Risk of Late-Onset Hypogonadism (Andropause) in Brazilian Men over 50 Years of Age with Osteoporosis: Usefulness of Screening Questionnaires

ABSTRACT

Objective: To analyze the relative risk of late-onset hypogonadism in men with osteoporosis and the usefulness of screening questionnaires. **Methods:** We correlated the Aging Male's Symptoms (AMS), Androgen Deficiency in Aging Male (ADAM) and International Index of Erectile Function (IIEF-5) questionnaires and the laboratory diagnosis of hypogonadism in 216 men aged 50-84 years (110 with osteoporosis and 106 with normal bone density, paired by age and ethnicity). **Results:** Hypogonadism presented in 25% of the osteoporotic and in 12.2 % of normal bone density men (OR 2.08; IC95%: 1.14-3.79) and was associated with ADAM first question (low libido, p=0.013). Levels of TT below 400 ng/dl correlated with an AMS score above 26 (p=0.0278). IIEF-5 showed no correlation with testosterone levels. **Conclusion:** Hypogonadism was 2.08 times more prevalent in osteoporotic men. The symptom that best correlated with late-onset hypogonadism was low libido (ADAM 1 positive). **(Arq Bras Endocrinol Metab 2008; 52/9:1439-1447)**

Keywords: Andropause; Screening questionnaires; Testosterone; Late-onset hypogonadism; Male osteoporosis

RESUMO

Risco Relativo de Hipogonadismo Tardio (Andropausa) em Brasileiros com Mais de 50 Anos com Osteoporose e a Utilidade de Questionários de Triagem.

Objetivos: Avaliar o risco relativo de hipogonadismo tardio em homens com osteoporose e a utilidade de questionários de triagem. **Métodos:** Correlacionamos a pontuação dos questionários *Aging Male's Symptoms* (AMS), *Androgen Deficiency of the Aging Male* (ADAM) e *International Index of Erectile Function* (IIEF-5) com dosagens de testosteronas em 216 homens entre 50 e 84 anos (110 com osteoporose e 106 com densidade óssea normal, pareados por idade e etnia). **Resultados:** Hipogonadismo ocorreu em 25% dos osteoporóticos e em 12,2% dos com densidade óssea normal (RR 2,08; IC95%: 1,14-3,79) e esteve associado à pergunta 1 do ADAM (diminuição de libido, p = 0,013). Testosterona total < 400 ng/dL associou-se a AMS > 26 (p = 0,0278). Disfunção erétil, avaliada pelo IIEF-5, não se correlacionou com dosagens de testosteronas. **Conclusão:** Hipogonadismo foi 2,08 vezes mais prevalente em homens com osteoporose e esteve associado à diminuição da libido (ADAM 1 positivo). **(Arq Bras Endocrinol Metab 2008; 52/9:1439-1447)**

Descritores: Andropausa; Questionários de triagem; Testosterona; Hipogonadismo masculino tardio; Osteoporose masculina

INTRODUCTION

The process of aging in men involves modifications in sexual steroid levels, with psycho-physical repercussions of variable intensity. In the serum of

original article

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young men, 54% of circulating testosterone is bound nonspecifically to albumin (low affinity binding) and 44% specifically to sex hormone binding globulin (SHBG, high affinity binding), while 1 to 3% is unbound, known as free testosterone (FT). FT and testosterone bound to albumin constitute the category of bioavailable testosterone (BT), as both have biological activity (1). As men age, there is a gradual reduction in the total testosterone serum concentration and a progressive increase in SHBG, so low androgen levels are best demonstrated by FT and BT dosages (2). "Gold standard" methods of assessment are equilibrium dialysis (for FT), and ammonium sulfate precipitation (for BT). Both methods are expensive, difficult to perform, and largely inaccessible to most clinicians. An alternative method calculates FT and BT via a formula that uses total concentration of serum testosterone, SHBG and albumin as input variables (2,3).

Aging men with low androgen levels may experience decreased libido, with or without sexual dysfunction, as well as low muscle strength, psychological changes, mainly depression and increased risk of osteoporosis (4-7). This array of psycho-somatic-sexual symptoms is referred to by many names, such as Late-onset Hypogonadism (LOH) or Andropause.

By definition, LOH is a clinical and biochemical syndrome associated with aging and characterized by a set of typical symptoms, as well as testosterone deficiency (8). However, these symptoms are not specific enough to be considered pathognomonic, which makes LOH difficult to clinically distinguish from aging.

Tools were recently developed to screen men exhibiting these general symptoms for a suite of other possible deficiencies, so that the chance of making the correct clinical diagnosis could be improved. These tools include the Androgen Deficiency of the Aging Male (ADAM) questionnaire (9), and the Aging Male Symptoms (AMS) scale (10). A frequent symptom associated with hypogonadism is erectile dysfunction (ED). The International Index of Erectile Function is a well-established tool for screening men with ED (11).

Men with osteoporosis represent a group with high risk of LOH (5). The current study sought to: (i) determine the relative risk of hypogonadism in men over 50 years of age in the city of Rio de Janeiro, with osteoporosis compared to men with normal bone density of the same age and ethnicity; (ii) evaluate the usefulness of the above questionnaires as screening tools for LOH, correlating their scores to the testosterone levels used for the laboratory diagnosis of hypogonadism.

SUBJECTS AND METHODS

Patients

The population analyzed in this paper was recruited from the Men's Osteoporosis Detection Program of the Instituto Nacional de Traumato-Ortopedia (INTO). The INTO program is a cross-sectional study that aims to determine the prevalence of male osteoporosis in the city of Rio de Janeiro. Up to January 2005, about 800 men voluntarily sought out the program after it was advertised in the midia (radio, newspaper and TV) that a free osteoporosis evaluation was being offered for all men over 50 years of age. Every men who spontaneously presented at INTO had a lumbar spine and hip bone densitometry performed.

Men diagnosed with osteoporosis (n=132) were contacted by telephone, telegram or letter to inquire whether they would participate in a complementary evaluation of male health that addressed sexual hormones, which would be performed at the Hospital da Lagoa. One hundred and ten men (81%) who had a diagnosis of osteoporosis through the INTO program accepted this invitation. In order to establish the relative risk of hypogonadism in osteoporotic men, a group of 106 men with normal bone densitometry from the same INTO program, matched by ethnicity and age, was also asked to participate.

Study Design

This cross-sectional study was designed to determine the prevalence of hypogonadism in men over 50 years of age who presented osteoporosis and normal bone mineral density; and to correlate laboratory and clinical data, through the responses to LOH screening questionnaires.

Data Collection

Patients were questioned individually about their medical history, with emphasis on morbidities such as genital surgery, drug use that could interfere with the synthesis or action of sexual hormones, depression and current use of anti-depressants. A general physical exam was performed, including the genitals, excluding prostate rectal exam.

Three questionnaires were given to each subject to determine the prevalence of signs and symptoms of male hypogonadism and erectile dysfunction (AMS, ADAM and IIEF-5).

During the first medical exam, the Aging Male's Symptoms (AMS) scale questionnaire was used. This scale was created to screen for male hormone alterations, not to provide a definitive diagnosis (12). Each patient received a sheet containing the AMS questionnaire (Figure 1), which a doctor read aloud to a group of four to six patients. Subjects recorded their responses on a paper with a certain degree of privacy, such that each patient could not read the answers of the others.

The AMS is a Health Related Quality of Life scale (HRQOL) consisting of 17 questions, which measures complaints and quality of life issues related to health. The questionnaire has been translated into 14 languages, including Portuguese (10). The AMS score increases point by point, indicating increasing severity, in patients with: "no complaints" (17-26 points), "mild" (27-36 points), "moderate" (37-49 points), and "severe" (≥ 50 points) complaints. The total score is di-

Symptoms	None 1	Mildm 2	Moderate 3	Severe 4	extremely severe 5	Score =
1. **Decline in your feeling of general well-being** (general state of health, subjective feeling)	☐	☐	☐	☐	☐	
2. **Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general back ache)	☐	☐	☐	☐	☐	
3. **Excessive sweating** (unexpected / sudden episodes of sweating, hot flushes independent of strain)	☐	☐	☐	☐	☐	
4. **Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)	☐	☐	☐	☐	☐	
5. **Increased need for sleep, often feeling tired**	☐	☐	☐	☐	☐	
6. **Irritability** (feeling aggressive, easily upset about little things, moody)	☐	☐	☐	☐	☐	
7. **Nervousness** (inner tension, restlessness, feeling fidgety)	☐	☐	☐	☐	☐	
8. **Anxiety** (feeling panicky)	☐	☐	☐	☐	☐	
9. **Physical exhaustion / lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)	☐	☐	☐	☐	☐	
10. **Decrease in muscular strength** (feeling of weakness)	☐	☐	☐	☐	☐	
11. **Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)	☐	☐	☐	☐	☐	
12. **Feeling that you have passed your peak**	☐	☐	☐	☐	☐	
13. **Feeling burnt out, having hit rock-bottom**	☐	☐	☐	☐	☐	
14. **Decrease in beard growth**	☐	☐	☐	☐	☐	
15. **Decrease in ability/frequency to perform sexually**	☐	☐	☐	☐	☐	
16. **Decrease in the number of morning erections**	☐	☐	☐	☐	☐	
17. **Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse	☐	☐	☐	☐	☐	
Do you have any other major symptoms?	Yes ☐	No ☐	If Yes, please describe:			

Evaluation						
Score Severity of symptoms	17-26 none	27-36 mild	37-49 moderate	>50 severe		

Figure 1. The Aging Males' Symptoms (AMS) scale – Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none" (12).

vided by three sub-scales: sexual, (questions 12 to 14 and 17), psychological (questions 6 to 9 and 11) and somato-vegetative (questions 1 to 5, 10 and 13). The total score and not the sub-scales should be used, with a cut-off ≥ 27 points (13). Heinemann et al.demonstrated that the AMS scale has a sensitivity of 73.6% and specificity of 70.4% for the improvement after androgen replacement therapy (14).

During the second medical exam, the St. Louis University questionnaire, also known as Androgen Deficiency of the Aging Male (ADAM), was given to the subjects (Figure 2) (9). Ten symptoms commonly observed in men with low bioavailable testosterone are assessed in the ADAM questionnaire. Affirmative answers to questions 1 or 7 or to any other three questions suggest hypogonadism. The ADAM questionnaire demonstrated a sensitivity of 88% and a specificity of 60% in men (9). This test has not yet been validated in Brazil. As an alternative way allowing us to use this questionnaire, the answers given by subjects from our sample, without osteoporosis or hypogonadism, were planned to be analyzed in separate. A non-statistical difference in testosterone values between normal subjects with positive and negative results for the ADAM questionnaire could empower us to use it for the study.

The IIEF-5 questionnaire, an abbreviated version of the International Index of Erectile Function (IIEF) to evaluate erectile function (15), was also given during the second medical exam. The IIEF-5 has a maximum score of 25, and was developed by Rosen et al. (Figure 3)

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased enjoyment of life?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Affirmative answers to questions 1 or 7, or to any other three questions provide a positive result on the ADAM questionnaire

Figure 2. ADAM's Questionnaire - Answer "Yes" or "No" (11).

1) How do you rate your confidence that you could keep an erection?
(1) Very low (2) low (3) Moderate (4) High (5) Very high

(2) When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
(1) Almost never or never (2) A few times (much less than half the time) (3) Most times (about half the time) (4) Much more than half the time (5) Almost always

3) During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
(1) Almost never or never (2) A few times (much less than half the time) (3) Most times (about half the time) (4) Much more than half the time (5) Almost always

4) During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
(1) Extremely difficult (2) Very difficult (3) Difficult (4) Slightly difficult (5) Not difficult

5) When you attempted sexual intercourse, how often was it satisfactory for you?
(1) Almost never or never (2) A few times (much less than half the time) (3) Most times (about half the time) (4) Much more than half the time (5) Almost always

Result: ≤ 21 has some degree of erectile dysfunction

Figure 3. Questionnaire IIEF-5 – Each question has 5 possible responses. Circle the number that best describes your own situation over the past six months. Select only one answer for each question (13).

(11). Scores above 21 are considered normal and without ED. Lower scores indicate ED of increasing severity: mild ED (17 to 21), mild to moderate ED (12 to 16), moderate ED (8 to 11), and severe ED (5 to 7). Using a cut-off of < 22 points, the IIEF-5 demonstrated a sensitivity of 98% and a specificity of 88% for the detection of the presence and severity of ED (11). This test was validated in Brazil by Rhoden et al. (16).

Laboratory measurements

Between the first and second medical exams, blood samples were collected at the laboratory of the Instituto Fernandes Figueira, between 8:30 and 10:00 in the morning, for measurement of: (i) general parameters used for detecting causes of osteoporosis; (ii) TSH for the exclusion of hypothyroidism as a clinical differential diagnosis of LOH; (iii) albumin. Part of the collected blood sample was separated and sent to the Diagnósticos

da América Laboratory, for measurement of total testosterone (TT) and SHBG. Free testosterone and BT were then calculated from the dosages of TT, SHBG and albumin with the formula of Vermeulen (17) through the website http://www.issam.ch/freetesto.htm.

Laboratory hypogonadism was defined as having cFT < 6.5 ng/dl in two samples collected at different times (5, 18, and 19).

During the second medical exam, the patient was informed about the results of his blood tests. If the calculated free testosterone (cFT) value was < 6.5 ng/dl, a second blood sample collection was scheduled to take place at least one month after the first, in the laboratory of the Instituto Fernandes Figueira. The total testosterone and SHBG blood samples were once again sent to the Diagnósticos da América Laboratory for new calculations of free and bioavailable testosterone. Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), and prolactin were measured at the Instituto Fernandes Figueira in order to exclude secondary causes of hypogonadism.

Total testosterone was measured by chemiluminescence, using an automatic kit from Advia Centaur (Bayer Diagnostics), analytical sensitivity of 100 ng/dl, and reference values in men of 241 to 827 ng/dl. SHBG was also measured by chemiluminescence, using the Immulite 1000 kit (Siemens), which has an analytical sensitivity of 0.2 nmol/l and reference values in men of 13 to 71 nmol/l. Albumin concentrations were determined by colorimetric spectrophotometry, with a kit from Targa BT Plus (Wiener Lab.), and reference values of 3.5 to 5.5 g/dl. The FSH, LH and prolactin concentrations were measured by chemiluminescence, with the VIDAS kit (Biolab Merieux). The male reference values used were: FSH (0.9-15 UI/L), LH (1.3-13 UI/L), prolactin (< 15 ng/ml).

The following factors were then analyzed: total AMS score, affirmative responses to questions 1 or 7 or to any other three questions of the ADAM questionnaire, and the total IIEF-5 score. Correlations were constructed between these scores and laboratory hypogonadism using TT levels, as well as FT and BT levels, which were calculated by Vermeulen's formula (17).

Statistical Analysis

The statistical analysis were done with the Student t test for continuous variables in the Graphpad Prism version 3.00 for Windows program (Graphpad Software, San Diego, CA, USA). For categoric variables, the chi-square test by Mantel-Haenszel was performed in the Epi-info 6.04 program (CDC, Atlanta). The significance level was set at $p< 0.05$.

Ethical aspects

The research objectives were explained to the men who attended the first medical exam in small groups, and each subject signed an informed-consent document approved under the Ethics Committee protocol.

RESULTS

Forty-one men (19% of the total sample) were diagnosed with hypogonadism by laboratory criteria (2 samples of cFT < 6.5 ng/dl): 28 in the osteoporosis group (25%) and 13 in the control group (12.2%). The OR for hypogonadism in osteoporotic men was 2.08 (IC95%:1.14-3.79). None of the subjects had hypogonadism secondary to hyperprolactinemia or pituitary insufficiency. Causes of osteoporosis that could mask the clinical diagnosis of hypogonadism were not demonstrated by the general exams.

When the AMS and ADAM questionnaires were used as screening tools, the percentages of subjects who exhibited symptoms compatible with late-onset hypogonadism were determined to be 84% (179 patients) and 60% (128 patients), respectively

With regard to the AMS questionnaire, total scores equal to or greater than 27 showed an association only with TT levels below 400 ng/dl; no association was found with cBT or cFT (Table 1).

The answers given by 91 subjects from our sample, with normal bone density and without hypogonadism, to the ADAM questionnaire were analyzed. The only criterion out of all those assessed that could be "validated" was the ADAM first question, such that there was no statistical difference between the percentages of subjects with a positive and a negative result for this question (54,94 and 45,05% respectively, p=0.18).

There was a significant association between an affirmative answer to ADAM question number 1 and a laboratory diagnosis of hypogonadism, as well as levels of cFT, cBT and TT comparable to those seen in patients with hypogonadism (Table 2). Among hypogonadal

Table 1. Comparisons of AMS score ≥ 27 with measurements of calculated free, bioavailable and total testosterone.

Hormone samples	AMS ≥ 27 n/total (%)	AMS < 27 n/total (%)	OR	95% CI	Sensitivity (%)	Specificity (%)
2 cFT samples < 6.5 ng/dl*	35/41 (85.4)	6/41 (14.6)	1.21	0.63-4.45	85.4	19.9
1 cFT sample < 6.5 ng/dl	51/58 (87.9)	14/58 (22.1)	1.69	0.65-4.54	87.9	18.8
1 cBT sample < 140 ng/dl	42/48 (87.5)	6/48 (22.5)	1.52	0.55-4.39	87.5	17.9
1 TT sample < 400 ng/dl	46/49 (93.9)	3/49 (6.1)	**3.69**	1.01-15.89	93.9	19.4

Number of patients who answered the AMS questionnaire = 214. OR = odds ratio; CI = confidence interval; TT = total testosterone; cFT = calculated free testosterone; cBT = calculated bioavailable testosterone; * Laboratory diagnosis of hypogonadism.

Table 2. Comparison of answer to ADAM question 1: "Do you have a decrease in libido (sex drive)?" and calculated free, bioavailable and total testosterone levels.

Hormone samples	Yes n/total (%)	No n/total (%)	OR	95% CI	Sensitivity (%)	Specificity (%)
2 cFT samples < 6.5 ng/dl*	31/40 (77.5)	9/40 (22.5)	**2.70**	1.15-6.52	77.5	43.9
1 cFT sample < 6.5 ng/dl	43/57 (75.4)	14/57 (24.6)	**2.57**	1.24-5.37	75.4	45.5
1 cBT sample < 140 ng/dl	34/46 (73.9)	12/46 (26.1)	**3.25**	1.01-4.86	73.9	43.7
1 TT sample < 400 ng/dl	35/48 (72.9)	13/48 (27.1)	**2.08**	0.97-4.49	72.9	43.6

Number of patients who answered the AMS questionnaire = 213; OR = odds ratio; CI = confidence interval; TT = total testosterone; cFT = calculated free testosterone; cBT = calculated bioavailable testosterone.

Table 3. Comparison of the prevalence of positive answers to question 1 of the ADAM questionnaire with cFT values.

	ADAM 1 test			
	Positive		Negative	
cFT (ng/dl)	n	%	n	%
< 4	5	100	0	0
≥ 4 and < 5	10	76.9	3	23.1
≥ 5 and < 6.5	16	72.7	6	27.3
Total	31	77.5	9	22.5

cFT = calculated free testosterone.

men, an inverse relationship was observed between cFT values and ADAM 1 positive status (Table 3). No correlations were detected between question 7 or the total ADAM score and levels of TT, cFT or cBT.

The IIEF-5 questionnaire revealed no correlation between laboratory-defined hypogonadism and ED (p=0.269). There was no difference between TT, cFT or cBT levels among men with IIEF-5 < 22 or ≥ 22. The correlations between IIEF-5 scores and hormone levels were very weak: TT: -0.04393, cFT: -0.05049 and cBT: -0.05077.

However, 147 men (74% of the subjects) complained of some degree of ED, expressed by IIEF-5 score < 22. Significant differences were found between the percentages of subjects without any ED seen in each age group: 41.4 % in the group of 50 to 59 years old, compared to 30.3% in the group of 60 to 69 years old and 16.3% in the group of 70 or older. Severe ED was more prevalent in men of 70 years or older (p=0.006), while in the 50 to 59 group, 31% had mild ED, 17.2% mild to moderate, 6.9% moderate and 3.4% severe. These differences were statistically significant (p=0.0002) (Table 4).

DISCUSSION

Most of the articles published in the scientific literature agree that hypogonadism should be defined with biochemical as well as functional criteria (8, 20, and 21). The functional criteria are typically assessed by questio-

Table 4. Prevalence of erectile dysfunction (ED) sorted by age.

	≤ 59 years		60-69 years		≥ 70 years		Total		p-value[1]
IIEF-5 score	N	%	N	%	N	%	N	%	
22-25 (no ED)	12	41.4	27	30.3	13	16.3	52	26.3	**0.0088**
17-21 (mild)	9	31.0	20	22.5	21	26.3	50	25.3	0.6311
12-16 (mild to moderate)	5	17.2	19	21.3	11	13.8	35	17.7	0.432
8-11 (moderate)	2	6.9	9	10.1	12	15.0	23	11.6	0.424
≤7 (severe)	1	3.4	14	15.7	23	28.8	38	19.2	**0.006**
Total	29	100.0	89	100.0	80	100.0	198	100.0	
p-value[2]		**0.0002**		**0.00320**		**0.03**			

p-value[1] = Refers to comparison of the degree of the percentage of erectile dysfunction in each age group; p-value[2] = Refers to comparison of the distribution of the degrees of erectile dysfunction in each age group.

nnaires, although the sensitivity and specificity of these tests should be individualized for each culture, to be proven useful. The biochemical criteria requires two measurements of calculated free and bioavailable testosterone, as demonstrated in our study.

Despite the great sensitivity for testosterone levels compatible with hypogonadism (88 to 94%), the AMS scale did not prove to be valid as an exclusive tool for screening, as shown by the low specificity we detected (18 to 19%). Using a cutoff of score ≥ 27, the only correlation found was with TT < 400 ng/dl (OR: 3.69; 95% CI: 1.01-15.89), a level that is not diagnostic of hypogonadism, but rather indicates the need for a preliminary screening by which elder men have a greater chance of showing a free or bioavailable testosterone concentration below reference ranges (7). Our findings agree with those in the literature (1). The AMS scale was designed to assess symptoms of aging (independent of those that are disease-related) between groups of males under different conditions, to evaluate the severity of symptoms over time, and to measure changes pre- and post androgen replacement therapy (10). When the AMS questionnaire was compared to ADAM for screening hypogonadism (22), a sensitivity of 83% was achieved but the specificity was only 39%, using a very low threshold for AMS, a score of only 17 points.

Regarding the ADAM scale, according to our attempt for an alternative validation, only ADAM 1 could be used as a screening tool for hypogonadism. In fact it was the only ADAM criterion that correlated with LOH laboratorial diagnosis in our sample. The first question in the ADAM questionnaire, "Do you have a decrease in libido (sex drive)?" was the most useful in screening for hypogonadism, with a sensitivity of 77.5% and a specificity of 43.9%. The other criteria that corresponded to a positive ADAM rating, however, correlated with neither the laboratory diagnosis of hypogonadism nor with the testosterone levels. Using ADAM 1, we observed sensitivity similar to that obtained for any ADAM criteria in other populations (77.5% *versus* 80-88%, respectively). The specificity for ADAM 1 in our study (43.9%) was intermediate between that reported for any ADAM criteria in Canadian (60%), Belgian (21.6%) and Taiwan (20%) men (11, 23, and 24).

One way to explain the different results generally found regarding ADAM and AMS was demonstrated by Ichioka et al. (25) which examined 2211 men, 86% above the age of 40. In this study, hypogonadism better correlated with sexuality, as measured by the sexual sub-score, than with the total AMS score (25). Similar results were found in the Belgian study by T'sjoen et al. (26). Delhez et al. also described that the psychological response to decreased androgen manifests as minor depressive symptoms, which are not pathological (27). The AMS scale adds three different dimensions, therefore diluting the results and generating a poor comparison with the ADAM questionnaire, which needs, in most cases, only one affirmative answer to yield a positive rating.

In our study, using AMS and ADAM-based criteria, 179 (84%) and 128 (60%) of the 216 subjects, respectively, would be suspected of hypogonadism. Using

the recommended laboratory criteria, only 41 (19%) of the subjects were judged hypogonadal after a second cFT exam, 28 in the osteoporosis group (25%) and 13 in the normal bone density group (12.2%). These numbers show that both questionnaires lack specificity. If applied to the general population, they would result in a large number of negative laboratory exams. Our findings support the Endocrine Society guidelines (5), in that questionnaires have not demonstrated to be a cost-effective strategy to detect LOH, and hormonal dosages should rather be performed in high risk individuals, such as osteoporotic men.

If only a positive response to the first ADAM question along with two samples of cFT < 6.5 ng/dl was considered, hypogonadism would be diagnosed only in 31 (15%) of the men. So, even the clinical criterion that demonstrated a better sensitivity and specificity overall, was not able to identify all men with laboratory-defined hypogonadism (Table 2), because some men denied diminished sexual desire and presented different complaints. This demonstrates the complexity of the clinical picture of late-onset hypogonadism and the necessity of using more than a single criterion or question for the clinical evaluation.

Sexuality combines libido and sexual function, and can be related to race, culture and religion. The IIEF-5 questionnaire, which was used to evaluate the association of sexual dysfunction and hypogonadism, did not demonstrate any correlation with laboratory hypogonadism or testosterone levels in our study. The IIEF-5 is an abridged five item version of the fifteen item International Index of Erectile Function (IIEF), an important questionnaire for the evaluation of sexual erection that has an excellent sensitivity (98%) and good specificity (88%) (11).

Although Chinese cohort studies have tried to establish androgen deficiency risks by using the IIEF-5 (28), in the majority of studies (29-31) including the Massachusetts Male Aging Study (MMAS), this correlation was not demonstrated (32). A possible explanation for the differences in these results was suggested in Mikhail's review (33). A conclusive diagnosis of hypogonadism in men in these studies cannot be confirmed, because many studies suffered from the lack of a second testosterone sample, which was collected in our study. His conclusion is that in most men, circulating levels of testosterone well below the normal range become essential for normal erections, and therefore only a pronounced hypogonadism would be evidenced by erectile dysfunction (33). Additionally, ED becomes very common with advancing age, again as observed in our study. The great majority of hypothesized causes relate to vascular pathology, diabetes, hypertension and the use of drugs (34), and only in some cases, hypogonadism (35).

CONCLUSIONS

The prevalence of late-onset hypogonadism was 25% in men with osteoporosis and 12.2% in men with normal bone density over 50 years of age (OR 2.08; IC95%: 1.14-3.79 for hypogonadism in osteoporotic men).

The symptom that best correlated with LOH was decreased sexual desire or libido (ADAM 1 positive). Among hypogonadal men, the lower the calculated free testosterone, the greater was the prevalence of a positive answer to ADAM 1.

AMS scores ≥ 27 correlated only with TT levels less than 400 ng/dl.

Erectile dysfunction of any degree varied from 58 to 84%, and increased in both prevalence and severity with age. There were no correlations between testosterone levels or hypogonadism and erectile dysfunction.

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