, 6].

To obtain more scientific information about LOH we launched over 10 years ago the EMAS study “The European Male Ageing Study” [7], whose purpose was to examine in a large cohort of community-dwelling European men the ex-

tent of ageing-related alterations in T, other reproductive and metabolic hormones, other laboratory parameters, anthropometry and health status, and to refine the diagnostic criteria and clinical significance of andropause/LOH. In this review we summarise some of the salient findings of the EMAS study and present the current state of the most prominent controversies in the field.

■ Definition and Pathogenesis of LOH

LOH is associated with a wide array of similar largely non-specific physical, psychological and sexual symptoms as are observed in true hypogonadism of young men, as well as in ageing in general. Several questionnaires have been designed to score the LOH symptoms and their magnitude, but they are generally considered inaccurate and not recommended to be used in the diagnosis [8–10]. In EMAS it was observed that of the multitude of symptoms ascribed to LOH only the frequencies of those of the sexual domain, i.e. erectile dysfunction, decreased sexual thoughts and decreased morning erections, were significantly and inversely associated with serum total T and free T [11]. Of note, there was a high background prevalence in sexual symptoms, about 25%, at all T concentrations, which greatly compromises the specificity even of this symptoms domain [11]. Frequencies of the physical and psychological symptoms used in the LOH questionnaires showed no significant associa-

tion with circulating T levels, and were roughly similar throughout the concentration range of T measured in the men. One can therefore almost categorically state that a man who does not have reduced sexual function does not have LOH. The other symptoms he may have, such as insomnia, depression, muscle weakness, irritability, do not alone justify the diagnosis of genuine andropause.

■ Diagnostic Criteria of LOH

It is obvious that documented T deficiency must be one of the criteria of the diagnosis of LOH. This is simplest to detect by measurement of peripheral serum total T, which should be below the lower limit of the reference range for young men, usually about 10 nmol/L. The measurement has to be done at least twice from a morning sample. Clearly reduced level, say below 8 nmol/L, can be considered diagnostic. If the concentration is in the “gray zone” of 8–11 nmol/L, determination of calculated free T from total T, sex hormone-binding globulin and albumin can strengthen the diagnosis. A concentration < 220 pmol/L can be considered hypogonadal. Opinions vary about the accuracy of the formulas used to calculate free T [12, 13], but the standard methods usually provide clinically reliable results. In contrast, the methods of direct free T assays are unreliable and not recommended. Low T alone is not sufficient for the LOH diagnosis, because the majority of ageing men with T below the reference range are asymptomatic.

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From the Imperial College, London, and the University of Turku, Finland.

Correspondence: Professor Ilpo T. Huhtaniemi, Institute of Reproductive and Developmental Biology, Department of Surgery and Cancer, Hammersmith Campus, Du Cane Road, Imperial College London, London W12 0NN, UK, and Department of Physiology, Institute of Biomedicine, University of Turku, Kiinamyllynkatu 10, 20520 Turku, Finland; e-mail: ilpo.huhtaniemi@imperial.ac.uk

The strict EMAS criteria for T to fulfill the diagnosis of LOH include total T < 8 nmol/L and free T < 220 pmol/l [11] in connection with the three sexual symptoms of erectile dysfunction, decreased morning erection and decreased sexual thoughts. However, as stated above, even men with low T may have sexual symptoms independent of low T, because of their high background prevalence.

■ Prevalence of LOH and its Subtypes

According to the strict EMAS criteria [11], i.e. low serum total and/or free T (see above) and three sexual symptoms, the prevalence of LOH in 40–79-year-old community-dwelling men is only 2.1%, increasing from 0.15–5.1% between 40 and 79 years. However, if a man complaining LOH symptoms visits the physician, it has been estimated that genuine LOH can be found in about 15% of this selected population [14]. Low T alone with diffuse symptoms does not justify the diagnosis of LOH, neither do sexual nor other symptoms in men with normal T.

Low T in connection with elevated LH indicates primary hypogonadism, i.e. testicular failure, and if LH is either low or inappropriately normal in the face of low T, hypogonadism is secondary, caused by a disturbance at the hypothalamic-pituitary level. According to the EMAS study, secondary hypogonadism is clearly more common and is associated with overweight and obesity, or poor general health in some men, but not with ageing. Primary hypogonadism is specifically associated with ageing [2]. Overall 73% of the men of the EMAS cohort fulfilling the strict criteria of LOH were overweight or obese [11]. In the rest, the lean men with secondary hypogonadism often had chronic health conditions (e.g. cardiovascular disease, diabetes, frailty), which could explain the finding. The condition remains idiopathic only in a minority of men, which means that there are targets for treatment, including lifestyle modification with weight loss and good treatment balance of comorbidities. TRT should not be the first option in LOH.

A third diagnostic group detected in the EMAS men was termed “compensated hypogonadism” [15]. These men have

normal T but elevated LH, and they accounted for 9.5% of the EMAS cohort. They have marginal signs and symptoms of androgen deficiency, in particular of limited physical capacity. Our recent (unpublished) follow-up data suggest that compensated hypogonadism represents a transitory phase in the trajectory from eugonadism to primary hypogonadism, and is very distinct from the obesity-related secondary hypogonadism.

■ Impact of low T on Health

Low T has been associated with increased mortality in a number of studies [16]. However, the natural history of symptomatic LOH, especially its relationship to mortality, still remains poorly explored. We recently investigated in the prospective part of EMAS the associations between symptomatic LOH, chemical LOH (only low T), and the sexual symptoms alone with mortality in 2599 men [17] during a mean follow-up period of 4.3 years. Fifty-five men (2.1%) were identified as having symptomatic LOH (31 moderate and 24 severe). After adjusting for age, centre, body mass index (BMI), current smoking, and poor general health, compared with healthy men, those with severe LOH (T < 8 nmol/L + sexual symptoms) had over 5-fold higher risk of all-cause and cardiovascular mortality. When only low T (< 8 nmol/L) was used as the diagnostic criterion, the multivariable-adjusted risk of mortality was only 2-fold higher than in eugonadal men. Hence, severe LOH is associated with substantially increased risk of all-cause and cardiovascular mortality, to which both the level of T and sexual symptoms contribute independently and additively.

We have recently observed that even men within the new diagnostic group “compensated hypogonadism” (i.e. normal T but elevated gonadotropins) [15] have 3-fold elevated mortality (unpublished). Symptomatic LOH, and even marginally suppressed hypothalamic-pituitary-testicular (HPT) function, are therefore not trivial findings, but the affected men need special care because of their increased risk of death.

■ Does improved health reverse LOH?

We described above how genuine LOH, decreased T – and even subclinical hypo-

gonadism – pose a health hazard for men, increasing their risk of death. It would therefore be important to know whether the reverse can occur, i.e. if LOH could be reversed, and what would be its consequences on health. In particular, would weight loss – obesity being the commonest cause of LOH – have positive effect on T production and health? We therefore explored how the age-related changes in T may be influenced by lifestyle modifications, by investigating the longitudinal relationships between changes in health and lifestyle factors with hormonal changes in the EMAS population. Paired T results were available for 2395 men, one at baseline and another after a mean of 4.3 year follow-up time [18]. Indeed, weight loss brought about a proportional increase, and weight gain a proportional decrease, in T and sex-hormone binding globulin (SHBG) levels. Free T showed a curvilinear relationship to weight change, and only in extreme weight changes (gain or loss > 15%) the change was significant (in the same direction as total T). Smoking cessation was associated with a greater decline in T than being a non-smoker, independent of weight change. Changes in the number of comorbid conditions or physical activity did not influence function of the HPT axis. We were able to conclude from these observations that weight and lifestyle factors do influence HPT axis function in ageing. Weight loss increases and weight gain decreases T, free T and SHBG levels. Weight management is therefore important in maintaining circulating T in ageing men, and obesity-associated changes in HPT axis hormones can be reversed by weight reduction.

Quite unexpectedly, normalization of T levels on men diagnosed as hypogonadal at baseline was not paralleled by similar positive changes in hypogonadal symptoms (unpublished). This finding questions the sense of reverting symptoms in LOH by treatment with exogenous T. Low T and the hypogonadal symptoms may be parallel, but independent events, where normalization of one does not affect the other.

These observations leave us with the “hen and egg” conundrum between serum T and health. Is low T the cause or consequence of ill health? The causality is apparently at least to some extent bi-

directional, but the evidence is mounting that low T is simply an indicator of ill health, not the cause of it.

■ Controversies in the Treatment of LOH

Two treatment options are available for LOH:

- 1.) T replacement therapy, and
- 2.) lifestyle modification with weight loss and good treatment balance of comorbidities.

It is tempting to conceptualise ageing-related hypogonadism as a deficiency state of T that is the cause for associated obesity and related health problems, and that simply replacing the reduced T production with exogenous hormone will revert the situation and correct the health problems. This approach is based on the conjecture that low T is the primary cause of the health problems. However, this concept is too simplistic and far from being convincingly proven. Admittedly, there are conditions where reduction of T production leads to obesity and other symptoms common in LOH, for example androgen blockage therapy of prostate cancer [19]. But it is equally possible that low T is the harbinger of ill health, and it could even be the body's desired adaptation mechanism to ill health [20], in which case its reversal by exogenous T would not only be undesirable but even harmful.

Several recent studies have warned about cardiovascular complication in ageing men during T replacement therapy [21–25]. Very recently, the United States Food and Drug Administration (FDA) has decided to require the manufacturers of T preparations to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking T (<http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm>).

Furthermore, it was stressed by FDA that health care professionals should prescribe T therapy only for men with low T levels caused by certain medical conditions, confirmed by laboratory tests, and not including ageing *per se*. The potential of cardiovascular risks remains under heated debate [5]. Although the evidence for or against is still unconvincing, it remains a fact that the safety of TRT of ageing men suffering from LOH has nev-

er been properly tested. Until the health issues of TRT are convincingly solved (which may not happen in the near future) it is prudent to be cautious with T subscribing to older men, say over 70 years, especially if they have a previous history of CVD. By and large, specific treatment of symptoms, whether obesity, sexual symptoms or osteoporosis, seems more logical than starting with TRT of uncertain benefit/risk ratio.

The studies that have shown health benefits of T replacement in LOH are invariably small, short in duration, retrospective, non-randomised and either uncontrolled or with biased controls. What appears as small statistically significant beneficial effect may not be clinically significant. A typical “controlled” study is where T is offered to a group of men with variable reduction of T and selected purported LOH symptoms, and the men who for any reason (e.g. contraindications) do not receive T form the controls. Very telling is one placebo controlled study where both placebo and T had similar statistically significant suppressive effects on the LOH symptoms score [26]. The largely anecdotal information or poor quality research data do not justify recommending T replacement for treatment of LOH. We have to wait for better information before the issue can be solved. Such a definitive treatment trial is currently underway in the US [27], and we should see its results in 2016.

■ Conclusions

LOH can be defined according to the strict EMAS criteria as a condition where an ageing man has low total T (< 8 nmol/L; or 8–11 nmol/L and free T < 220 pmol/L) with a triad of sexual symptoms (erectile dysfunction, reduced sexual thoughts and reduced morning erections). According to these criteria, the frequency of the condition in 40–79-year old community-dwelling men is 2.1%. The condition is associated in 75% of the cases with overweight or obesity, and weight reduction reverses effectively the suppressed T levels. LOH is not a trivial condition because men with severe LOH have 5-fold elevated risk of all-cause and CVD mortality over a 4.3-year follow-up period. Information on long-term benefit/risk ratio of T therapy is largely missing, but data on harmful effects of T on CVD are mounting. Before more infor-

mation about the real benefits and risks of T therapy is available, T therapy of LOH must be considered experimental, and the existing uncertainties must be explained to the patients. It would be more prudent to motivate men with LOH to lifestyle modification, weight loss and close screening and specific treatment of their symptoms and comorbidities, rather than embarking on nonspecific TRT with uncertain benefits and unknown long-term risks.

■ Conflict of Interest

The author declares no conflict of interest.

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