

The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: can a case be made for a 3-month therapeutic trial?

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Accepted for publication 1 July 2004

OBJECTIVE

To assess whether testosterone (T) supplementation in men considered to have symptomatic late-onset hypogonadism (SLOH) can be evaluated clinically and biochemically.

PATIENTS AND METHODS

To assess the relevance of the clinical and biochemical diagnosis of hypogonadism we investigated patients referred for the diagnosis and treatment of SLOH. Patients were assessed clinically and completed a screening questionnaire. The pituitary-adrenal-gonadal axis was comprehensively assessed biochemically. Those with a clinical diagnosis of hypogonadism and serum levels of T supporting such a diagnosis received

exogenous T for ≥ 3 months and were assessed for any clinical and biochemical response. Of an initial group of 45 men (mean age 59.2 years) 38 completed the study.

RESULTS

Most men presented with symptoms of sexual dysfunction, lack of energy and/or depression. There were differences before and after treatment only in bioavailable T (BT), with none in the levels of total T (TT). There was a strong correlation before and after treatment in the levels of luteinizing hormone and follicle-stimulating hormone, and a weak negative correlation between gonadotrophins and BT. Neither TT nor BT had predictive value for the treatment response. There was a trend to a correlation between BT levels and treatment success. Changes in serum prostate

specific antigen were insignificant during the limited period.

CONCLUSION

The lack of accurate methods for diagnosing SLOH suggests that a therapeutic trial of T supplementation is warranted in men in whom there are no contraindications. The 3-month period largely circumvents the placebo effect and has minimal risks for serious adverse effects (mostly in relation to prostate safety). This controversial position needs further evaluation with a larger cohort and other biochemical measurements.

KEYWORDS

testosterone, hypogonadism, biochemistry, supplementation

INTRODUCTION

Clinicians face considerable controversy when managing men suspected of having hypogonadism associated with ageing, also known as late-onset hypogonadism (LOH) or androgen deficiency in the ageing male (ADAM). The existence of the condition has been vigorously challenged; a few vocal writers in the lay press argue that it is a creation of the pharmaceutical industry [1], and medical opinion is not unanimous [2,3]. However, the many physicians who treat ageing men and consequently accept the existence of LOH are sceptical about the accuracy of the clinical diagnosis because its manifestations are not specific. In addition, the biochemical assays for sex steroids, which should be reliable and reproducible, do not appear to be precise enough diagnostically. These difficulties are important because practising physicians are advised to defer treatment for men with LOH until two

diagnostic criteria are met, i.e. a clear clinical picture together with biochemical support [4]. Unfortunately, the most appropriate biochemical assays and the normal ranges for serum testosterone (T) remain undefined.

To assess in practice the relevance of the clinical and biochemical diagnosis, we investigated consecutive men referred with a suspected diagnosis of LOH, using the diagnostic instruments commonly available to physicians treating patients with LOH outside specialized centres with particular interest and expertise in this condition. The lead indicators for treatment were the presence of two or more clinical manifestations of ADAM and levels of serum T below the normal range by measuring either total (TT) or bioavailable T (BT). The study aimed to manage the situation as presented to a family physician, overwhelmed by patients' demands for treatment, and the controversial nature of the advice emanating

from learned societies and leading experts in the field.

PATIENTS AND METHODS

The study was approved by the University's Ethics Review Board and all patients were given a thorough explanation of the implications of treatment and the importance of follow-up. They had all been referred by family physicians because of the suspicion of hypogonadism, most frequently because of hypoactive sexual desire and/or erectile dysfunction. To participate a man had to have no previous history of androgen-replacement therapy (ART). All patients completed the ADAM questionnaire [5], were further assessed with a focused history and physical examination, and had a hormonal screen, as detailed below. If the clinical and biochemical assessment indicated the presence of hypogonadism (two or more clinical manifestations and serum T levels at or below

TABLE 1 The frequency of presenting symptoms in 45 men and their initial choice of T formulation

Symptom or choice	n (%)
Erectile dysfunction	41 (90)
Hypoactive sexual desire	37 (82)
Tiredness, lack of energy	32 (71)
Depression/irritability	24 (50)
T:	
undecanoate (oral)	26 (58)
enanthate	12 (27)
gel	5 (11)
patch	2 (4)

the normal range of the laboratory serving the clinic), the man was considered to have met the criteria for LOH and was offered treatment with supplemental androgens for ≥ 3 months. At the end of this period the clinical response was assessed and the biochemical serum evaluation repeated.

The hormonal assessment included measurements of gonadotrophins (FSH, normal <7 U/L; LH, normal <9 U/L), prolactin (normal range 4–18 $\mu\text{g/L}$) and serum TT (normal range 11–28 nmol/L), by chemiluminescent immunoassay (Elecys 2010, Roche Diagnostics, Laval, PQ, Canada). BT was measured by the ammonium sulphate precipitation method, as described previously [6]. The PSA level was measured using a radioimmunoassay kit (Abbott Laboratories, Abbott Parks, Illinois). Other investigations (dehydroepiandrosterone, liver function studies, lipid profiles, haematology, etc.) were also carried out but are not germane to this study and are not reported.

A man was considered hypogonadal (LOH) if he had two or more manifestations of the condition, as previously defined [2] and had serum T levels (TT or BT) at or below the normal range at our institution (TT <11.0 nmol/L or BT <2.5 nmol/L).

The first visit was defined as the baseline and indicated the initial contact with the patient when clinically assessed, the clinical diagnosis of LOH was made and blood was taken to confirm the clinical impression. The follow-up after treatment was the next visit with complete data nearest to the 3-month period after the patient started receiving ART. At this

TABLE 2 The overall response according to the formulation of T used, as n or n (%), and the response by domain. The denominator in each domain is variable as some patients did not report symptoms related to all domains. Four men in the 'mood' and two in the 'energy' domains who reported no problems initially reported an improvement during ART

T or domain	Complete	Moderate	Poor
T:			
undecanoate	14 (52)	6 (24)	6 (24)
enanthate	1	8	1
gel	2	3	0
patch	0	1	1
Domain			
sexual (37)	9 (24)	19 (51)	9 (24)
mood (24)	9 (35)	4 (16)	7 (29)
energy (25)	9 (36)	10 (40)	4 (16)

visit a history was taken and the man examined physically, and blood was drawn for a biochemical assessment identical to that at baseline.

After ART for 3–4 months, patients were evaluated, as indicated above, and the response to ART defined on a three-point ordinal scale, i.e. 1, complete (complete or nearly complete resolution of their symptoms, with the patient requesting continuation of treatment); 2, moderate (an improvement in symptoms, the patient still dissatisfied with the response, but willing to continue treatment); and 3, poor (minimal or no improvement in symptoms, the patient mostly dissatisfied with the response or unwilling to continue with treatment for reasons other than intolerance to the medication). The clinical response was correlated with the change in serum androgens, as determined by TT, BT and gonadotrophins.

Differences in TT, BT and PSA before and after ART were assessed with the Wilcoxon signed-rank test for paired differences. The potential ability of both TT and BT to predict the response to ART was analysed by Spearman's correlation and box plots drawn to illustrate the results. Finally, receiver operating characteristic (ROC) curves were used to illustrate the specificity and sensitivity of both measurements in their accuracy to predict success. In all, 45 men (mean age 59.2 years, range 35–82) participated in the study.

RESULTS

Seven men either did not comply with the evaluation after treatment or had ART for

<8 weeks; the analysis of the results is therefore based on the 38 (85%) who fulfilled the protocol criteria. They were all diagnosed as having symptomatic LOH (SLOH), by having two or more of the clinical manifestations of hypogonadism and a serum T (TT or BT) supporting the clinical impression. The frequency of symptoms is shown in Table 1; the men all had a positive response to the ADAM questionnaire [4].

The choice of ART preparation was left to the discretion of the patient, after a careful explanation of the advantages and disadvantages of each, including cost. The distribution on their choice of commercial T preparation is listed in Table 1. At the time the study was initiated the only available T preparations in Canada were injectables and oral; thus most patients were treated with either. When transdermal preparations became available they were also offered to the patients. In addition to the overall response and response by T formulation (Table 2), the results were assessed in three separate areas, i.e. sexual, mood and energy domains; denominators in each domain are not the same as some patients did not have symptoms on presentation. A few men noticed a better performance, although they had not reported shortcomings initially in the mood and energy domains. Twelve men were treated for ≥ 12 weeks while the remaining 26 were treated for 16 weeks.

The values of TT, BT and PSA before and after ART are shown in Table 3; the mean increase in BT was significant ($P=0.02$) but there was no significant change in the TT or PSA values ($P=0.6$). The proportion of patients with a

PSA level of >4 ng/L was similar at baseline (three of 42, 7%) as after ART (one of 43, 2%). Table 4 provides the nonparametric Spearman correlations between the variables before and after ART.

The ROC curves (Fig. 1) to assess the balance between sensitivity and specificity show that neither TT or BT levels before ART were reliable for predicting the success of ART (defined by the three-point scale). There was a suggestion that after ART the BT levels were associated with greater success ($r = 0.34$; $P = 0.02$, Spearman's correlation). The TT levels after ART tended to be, although less strongly, in the same direction. Box plots of the BT and TT values by success category are shown in Fig. 2a,b.

PSA levels increased in 23 patients (60%) and decreased in 13 (34%); the median (range) increase was 0.2 (0.01–1.32) ng/mL, and decrease 0.2 (0.02–1.03) ng/mL. In two men the levels were the same before and after treatment. The man with the large PSA increase had an initial value of 4.5 ng/mL and a negative biopsy of the prostate. After ART the PSA increased to 5.6 ng/mL and he was advised to discontinue ART. He refused on the basis that 'as long as I am alive, I want to live'. A second biopsy was also negative. At the time of preparing this report he continued on ART for over 2 years with a stable PSA at 5.8 ng/mL.

DISCUSSION

SLOH is of increasing interest and debate; although the decrease in androgen levels in association with age is irrefutable, the clinical implications of such a decrease are not universally accepted. In part the problem arises because the decreased production of androgens and the manifestations associated with it are not universal, as seen in women. Nevertheless, there is a much inconsistency and controversy in the results reported on the clinical assessment of the condition [7], the significance of the various biochemical investigations, and even more on whether the condition exists. In clinical practice this situation is not conducive to the appropriate management of men with SLOH, of whom there are increasingly more (http://www.fda.gov/fdac/departs/196_upd.html) because of the ageing of the world's population. The eventual result is that SLOH is largely neglected by physicians, who find the

TABLE 3 Median, means and ranges of BT, TT (nmol/L) and PSA ($\mu\text{g/mL}$) before and after ART

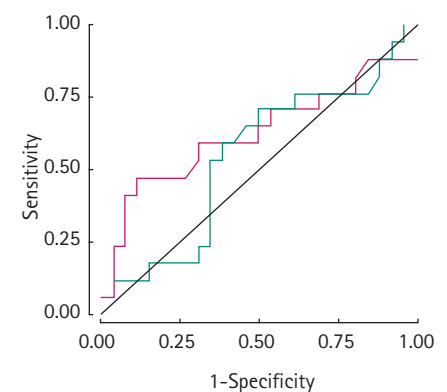
Analyte	Before	After	Δ
BT	2.10 (2.63, 0.39–7.50)	2.53 (3.80, 0.22–24.24)	0.28 (1.21, –5.05–20.96)
TT	10.50 (11.67, 4.3–23.8)	9.80 (12.71, 1.23–41.2)	0.0 (1.04, –12.50–30.7)
PSA	0.95 (1.49, 0.10–5.10)	1.0 (1.40, 0.11–5.67)	0.01 (0.02, –1.03–1.28)

	BT	TT	FSH	LH	Prolactin	TABLE 4
BT	1.0	0.717	–0.277	–0.106	0.109	<i>Spearman correlations</i>
<i>P</i>	–	<0.001	0.139	0.545	0.525	<i>between hormonal</i>
<i>N</i>	45	45	30	35	36	<i>variables before and after</i>
TT	–	1.0	–0.211	–0.028	–0.063	<i>treatment; there is a strong</i>
<i>P</i>	–	–	0.264	0.871	0.716	<i>correlation between FSH</i>
<i>N</i>	–	45	30	35	36	<i>and LH and a trend for a</i>
FSH	–	–	1.0	0.790	–0.156	<i>negative correlation</i>
<i>P</i>	–	–	–	<0.001	0.418	<i>between BT and FSH and LH</i>
<i>N</i>	–	–	30	29	29	
LH	–	–	–	1.0	–0.381	
<i>P</i>	–	–	–	–	0.031	
<i>N</i>	–	–	–	35	32	
Prolactin	–	–	–	–	1.0	
<i>P</i>	–	–	–	–	–	
<i>N</i>	–	–	–	–	36	

situation too confusing and prefer to ignore it in favour of more pressing health issues.

The problem is compounded with issues related to therapeutic safety. This is adequately illustrated by the frequent extrapolation of the results of the Women's Health Initiative, that reported an increased incidence in breast cancer and cardiovascular diseases in a group of postmenopausal women treated with a combination of oestrogens plus progesterone, compared to a placebo cohort [8]. This extrapolation is uninformed and unwarranted, because the hormones used are different in molecular structure and biological activity, and because such extrapolation ignores the large gender differences in the development of atherosclerosis [9] in relation to T serum levels. However, studies of the magnitude of the Women's Health Initiative have not been conducted in men; indeed, they are only at the recommendation stage. The Institute of Medicine [10] recently produced a series of recommendations suggesting that the response to T be assessed in a few men, and if there is a positive response, then proceed to large trials focused on safety. This implies that definitive answers will not be available for 10–15 years.

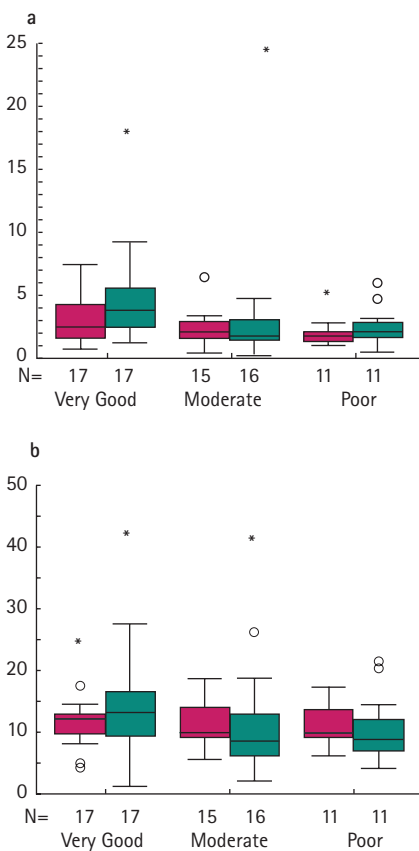
FIG. 1. The ROC curve before TT (green) and BT (red) to predict the success after evaluation. Neither TT or BT were accurate for predicting success (reference, black line).



Diagonal segments are produced by ties.

Many long forgotten [11] and recent [12] studies support the present finding that most men presenting with SLOH report sexual difficulties. These findings also support previous studies [13] showing that only about a third of hypogonadal men with erectile dysfunction respond adequately to ART. Hypogonadism therefore has not been considered a major cause of diminished

FIG. 2. Measurements of BT (A) and TT (B) before (red) and after (green) treatment for very good, moderate and poor response. After treatment there were 17 (39%), 16 (36%) and 11 (25%) patients in each category, respectively. The response for BT largely depended on the sexual domain. There was a trend for higher BT levels before and after treatment to be associated with a greater success (asterisks, $r = 0.25, P = 0.10$, and $r = 0.34, P = 0.02$, respectively, Spearman's correlation). There was no significant correlation between TT levels and success, although the TT levels after ART, as with BT, tended to be in the same direction. In each plot the central line is the median, the box the interquartile range, the bars the SD and the points the outliers.



sexual performance, until recently. Others [14–16] have independently shown that men with (sometimes mild) hypogonadism, in whom an appropriate trial of sildenafil failed, can be rescued with the addition of T, and that the combination of a phosphodiesterase-5 inhibitor and androgens works better than either alone. This is not surprising, considering that T and other androgens such as dehydroepiandrosterone are known to have a significant effect in the production of nitric oxide in the central and peripheral nervous

system, and direct action in the vascular endothelium [17–19]. Taken together these findings support the concept of assessing hormone levels in men with sexual and other symptoms associated with ageing.

For the interested and informed physician facing the vagaries of a nonspecific clinical picture, and a disparate and confusing array of biochemical assays, the situation is perplexing. Under most circumstances a simple measure of total T is sufficient to confirm the diagnosis of SLOH. However, a more appropriate test is the (more expensive and not universally accessible) determination of BT. However, either test shows very large intra-individual variability within a relative short time; indeed, an individual can easily have values in and out of the normal eugonadal range from week to week [20]. The present results indicate that the predictive value of one initial T measurement in relation to therapeutic response is unreliable, but the T level after ART correlated better with the response to ART. This, of course, is of little help in guiding the initial indications for ART in the symptomatic patient. These findings then beg the question; should a therapeutic trial of ART be considered in men with SLOH and borderline to normal levels of serum T? This is not easy to answer; currently a cautious positive reply appears warranted, although controversial. The suggestion of a 3-month treatment is aimed at minimizing a possible placebo effect. Safety is obviously the main consideration. There is minimal risk of serious adverse effects during this short period of ART [21] and the careful assessment at the end of the trial period may indicate pre-existing conditions (e.g. subclinical prostate cancer) that can then be investigated and treated.

The finding of a negative correlation between gonadotrophins and BT suggests that, indeed, the present men had primary testicular failure. It was gratifying to find a correlation between the levels TT and BT. However, even when the two assays are on the same aliquot of serum, it is not infrequent to find significant discrepancies in the results. Whether it represents technical shortcomings, intrinsic problems with the methods used or a true lack of correlation is not known. However, physicians managing men with SLOH not uncommonly encounter these perplexing results. Of course, discrepancies between TT and BT are anticipated, particularly in elderly men, because of

increased levels of sex-hormone binding globulin, which was not measured in the present study. These findings support the many studies indicating that measuring BT has better discriminatory value than TT [19]. It is also well established [19] that there are significant intra-individual variations in serum T levels as a function of time, but this does not apply here as the values were measured in aliquots from the same blood sample. Other than repeating the assays and hoping for close correlations, the only other solution appears to be a limited trial of ART to assess a patient's response.

The shortcomings of the study were primarily the relatively few patients and no repeated or more comprehensive hormonal measurements before, during and after ART. For further clarification, it would have been ideal to have sex-hormone binding globulin levels and a calculated free T, which correlates well with BT [19]. However, our intention was to assess the situation facing most clinicians with a practice not devoted exclusively to investigating and treating ageing men, and of those with androgen deficiency in particular.

A limited (3-month) trial of ART is indicated in a man with a clinical picture compatible with the diagnosis of SLOH in whom the condition is affecting his quality of life. This period is suggested because it minimizes the placebo effect and allows an early evaluation of response and possible adverse effects [20]. Although biochemical confirmation of hypogonadism is ideal, borderline levels should not be considered a deterrent to ART in the presence of clinical evidence. Until a more reliable and consistent objective measure of androgen levels in the peripheral circulation or tissue becomes available, good clinical judgement, understanding of the shortcomings of the biochemical assays, and careful and competent monitoring should allow the safe and effective treatment of SLOH.

ACKNOWLEDGEMENTS

Sponsored by unrestricted grants from the Canadian Society for the Study of the Ageing Male, Solvay Pharma Canada and Organon Canada.

CONFLICT OF INTEREST

A. Morales is an Executive Member of the Canadian Society for the Study of the Aging

Male. Source of funding: Canadian Society for the Study of the Aging Male, Solvay Pharma Canada and Organon Canada.

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Abbreviations: (B)(T)T, (bioavailable) (total) testosterone; (S)LOH, (symptomatic) late-onset hypogonadism; ADAM, androgen deficiency in the ageing male; ART, androgen-replacement therapy; ROC, receiver operating characteristic (curve).