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Characteristics of Androgen Deficiency in Late-Onset Hypogonadism: Results from the European Male Aging Study (EMAS)

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Context: Late-onset hypogonadism (LOH) has been defined as a syndrome in middle-aged and elderly men reporting symptoms in the presence of low testosterone (T).

Objective: The objective of the study was to seek objective biochemical and end-organ evidence of androgen deficiency in men classified as having LOH according to our previously published criteria.

Design, Setting, and Participants: The design of the study included cross-sectional data from the European Male Aging Study on 2966 community-dwelling men aged 40–79 years in eight European countries.

Main Outcome Measure(s): Waist circumference, body mass index, muscle mass, estimated heel bone mineral density (eBMD), hemoglobin, insulin sensitivity, physical activity, metabolic syndrome, insulin resistance index, and cardiovascular disease were measured.

Results: Sixty-three men (2.1%) were classified as having LOH: 36 moderate and 27 severe. They were older and more obese than eugonadal men and had, in proportion to the graded T deficiency, lower muscle mass, eBMD, and hemoglobin, with poorer general health. Both moderate and severe LOH was associated with lower hemoglobin, mid-upper arm circumference, eBMD, physical function (measured by the Short Form-36 questionnaire), slower gait speed and poorer general health. Only men with severe LOH showed significant associations with larger waist circumference (β= 1.93cm; 0.04–3.81), insulin resistance (β= 2.81; 1.39–4.23), and the metabolic syndrome (odds ratio 9.94; 2.73–36.22) after adjustments for confounders. Men with low testosterone only (irrespective of symptoms) showed lesser magnitudes of association with the same end points.

Conclusions: LOH is associated with multiple end-organ deficits compatible with androgen deficiency. These data support the existence of a syndrome of LOH in only a minority of aging men, especially those with T below 8 nmol/liter. **(*J Clin Endocrinol Metab* 97: 1508–1516, 2012)**

The clinical significance of the age-related decline in testosterone (T) (1, 2) in men continues to attract much attention and debate (3). Recent guidelines have attempted to establish a syndrome of late-onset hypogonadism (LOH) as a clinical and biochemical state with advancing age, characterized by typical symptoms and low serum T (4). However, the concept of hypogonadism of aging remains controversial (3, 5) in the absence of objective evidence of T deficiency in symptomatic older men (6, 7).

We have recently proposed the minimum criteria for the identification of LOH, which entailed the presence of three sexual symptoms (decreased sexual interest and morning erections and erectile dysfunction) in combination with total T below 11 nmol/liter and free T below 220

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; E2, estradiol; eBMD, estimated heel bone mineral density; EMAS, European Male Aging Study; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, insulin resistance calculated using the homeostatic model; LOH, late-onset hypogonadism; MUAC, mid-upper arm muscle circumference; OR, odds ratio; PASE, Physical Activity Scale for the Elderly; SF-36, Short Form-36; T, testosterone.

pmol/liter (8). Nevertheless, putative symptoms of hypogonadism in aging men are highly nonspecific (8). Although we underscored the higher specificity conferred by three sexual symptoms with the lower total T threshold of less than 8.0 nmol/liter, the nature and extent of T deficiency in symptomatic aging men remain uncertain (9, 10). Hypogonadism is a state of androgen deficiency that has an adverse impact on functions of multiple organ systems and quality of life. In addition to reported symptoms, objective manifestations of hypogonadism may include decreased muscle mass and strength, increased body fat, decreased bone mineral density (BMD), and lower hemoglobin (11).

The aim of this study was to seek objective evidence of androgen deficiency based on pertinent biochemical, end-organ, disease state, and quality-of-life alterations in middle-aged and elderly men classified as having LOH according to the criteria previously defined in a general population study (8). In addition, we examined whether the observed associations could be explained by other factors that vary concurrently with gonadal status.

Materials and Methods

Subjects and study design

An age-stratified probability sample of 3369 men aged 40–79 (mean ± SD 60 ± 11) yr were recruited from population registers in eight European centers (Florence, Italy; Leuven, Belgium; Malmö, Sweden; Manchester, UK; Santiago de Compostela, Spain; Lódz, Poland; Szeged, Hungary; Tartu, Estonia). After completing a postal health questionnaire, subjects attended the research clinics for further assessments as previously described (vide infra) (12). Ethical approval for the study was obtained in accordance with local institutional requirements in each center, and written informed consent was obtained from each participant.

Assessments

Participants completed an interviewer-assisted questionnaire including the Short Form-36 (SF-36) health survey and a European Male Aging Study (EMAS) sexual function questionnaire (EMAS-SFQ) as previously described (12). Physical function assessments included reported levels of activity by the Physical Activity Scale for the Elderly (PASE) (13) and gait speed in a timed 50-ft walk (14). BMD at the heel was estimated by the Sahara Sonometer (Hologic, Bedford, MA) from the machine outputs broadband ultrasound attenuation and speed of sound using the equation: estimated heel bone mineral density (eBMD) = 0.002592 × (broadband ultrasound attenuation + speed of sound) − 3.687 (15). Mid-upper arm muscle circumference (MUAC) − $\pi \times$ triceps skinfold was used as an indicator of lean body mass (16). Body mass index (BMI) was calculated as body weight (kilograms) divided by the square of height (meters).

Hormones, biochemistry, and hematology

A single fasting morning (before 1000 h) venous blood sample was obtained from each subject. Measurement of T and estradiol (E2) were carried out by gas chromatography-mass spectrometry as described previously (17). The lower limit of quantitation was 0.17 nmol/liter for T and 7.34 pmol/liter for E2. The coefficients of variation of T measurements were 2.9% within runs and 3.4% between runs and for E2 3.5% within runs and 3.7% between runs. SHBG, LH, and FSH were measured by the Modular E170 platform electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Free T levels were derived from total hormone, SHBG, and albumin concentrations as previously described (18).

Total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, hemoglobin, and glucose were measured in a fasting venous blood sample using standard methods as described elsewhere (19). Insulin was assayed using chemiluminescence. Insulin resistance was calculated using the homeostatic model (HOMA-IR) (20).

Statistical analysis

LOH was defined as the presence of three sexual symptoms (decreased frequency of morning erections and sexual thoughts and erectile dysfunction) in combination with total T less than 11 nmol/liter and free T less than 220 pmol/liter (8). LOH was further divided into two subgroups: moderate = total T of 8 nmol/liter or greater and less than 11 nmol/liter and free T less than 220 pmol/liter and severe = total T less than 8 nmol/liter and free T less than 220 pmol/liter. Men without LOH were considered as eugonadal.

Smoking status was categorized as current *vs.* never and ex-smokers. Comorbidity was classified as none, one, and two or more reported morbid conditions. Poor health was defined as subjects who rated their general health as fair or poor in the SF-36 questionnaire. The metabolic syndrome was defined using the Adult Treatment Panel III guidelines (21) as having at least three of the following risk factors: waist circumference 102 cm or greater, triglyceride level of 1.7 mmol/liter or greater, a HDL cholesterol level less than 1.03 mmol/liter, systolic blood pressure of 130 mm Hg or greater and/or a diastolic blood pressure of 85 mm Hg or greater, and a fasting glucose of 5.6 mmol/liter or greater.

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ANOVA and χ^2 tests were respectively used to determine whether there were differences between the LOH (moderate and severe) and eugonadal groups for anthropometrics, hormones, hemoglobin, BMD, and other continuous and categorical variables.

Linear and logistic regression models (unadjusted and adjusted) were used to assess the association between LOH status (independent variable) with various continuous and binary outcome variables respectively, with the eugonadal group as reference category. The analyses were repeated using just the T thresholds of 8–11 nmol/liter and less than 8 nmol/liter irrespective of sexual symptoms with the eugonadal group as the reference category.

Multiple (linear or logistic) regression analyses were performed with serial adjustment for age, BMI, smoking status, and morbid conditions where appropriate. Results from linear regression models were presented as β-coefficients and 95% confidence intervals (CI) and from logistic regression models as odds ratios (OR) and 95% CI. All statistical analyses were conducted using Intercooled STATA version 9.2 (StataCorp, College Station, TX).

Results

From the initial probability sample of 3369 participants, 150 were excluded because of known pituitary, testicular, or adrenal diseases or current use of medications affecting pituitary/testicular functions or clearance of sex steroids.

TABLE 1. Subject characteristics: analysis sample and by gonadal status

	All (n = 2966)	Eugondal (n = 2903)	LOH (moderate) (n = 36)	LOH (severe) (n = 27) [Mean (SD)]	*P* value
Physiological measures					
Study age (yr)	59.15 (10.82)	58.92 (10.77)	71.08 (6.58)	68.39 (7.30)	<0.001
Systolic blood pressure (mmHg)	145.83 (20.70)	145.56 (20.59)	158.06 (23.93)	158.07 (20.68)	<0.001
Diastolic blood pressure (mmHg)	87.35 (12.32)	87.29 (12.32)	89.78 (11.68)	90.41 (13.55)	0.209
Body size and composition					
Body mass index (kg/m^2)	27.64 (4.10)	27.55 (4.02)	30.68 (5.05)	33.15 (6.17)	<0.001
Waist circumference (cm)	98.32 (11.08)	98.07 (10.91)	106.23 (11.47)	114.63 (13.04)	<0.001
MUAC (cm)	27.74 (2.69)	27.74 (2.70)	27.69 (2.14)	28.41 (2.93)	0.436
eBMD (g/cm^2)	0.54 (0.14)	0.55 (0.14)	0.50 (0.11)	0.47 (0.14)	0.002
Hormones					
Total T (nmol/liter)	16.60 (5.91)	16.78 (5.83)	9.63 (0.79)	5.90 (2.02)	<0.001
Free T (pmol/liter)	294.26 (86.64)	297.21 (84.92)	181.65 (24.08)	127.08 (52.34)	<0.001
LH (U/liter)	6.06 (4.17)	6.01 (3.96)	7.78 (6.19)	10.07 (12.81)	<0.001
FSH (U/liter)	8.33 (8.50)	8.19 (8.31)	12.75 (11.63)	16.91 (15.50)	<0.001
SHBG (nmol/liter)	42.35 (19.28)	42.53 (19.31)	35.33 (10.93)	31.86 (20.14)	0.001
E2 (pmol/liter)	74.03 (24.72)	74.36 (24.75)	63.15 (16.13)	51.98 (16.19)	<0.001
Biochemistry					
Total cholesterol (mmol/liter)	5.56 (1.05)	5.57 (1.05)	5.48 (1.03)	5.08 (1.34)	0.049
LDL cholesterol (mmol/liter)	3.47 (0.91)	3.47 (0.91)	3.24 (0.89)	3.04 (1.08)	0.016
HDL cholesterol (mmol/liter)	1.41 (0.37)	1.41 (0.37)	1.38 (0.42)	1.20 (0.38)	0.012
Triglycerides (mmol/liter)	1.45 (0.74)	1.44 (0.74)	1.66 (0.85)	1.84 (0.64)	0.005
Glucose (mmol/liter)	5.62 (1.33)	5.60 (1.29)	5.89 (2.17)	7.09 (2.44)	<0.001
Insulin (μIU/ml)	11.98 (10.84)	11.85 (10.73)	14.17 (10.25)	22.75 (16.18)	<0.001
HOMA-IR	3.18 (3.93)	3.13 (3.86)	3.70 (3.17)	7.84 (7.67)	<0.001
Hematology					
Hemoglobin (g/liter)	14.98 (1.09)	15.00 (1.08)	14.41 (1.10)	13.96 (1.57)	<0.001
Quality of life					
SF-36 physical function	50.28 (8.05)	50.46 (7.93)	41.87 (9.43)	41.71 (8.38)	<0.001
SF-36 mental function	51.76 (9.17)	51.80 (9.10)	49.71 (11.35)	50.19 (13.31)	0.286
Physical activity/cognition					
PASE score	200.26 (91.22)	201.33 (91.03)	155.99 (88.42)	144.34 (86.19)	<0.001
15-ft walk gait speed (sec)	13.45 (3.27)	13.39 (3.21)	15.98 (4.89)	16.68 (4.07)	<0.001
Digit symbol substitution	28.11 (8.71)	28.22 (8.69)	21.60 (8.18)	24.31 (7.40)	<0.001
Health status			Count (%)		
General health (fair or poor)	750 (25.39)	711 (24.59)	22 (61.11)	17 (65.38)	<0.001
2 or more morbid conditions	637 (21.81)	604 (21.13)	19 (52.78)	14 (53.85)	<0.001
CVD	1,034 (34.86)	990 (34.10)	27 (75.00)	17 (62.96)	<0.001
Diabetes	204 (6.98)	191 (6.68)	5 (13.89)	8 (30.77)	<0.001
Metabolic syndrome	668 (22.74)	629 (21.87)	17 (47.22)	22 (84.62)	<0.001

Values in first four columns are expressed as mean (SD).

P value: ANOVA for continuous variables (tests whether or not the means of the three groups are all equal) and χ^2 for categorical variables (a test of independence). Extremely high levels of total cholesterol, LDL cholesterol, hemoglobin (levels > 40), and triglycerides (levels >4.29) were excluded from the analyses. CVD, Cardiovascular disease.

Complete data on T and sexual symptoms were available among 2966 men. Table 1 shows the baseline characteristics of the entire analysis cohort and after subdivision by gonadal status (eugonadal, moderate LOH, and severe LOH).

There were 63 men with LOH, *i.e.* with three sexual symptoms and low T (2.1% of the 2966 men). Among them, 36 (1.2%) had total T between 8 and 11 nmol/liter and free T less than 220 pmol/liter (moderate LOH), and 27 (0.9%) had total T levels below 8 nmol/liter and free T less than 220 pmol/liter (severe LOH). LH and FSH were higher than in eugonadal men in both LOH groups, and SHBG and E2 levels were lower in the severe LOH group (Table 1).

Compared with eugonadal men, both LOH groups were older and had higher BMI and waist circumference and lower eBMD (Table 1). They also had lower hemoglobin lower HDL cholesterol, higher triglycerides, and

TABLE 2. Relationship between gonadal status and candidate attributes of androgen deficiency: linear regression

Model	Model I: unadjusted	Model II: adjusted for age [β-Coefficient (95% CI)]	Model III: adjusted for age and BMI	Model IV: adjusted for age, BMI, smoking status, and comorbidity
Primary end points				
Hemoglobin (g/liter)				
Moderate	−0.58 (−0.94, −0.23)[b]	−0.42 (−0.77, −0.06)[a]	−0.48 (−0.84, −0.12)[b]	−0.46 (−0.82, −0.11)[a]
Severe	−1.04 (−1.45, −0.62)[c]	−0.91 (−1.32, −0.50)[c]	−1.02 (−1.43, −0.61)[c]	−1.06 (−1.48, −0.64)[c]
MUAC (cm)				
Moderate	−0.05 (−0.93, 0.84)	0.62 (−0.25, 1.49)	−0.71 (−1.36, −0.07)[a]	−0.71 (−1.36, −0.06)[a]
Severe	0.67 (−0.35, 1.69)	1.19 (0.19, 2.19)[a]	−1.22 (−1.97, −0.48)[b]	−1.24 (−2.01, −0.48)[b]
eBMD (g/cm^2)				
Moderate	−0.05 (−0.09, −0.005)[a]	−0.04 (−0.08, 0.01)	−0.05 (−0.09, −0.002)[a]	−0.05 (−0.09, −0.002)[a]
Severe	−0.07 (−0.13, −0.02)[b]	−0.06 (−0.12, −0.01)[a]	−0.09 (−0.14, −0.03)[b]	−0.09 (−0.14, −0.04)[b]
Waist circumference (cm)				
Moderate	8.16 (4.56, 11.752)[c]	6.63 (3.03, 10.225)[c]	−0.67 (−2.28, 0.939)	−0.76 (−2.37, 0.838)
Severe	16.56 (12.41, 20.70)[c]	15.37 (11.24, 19.50)[c]	2.13 (0.28, 3.99)[a]	1.93 (0.04, 3.81)[a]
Secondary end points				
Glucose (mmol/liter)				
Moderate	0.28 (−0.15, 0.72)	0.11 (−0.32, 0.55)	−0.07 (−0.50, 0.35)	−0.13 (−0.56, 0.30)
Severe	1.49 (0.99, 1.99)[c]	1.36 (0.86, 1.86)[c]	1.01 (0.52, 1.51)[c]	1.06 (0.56, 1.57)[c]
Insulin (μIU/ml)				
Moderate	2.32 (−1.22, 5.87)	2.23 (−1.34, 5.81)	−0.96 (−4.23, 2.31)	−1.22 (−4.51, 2.07)
Severe	10.90 (6.81, 14.99)[c]	10.83 (6.72, 14.93)[c]	5.00 (1.23, 8.78)[b]	4.88 (1.01, 8.74)[a]
HOMA-IR				
Moderate	0.57 (−0.71, 1.85)	0.42 (−0.88, 1.71)	−0.58 (−1.78, 0.63)	−0.69 (−1.90, 0.52)
Severe	4.71 (3.23, 6.19)[c]	4.59 (3.10, 6.07)[c]	2.76 (1.38, 4.15)[c]	2.81 (1.39, 4.23)[c]
Total cholesterol (mmol/liter)				
Moderate	−0.09 (−0.44, 0.25)	−0.004 (−0.35, 0.34)	0.03 (−0.32, 0.38)	0.06 (−0.28, 0.41)
Severe	−0.49 (−0.89, −0.09)[a]	−0.42 (−0.82, −0.02)[a]	−0.36 (−0.76, 0.04)	−0.32 (−0.73, 0.08)
LDL cholesterol (mmol/liter)				
Moderate	−0.24 (−0.55, 0.07)	−0.18 (−0.49, 0.13)	−0.14 (−0.46, 0.17)	−0.11 (−0.42, 0.19)
Severe	−0.43 (−0.78, −0.09)[a]	−0.39 (−0.74, −0.04)[a]	−0.33 (−0.68, 0.02)	−0.28 (−0.63, 0.07)
HDL cholesterol (mmol/liter)				
Moderate	−0.03 (−0.15, 0.09)	−0.05 (−0.17, 0.07)	0.03 (−0.09, 0.15)	0.03 (−0.08, 0.15)
Severe	−0.21 (−0.35, −0.07)[b]	−0.22 (−0.36, −0.08)[b]	−0.09 (−0.22, 0.05)	−0.11 (−0.25, 0.03)
Triglycerides (mmol/liter)				
Moderate	0.22 (−0.03, 0.47)	0.29 (0.04, 0.54)[a]	0.16 (−0.09, 0.40)	0.14 (−0.10, 0.39)
Severe	0.40 (0.12, 0.68)[b]	0.45 (0.17, 0.73)[b]	0.20 (−0.08, 0.47)	0.21 (−0.07, 0.49)
Systolic blood pressure (mm Hg)				
Moderate	12.49 (5.71, 19.28)[c]	6.04 (−0.53, 12.61)	2.78 (−3.66, 9.22)	2.69 (−3.74, 9.13)
Severe	12.51 (4.69, 20.33)[b]	7.49 (−0.06, 15.03)	1.57 (−5.85, 9.00)	2.32 (−5.24, 9.88)
Diastolic blood pressure (mm Hg)				
Moderate	2.49 (−1.56, 6.54)	2.52 (−1.56, 6.60)	0.18 (−3.78, 4.15)	0.25 (−3.71, 4.21)
Severe	3.12 (−1.55, 7.79)	3.14 (−1.55, 7.83)	−1.10 (−5.67, 3.47)	−0.16 (−4.82, 4.49)
SF-36 physical function				
Moderate	−8.59 (−11.28, −5.90)[c]	−6.11 (−8.71, −3.50)[c]	−5.38 (−7.94, −2.81)[c]	−4.79 (−7.24, −2.33)[c]
Severe	−8.75 (−11.82, −5.67)[c]	−6.69 (−9.65, −3.73)[c]	−4.87 (−7.81, −1.93)[b]	−4.11 (−6.97, −1.24)[b]
PASE score				
Moderate	−45.33 (−76.11, −14.55)[b]	−2.91 (−31.13, 25.32)	−2.01 (−30.22, 26.21)	−0.15 (−28.15, 27.86)
Severe	−56.99 (−92.82, −21.16)[b]	−25.57 (−58.29, 7.14)	−23.93 (−56.79, 8.94)	−20.16 (−52.79, 12.47)
50-ft walk gait speed (sec)				
Moderate	2.59 (1.53, 3.66)[c]	1.53 (0.50, 2.56)[b]	1.34 (0.36, 2.33)[b]	1.26 (0.28, 2.24)[a]
Severe	3.30 (2.07, 4.53)[c]	2.47 (1.29, 3.65)[c]	2.13 (0.99, 3.26)[c]	1.90 (0.75, 3.05)[b]

Referent is the eugonadal group. Extremely high levels of total cholesterol, LDL cholesterol, hemoglobin (levels >40), and triglycerides (levels >4.29) were excluded from the analyses.

[a] $P < 0.05$.

[b] $P < 0.01$.

[c] $P < 0.001$.

higher systolic blood pressure. In addition, LOH men had higher levels of glucose, insulin, and HOMA-IR. Physical activity (PASE), gait speed, and physical function (SF-36) were lower in the LOH groups. A higher proportion of men with moderate and severe LOH had diabetes (13.9 and 30.8%, respectively) compared with the eugondal (6.7%), the metabolic syndrome (47.2 and 84.6 *vs.* 22.7%), and cardiovascular disease (75.0 and 63.0 *vs.* 34.1%) (Table 1).

The relationship between LOH and the various outcomes were further explored (Tables 2 and 3 and Fig. 1A). Both moderate and severe LOH were significantly associated with lower hemoglobin, MUAC, eBMD, and physical function and slower gait speed after adjustment for age, BMI, smoking status and comorbidity, the magnitude of these variations being greater in the severe than moderate group. However, only severe LOH was associated with a larger waist circumference, higher glucose, insulin levels, and HOMA-IR in the fully adjusted models. In men with low T irrespective of sexual symptoms, T of 8–11 nmol/liter (n = 247) and less than 8 nmol/liter (n = 129) were associated with lower hemoglobin levels and higher glucose, insulin levels, and HOMA-IR (Fig. 1B and Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org), whereas T less than 8 nmol/liter was also associated with lower MUAC and eBMD. However, the magnitude of these associations with low T was considerably smaller than those observed with LOH (Fig. 1).

In the logistic regression models, both moderate and severe LOH was associated with poorer general health after adjustment for confounders (Table 3). Severe LOH was also associated with a marked increase in risk of the metabolic syndrome (OR 9.9), mirroring the marked difference in insulin resistance between the two groups. Similarly, a T level of less than 8 nmol/liter, irrespective of sexual symptoms, was associated with the metabolic syndrome, although the magnitude of the effect was considerably smaller (OR 3.0, Supplemental Table 2). A T of 8–11 nmol/liter was associated with only a slight increase in risk of cardiovascular disease (Supplemental Table 2).

Discussion

The present study provides a novel and extensive exploration of biochemical and end organ phenotypic features associated with LOH in a large population of community-dwelling middle-aged and elderly European men.

The relationships between T deficiency and reduced muscle mass, low bone density/osteoporosis, and mild anemia are well recognized (22). These changes in androgen-sensitive target tissues are often sought in clinical practice as corroboratory evidence (tissue markers of androgen deficiency) to support the diagnosis of hypogonadism and to monitor subsequent response to T replacement therapy. The present results demonstrate that a small minority of men from the general population, identified on the basis of sexual symptoms and low T as candidates for LOH, do show variations in multiple tissue sites that are highly compatible with reduced androgen action. The graded and significant associations in three independent

TABLE 3. Relationship between gonadal status and clinical outcomes: logistic regression

	Model I: unadjusted	Model II: adjusted for age	Model III: adjusted for age and BMI	Model IV: adjusted for age, BMI, smoking status, and comorbidity[a]
	Odds ratios (95% CI)			
General health (fair or poor)				
Moderate	4.82 (2.45, 9.47)[d]	2.97 (1.49, 5.90)[c]	2.46 (1.22, 4.95)[b]	2.35 (1.14, 4.87)[b]
Severe	5.79 (2.57, 13.06)[d]	3.99 (1.75, 9.10)[c]	2.72 (1.18, 6.27)[b]	3.05 (1.23, 7.54)[b]
Diabetes				
Moderate	2.25 (0.87, 5.86)	1.30 (0.49, 3.43)	0.85 (0.31, 2.32)	0.85 (0.31, 2.34)
Severe	6.21 (2.67, 14.46)[d]	4.26 (1.80, 10.08)[c]	2.25 (0.91, 5.54)	2.26 (0.92, 5.58)
CVD				
Moderate	5.80 (2.72, 12.37)[d]	2.69 (1.23, 5.88)[b]	1.93 (0.85, 4.36)	1.91 (0.85, 4.33)
Severe	3.28 (1.50, 7.20)[c]	1.83 (0.81, 4.12)	0.89 (0.38, 2.07)	0.89 (0.39, 2.07)
Metabolic syndrome				
Moderate	3.20 (1.65, 6.19)[c]	2.65 (1.36, 5.16)[c]	1.04 (0.44, 2.48)	1.06 (0.44, 2.51)
Severe	19.65 (6.75, 57.22)[d]	17.17 (5.88, 50.14)[d]	9.81 (2.70, 35.66)[c]	9.94 (2.73, 36.22)[c]

Referent is the eugonadal group. CVD, Cardiovascular disease.

[a] For diabetes and CVD, comorbidity was not included as a covariate in model IV.

[b] $P < 0.05$.

[c] $P < 0.01$.

[d] $P < 0.001$.

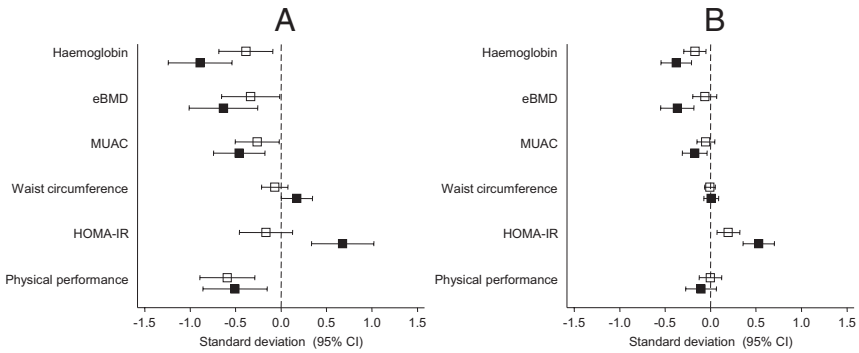

FIG. 1. Association between selected end points and LOH (A) and low T (B) (irrespective of symptoms). Values are standardized β-coefficients (per SD) and 95% CI for the difference in mean values of the end point between moderate (□) and severe (■) LOH (A) and T 8–11 nmol/liter (□) and T < 8 nmol/liter (■) (B) compared with the eugonadal group. Results are adjusted for age, BMI, smoking status, and comorbidity.

target tissue responses, *i.e.* hemoglobin, BMD, and lean mass, from eugonadal through moderate to severe hypogonadism provide strong face and construct validity for our proposed criteria to define LOH in aging men. These findings are also externally consistent with the consequences of androgen deprivation therapy (23) for prostate cancer, which induce changes in the same androgen targets (24, 25).

Interestingly, compared with LOH, much smaller effect sizes were observed in the same end points in those with low T irrespective of the presence of sexual symptoms (Fig. 1). This highlights the importance and relevance of sexual symptoms to the identification of LOH with respect to tissue variables compatible with androgen deficiency. By differentiating LOH from simply low T, the presence of the three sexual symptoms serves to confer specificity to the clinical syndrome of LOH. This may improve future clinical management of middle-aged and elderly men with low T.

The magnitude of observed differences (β-coefficient from the fully adjusted models) in hemoglobin (−0.46 and −1.06 g/liter equivalent to a percentage difference of −3.1 and −7.1%) and eBMD (−0.05 and −0.09 g/cm^2, equivalent to −8.3 and −16%) between LOH (moderate and severe) compared with eugonadal men were similar to those reported in untreated patients with pathological hypogonadism and the subsequent improvement in response to T replacement. Thus, hypogonadal patients showed lower hemoglobin (6% or 0.83 g/liter), which increased after T replacement by 6–8% (26, 27). In older healthy men with short-term experimental GnRH agonist-induced hypogonadism, hemoglobin decreased by 0.36 g/liter or 2.6% (28) in 20 wk. Similarly, heel ultrasound eBMD was reduced by 0.08 g/cm^2 or 13.4% in prostate cancer patients receiving GnRH agonist androgen-deprivation therapy (29). BMD, as measured by dual energy x-ray absorptiometry, in Klinefelter patients was reduced by 18 and 27% in the femoral and lumbar regions, respectively (30). T replacement increased BMD by an average of 3.7% in middle-aged men with low T (31). Taken together, these comparisons support the existence of significant androgen deficiency at the tissue level in men considered to have LOH based on clinical and hormonal criteria.

The use of MUAC as a surrogate for lean mass is not widespread in clinical practice [but valid in epidemiological studies (16)]. The lower MUAC was corroborated by the lower physical quality of life and slower gait speed, especially in the severely hypogonadal group, suggesting that both upper and lower limb muscle mass and physical function are reduced in LOH.

Although it is anticipated to find evidence of androgen deficiency in symptomatic men with T less than 8 nmol/liter (mean total T 5.9 nmol/liter in severe LOH), it is noteworthy that even moderate LOH with T between 8 and 11 nmol/liter, regarded as borderline rather than overtly hypogonadal (32), also showed some (albeit weaker) evidence of androgen deficiency at the end-organ level (even after adjustment for age, adiposity, and other potential confounders). This suggests that moderate LOH may not be a transient state with labile T levels. However, it remains unclear whether men with moderate LOH should be candidates for intervention, nor is it apparent which is the optimal treatment modality to correct this moderate T deficiency.

The present results confirm the strong association between low T and obesity (33). This relationship is complex and highly confounded and likely to be bidirectional (34). Obesity can give rise to low T, but hypogonadism can also promote fat accumulation, insulin resistance, and the metabolic syndrome (35). Mechanisms underlying these associations are unclear, but the low or inappropriately normal levels of LH commonly associated with the moderately suppressed T levels observed in obese middle-aged men suggest suppression of hypothalamic-pituitary function in obesity (18, 33). However in the present study, elevated LH and FSH levels were observed in both groups of symptomatic men with low T, suggesting that the predominant primary defect in LOH is testicular dysfunction rather than hypothalamic suppression.

Although we found that LOH men had lower total and LDL cholesterol and higher triglyceride levels in the unadjusted analysis, these differences became nonsignificant after adjustment for BMI. This is in keeping with the lack

of changes in plasma lipids in experimental hypogonadism (36). Because the risk of diabetes and cardiovascular disease was nonsignificant after adjustment for age and BMI in both LOH groups, our data suggest that low T is unlikely to be directly responsible for the apparent association of LOH with these conditions. This is congruent with the current guidelines from U.S. Endocrine Society (4), which does not recommend T therapy in diabetic men with low T. In contrast, the odds ratio for the metabolic syndrome remains inordinately high (OR 9.9), even after full adjustment, in the severe but not moderate LOH group. This reflects the similarly dramatic between-group difference in insulin sensitivity, suggesting that the apparent increased cardiometabolic risks in LOH is mostly explained by obesity and age and is unrelated to T until the level drops below 8 nmol/liter. This clear differentiation in central obesity and insulin sensitivity between the two categories of LOH suggests that there is a threshold T level (of around 8 nmol/liter) below which insulin action becomes impaired (either directly from T deficiency or more likely secondarily to visceral obesity). This finding is supported by two independent pieces of evidence. In dose-response studies of T, in which older (60–75 yr) healthy nonobese men with experimentally induced hypogonadism were replaced with graded doses of T enanthate, fat mass started to increase minimally only at the lowest dose giving a trough T level of 6.1 nmol/liter (28), whereas there was no change in insulin sensitivity (36). Profound T deficiency (<1 nmol/liter) induced by androgen deprivation therapy using GnRH agonists or surgical castration for prostate cancer markedly increased visceral obesity and insulin resistance within 3–6 months (23). Our results are therefore compatible with the bidirectional relationship between T and obesity (18, 23). Thus, although obesity may predispose men to borderline low levels of T, only severe T deficiency (LOH) appears to be associated with visceral fat excess to the extent that increases insulin resistance.

The main strength of our study is the detailed phenotyping of men from a large population-based sample stringently identified to be likely candidates for hypogonadism. Methodological limitations inherent to the EMAS study have been described in detail previously (12). For instance, the data were obtained from a predominantly European population, and results should be extrapolated beyond this setting with care. Also, the cross-sectional nature of the present data constrains making definite causal links between LOH and the explored outcomes. Notwithstanding these reservations, the partition of LOH into moderate and severe categories has revealed significant differences in the T-associated phenotypic features, especially the metabolic end points, which could have clinical implications. In moderate LOH, lipid abnormalities or insulin resistance may be attributable to obesity rather than gonadal status (*i.e.* low T). Despite some evidence compatible with modest androgen deficiency at the tissue level, our findings would imply that T supplementation for moderate LOH may be unlikely to improve the lipid disturbance, insulin resistance, or glucose homeostasis. In keeping with this, most interventional studies on the effects of T in obese/diabetic men chose an inclusion threshold T level of 11 or 12 nmol/liter (37) and showed only modest effects on insulin action. For this reason, clinical trials of T intervention for LOH with metabolic end points that target men with T less than 8 nmol/liter may show greater effects.

In summary, LOH, as defined by the presence of three sexual symptoms and low T in a small minority of aging men, showed consistent associations with multiple objective features compatible with androgen deficiency: lower hemoglobin, BMD, and lean body mass as well as reduced physical quality of life. These features were more marked in severe than moderate LOH, suggesting a graded relationship with the degree of T deficiency. The same features were less marked in men with low T only, irrespective of symptoms emphasizing the relevance of sexual symptoms in LOH. The present results further highlight the important confounding influence of obesity and age in a number of metabolic and physical function end points frequently found to be abnormal in LOH. These observations impart new insights into the pathophysiology of LOH that could inform the design of future clinical trials and potentially improve current management of symptomatic aging men with low or borderline T.

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