

Characteristics of Secondary, Primary, and Compensated Hypogonadism in Aging Men: Evidence from the European Male Ageing Study

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Context: The diagnosis of late-onset hypogonadism (LOH) in older men with age-related declines in testosterone (T) is currently not well characterized.

Objective: Our objective was to investigate whether different forms of hypogonadism can be distinguished among aging men.

Design: The study was a cross-sectional survey on 3369 community-dwelling men aged 40–79 yr in eight European centers.

Methods: Four groups of subjects were defined: eugonadal (normal T and normal LH), secondary (low T and low/normal LH), primary (low T and elevated LH), and compensated (normal T and elevated LH) hypogonadism. Relationships between the defined gonadal status with potential risk factors and clinical symptoms were investigated by multilevel regression models.

Results: Among the men, 11.8, 2.0, and 9.5% were classified into the secondary, primary, and compensated hypogonadism categories, respectively. Older men were more likely to have primary [relative risk ratio (RRR) = 3.04; $P < 0.001$] and compensated (RRR = 2.41; $P < 0.001$) hypogonadism. Body mass index of 30 kg/m² or higher was associated with secondary hypogonadism (RRR = 8.74; $P < 0.001$). Comorbidity was associated with both secondary and primary hypogonadism. Sexual symptoms were more prevalent in secondary and primary hypogonadism, whereas physical symptoms were more likely in compensated hypogonadism.

Conclusions: Symptomatic elderly men considered to have LOH can be differentiated on the basis of endocrine and clinical features and predisposing risk factors. Secondary hypogonadism is associated with obesity and primary hypogonadism predominately with age. Compensated hypogonadism can be considered a distinct clinical state associated with aging. Classification of LOH into different categories by combining LH with T may improve the diagnosis and management of LOH. (*J Clin Endocrinol Metab* 95: 1810–1818, 2010)

Circulating testosterone (T) in men declines progressively by 0.4–2% per year from the third decade onward (1–3). The consequences of aging, such as decreases in muscle mass and strength, energy, mood, libido, erectile function, and bone density (4), are reminiscent of typical features of androgen deficiency in pathological hy-

pogonadism due to pituitary or testicular disease in young patients. Attempts to clarify the relationships between the decline in circulating T and the aging phenotype has demonstrated only weak associations (4). Nevertheless, an increasing number of symptomatic older men are being considered for androgen replacement therapy (5) despite a

poor understanding of the underlying pathophysiological mechanisms or etiological factors and a lack of well-validated criteria for defining the syndrome that some regard as late-onset hypogonadism (LOH) (6, 7), whereas others have used various terms including andropause, male menopause, and androgen deficiency syndrome of the aging male. This raises concerns regarding the appropriate patient selection, likely efficacy, and potential risks of empirical T treatment in an increasingly aging population (7, 8).

Patients with classical hypogonadism are routinely classified into those with secondary hypogonadism (hypothalamic-pituitary failure) with low T and low or normal gonadotropins or primary hypogonadism (testicular failure) characterized by low T and elevated gonadotropins. Given that the underlying etiologies and clinical management of secondary and primary hypogonadism are different, it may be informative to differentiate older men who are candidates for the diagnosis of LOH into different hypogonadal categories by coupling T with LH levels.

In previous studies (3, 9, 10), a significant proportion of older men have been shown to have high gonadotropins and T within the normal range. This raises the possibility of a state of compensated, or subclinical, hypogonadism that may eventually develop into overt primary hypogonadism. An analogous situation is well recognized in the pituitary-thyroid axis where high TSH, in the face of normal thyroid hormone levels, is the hallmark of subclinical hypothyroidism (11, 12).

In this study, we investigated whether specific risk factors or clinical features can differentiate between secondary, primary, and the new putative form of compensated hypogonadism categorized biochemically in participants from the European Male Ageing Study (EMAS), a community-based study of middle-aged and elderly men (13).

Subjects and Methods

Subjects

A total of 3369 men aged 40–79 yr were recruited from population registers in eight European centers: Manchester (UK), Leuven (Belgium), Malmö (Sweden), Tartu (Estonia), Łódź (Poland), Szeged (Hungary), Florence (Italy), and Santiago de Compostela (Spain). The men were invited to attend by letter of in-

itation for an interviewer-assisted questionnaire, assessment of height and weight, several performance measures, and a fasting blood test. Ethical approval for the study was obtained in accordance with local institutional requirements in each center. The detailed methodologies of EMAS are described elsewhere (13).

Questionnaire and anthropometric measurements

Personal and health status information were documented by self-completed questionnaires including the SF-36 V2 (14) and a validated questionnaire on sexual function (EMAS-SFQ) (15). Height, weight, and waist circumference were measured using standard, calibrated instruments. Body mass index (BMI) was calculated as body weight (kilograms) divided by the square of height (square meters).

Hormone measurements

A single fasting morning (before 1000 h) venous blood sample was obtained. Measurement of T and estradiol (E2) were carried out by gas chromatography-mass spectrometry (16). The coefficients of variation of T and E2 measurements were 2.9% within runs and 3.4% between runs for T and were 3.5% within runs and 3.7% between runs for E2. LH and SHBG were measured by the Modular E170 platform electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) (3). Free T (fT) levels were derived from total T, SHBG, and albumin concentrations (17).

Statistical methods

A four-category variable of gonadal status was constructed from the baseline data of EMAS using two thresholds: a T level of 10.5 nmol/liter and LH level of 9.4 U/liter. The four categories were normal or eugonadal (T \geq 10.5 nmol/liter and LH \leq 9.4 U/liter), secondary hypogonadism (T < 10.5 nmol/liter and LH \leq 9.4 U/liter), primary hypogonadism (T < 10.5 nmol/liter and LH > 9.4 U/liter), and compensated hypogonadism (T \geq 10.5 nmol/liter and LH > 9.4). The chosen T cutoff point of 10.5 nmol/liter was similar to that used in previous studies (18, 19). The LH threshold corresponded to the 97.5th centile (the upper limit of normal) value in the youngest group (40–44 yr) in our analysis cohort (after exclusion; see *Results*).

Multilevel regression models (20), which adjust for center as a random-effect variable, were used to account for the hierarchical study design (individuals nested within centers). The relationships between gonadal status and putative risk factors were assessed using multilevel multinomial regression models, where gonadal status was the outcome with the eugonadal group being the referent category. Five key factors were included as fixed-effect predictors: age (continuous), BMI [categorized into <25 kg/m² (referent), \geq 25–<30 kg/m², and \geq 30 kg/m²], smoking status [dichotomized as never and ex-

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TABLE 1. Subject characteristics: entire cohort and after categorization by gonadal status

	Entire cohort	Eugonadal	Secondary hypogonadism	Primary hypogonadism	Compensated hypogonadism	P ^a
n	3119	2436 (76.7%)	375 (11.8%)	63 (2.0%)	303 (9.5%)	
Mean (sd)						
Age (yr)	59.7 (11.0)	58.5 (10.7)	59.4 (10.4)	70.0 (9.0)	67.3 (9.9)	0.00
Height (m)	173.7 (7.3)	174.1 (7.3)	173.3 (7.4)	170.5 (6.6)	172.2 (7.2)	0.35
Weight (kg)	83.6 (14.0)	82.6 (13.1)	92.8 (17.2)	84.2 (12.3)	79.7 (13.0)	0.00
BMI (kg/m ²)	27.7 (4.1)	27.3 (3.8)	30.8 (4.8)	29.0 (3.9)	26.8 (3.6)	0.00
Total T (nmol/liter)	16.6 (6.0)	17.8 (5.3)	8.7 (1.6)	7.5 (2.5)	18.3 (5.6)	0.00
fT (pmol/liter)	292.3 (87.3)	314.7 (77.5)	194.4 (45.6)	138.7 (59.8)	265.1 (81.4)	0.00
LH (U/liter)	6.2 (4.3)	5.2 (1.8)	4.4 (1.9)	18.0 (10.3)	14.1 (6.5)	0.00
SHBG (nmol/liter)	42.8 (19.7)	43.2 (17.9)	26.5 (12.3)	40.1 (18.5)	60.1 (25.2)	0.00
E2 (pmol/liter)	74.1 (25.1)	75.9 (24.0)	57.2 (17.8)	54.8 (25.4)	84.9 (29.3)	0.00
No. of subjects (%)						
Current smokers	682 (21.4)	521 (21.6)	67 (18.1)	5 (8.1)	80 (26.5)	0.00
Alcohol intake \geq 5 d/wk	739 (23.1)	553 (22.8)	90 (24.5)	18 (28.6)	66 (22.0)	0.62
Morbidity 1 or more ^b	1582 (50.0)	1091 (45.5)	225 (61.0)	51 (83.6)	192 (64.7)	0.00
Marital/partner status ^c						
Partner, live apart	195 (6.3)	156 (6.6)	17 (4.7)	2 (3.5)	18 (6.3)	
No partner	257 (8.3)	181 (7.6)	41 (11.3)	8 (14.0)	25 (8.7)	0.13
ESFQ: decreased morning erections	1195 (38.6)	829 (35.1)	159 (44.5)	37 (66.1)	153 (53.5)	0.00
MMAS: erectile dysfunction	905 (29.6)	607 (26.0)	111 (31.4)	29 (55.8)	142 (50.5)	0.00
ESFQ: decreased frequency of sexual thoughts	842 (27.1)	594 (25.1)	94 (26.3)	30 (51.7)	115 (39.7)	0.00
SF36: decreased vigorous activity	767 (24.2)	504 (21.0)	110 (29.8)	28 (45.2)	115 (38.6)	0.00
SF36: limited in walking >1 km	231 (7.3)	132 (5.5)	35 (9.6)	12 (19.4)	46 (15.4)	0.00
SF36: unable to bend	201 (6.3)	122 (5.1)	31 (8.4)	7 (11.3)	35 (11.8)	0.00

ESFQ, EMAS Sexual Function Questionnaire; MMAS, Massachusetts Male Aging Study; SF36, Short-Form V2 Health Survey Domains (<http://www.qualitymetric.com>). Missing values were excluded from the analyses. Nanomoles per liter can be converted to nanograms per deciliter by dividing by 0.03467.

^a P value for ANOVA for age, analysis of covariance test (age adjusted) for continuous variables and χ^2 for categorical variables.

^b Self-reported health conditions including heart condition, high blood pressure, cancer ever, bronchitis, asthma, peptic ulcer, epilepsy, diabetes, liver disease, kidney disease, prostate disease, and stroke.

^c Referent category (living with wife or partner).

smokers (referent) and current smokers], alcohol intake (dichotomized as consumption on \geq 5 and $<$ 5 d/wk (referent)), and comorbidity [categorized as none (referent) or at least one self-reported disorder] (Table 1). The relationship between gonadal status and clinical features of hypogonadism was investigated using multilevel binary logistic regression models with the symptom variable (dichotomized) as the outcome. Six symptoms (three sexual and three physical) considered to be related to low T (21) were included. These were poor morning erection, diminished sexual thoughts, erectile dysfunction, unable to do vigorous activity, limited in walking more than 1 km, and unable to bend (details in Supplemental Appendix published as supplemental data on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). The symptom models (models with symptoms as outcomes) were adjusted for age (continuous) and then further adjusted where appropriate for BMI (continuous), smoking status, alcohol intake, comorbidity, and marital/partner status. Interactions between age and gonadal status were examined for all symptoms and then incorporated in the final models if it was found to be statistically significant. Results from the multilevel multinomial or binary logistic models are expressed as relative risk ratios (RRR) or odds ratios (OR), respectively, and 95% confidence intervals (CI). All statistical analyses

were conducted using Intercooled STATA version 9.2 (Stata-Corp, College Station, TX).

Results

Categories of hypogonadism

From 3369 participants in EMAS, 150 were excluded because of known pituitary, testicular, or adrenal diseases or current use of medications affecting pituitary/testicular functions (T, dehydroepiandrosterone, anti-androgens, GnRH agonists, and psycholeptic agents) or clearance of sex steroids (e.g. anticonvulsants), leaving 3219 (mean \pm SD age, 59.7 \pm 11.0 yr) in the analysis sample (Table 1). The relationship between T and LH in these men is shown in Fig. 1 where the four categories of gonadal status were differentiated according to the T and LH thresholds. The majority of subjects (76.7%) were eugonadal, whereas 11.8, 2, and 9.5% had secondary, primary, and compensated hypogonadism, respectively. The proportion of men with primary and

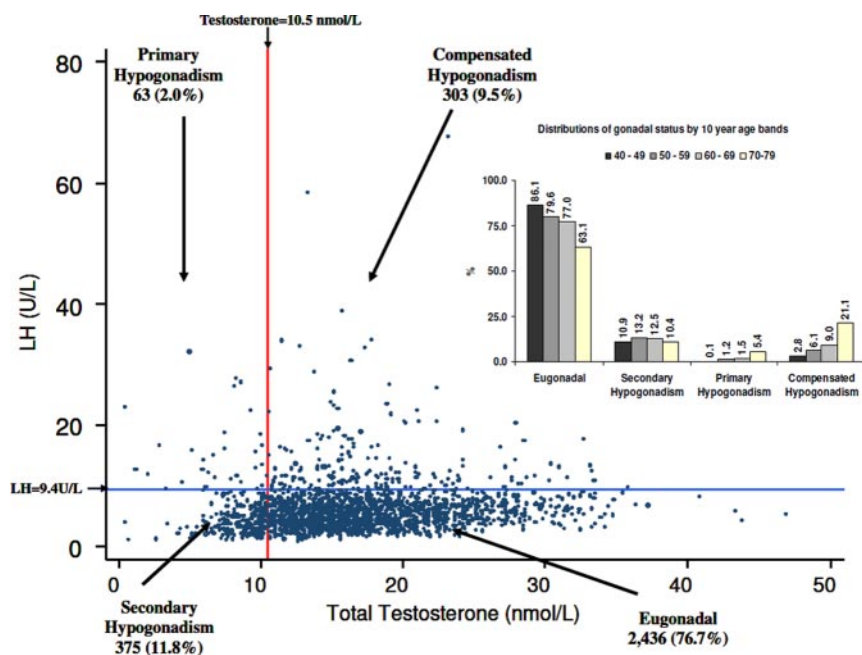


FIG. 1. The vertical line corresponds to total T = 10.5 nmol/liter, and the horizontal line corresponds to LH = 9.4 U/liter. The majority of subjects (76.7%) were eugonadal, 11.8% had secondary hypogonadism, 2.0% had primary hypogonadism, and the remaining 9.5% had compensated hypogonadism. The proportions of men with primary and compensated hypogonadism increased with age from 0.1–5.4% and from 2.8–21.1%, respectively (inset), across the four decades. The prevalence of secondary hypogonadism did not increase significantly with age (8.2% at 40–49 yr; 8.8% at 70–69 yr). Nanomoles per liter can be converted to nanograms per deciliter by dividing the values by 0.03467.

compensated hypogonadism increased with age from 0.1–5.4% and from 2.8–21.1%, respectively (Fig. 1, inset). However, the prevalence of secondary hypogo-

gonadism group had the highest mean SHBG level (60.1 ± 25.2 nmol/liter) and largest proportion of current smokers (26.5%) (Table 1 and Fig. 2). The E2 levels were also higher in the compensated hypogonadism group (84.88 ± 29.32 pmol/liter).

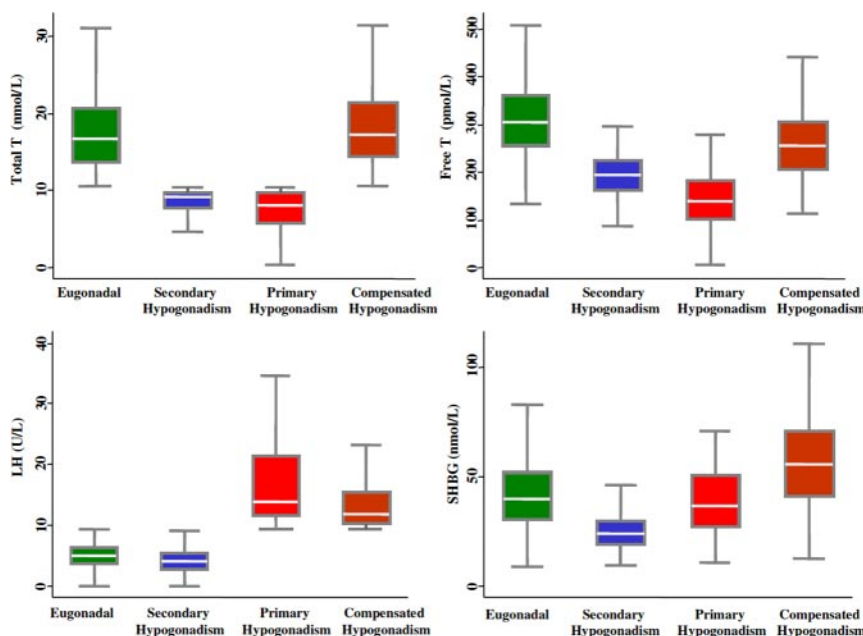


FIG. 2. Distributions (box and whisker plots) of total T, fT, LH, and SHBG in eugonadal (n = 2436, 76.7%), secondary (n = 375, 11.8%), primary (n = 63, 2.0%), and compensated (n = 303, 9.5%) hypogonadism groups. Nanomoles per liter can be converted to nanograms per deciliter by dividing the values by 0.03467.

gonadism did not increase significantly with age (10.9% at 40–49 yr; 10.4% at 70–79 yr).

Men in the primary (70.0 ± 9.0 yr) and compensated (67.3 ± 9.9 yr) hypogonadism groups were older than the eugonadal group (58.5 ± 10.7 yr, $P < 0.001$; Table 1), BMI in the secondary hypogonadism group (30.8 ± 4.8 kg/m²) was higher than in the other groups. T levels were lowest in the primary (T 7.5 ± 2.5 nmol/liter; fT 138.7 ± 59.8 pmol/liter) and secondary (T 8.7 ± 1.6 nmol/liter, fT 194.4 ± 45.6) hypogonadism groups (Table 1 and Fig. 2). The compensated hypogonadism group had normal T (17.9 ± 5.4 nmol/liter) and normal but slightly lower fT (265.1 ± 81.4 pmol/liter) compared with the eugonadal group (314.7 ± 77.5 pmol/liter). Mean LH was highest in the primary (18.0 ± 10.3 U/liter) and the compensated (14.1 ± 6.5 U/liter) hypogonadism group ($P < 0.001$) but not different in the secondary hypogonadism compared with the eugonadal group. The compensated hypogonadism group had the highest mean SHBG level (60.1 ± 25.2 nmol/liter) and largest proportion of current smokers (26.5%) (Table 1 and Fig. 2). The E2 levels were also higher in the compensated hypogonadism group (84.88 ± 29.32 pmol/liter).

Risk factors

Men with a high BMI were more likely to have secondary hypogonadism with a RRR of 3.30 ($P < 0.001$) and 8.74 ($P < 0.001$) for BMI of 25 to less than 30 kg/m² and 30 kg/m² or higher, respectively (Table 2). Those who reported more than one comorbid condition had RRR of 1.44 ($P < 0.01$) and 2.25 ($P < 0.05$) for secondary and primary hypogonadism, respectively. Older men were more likely, with RRR of 3.04 ($P < 0.001$) and 2.41 ($P < 0.001$) per decade, to have primary or compensated hypogonadism, respectively (Table 2). Secondary hypogonadism was not associated with age. Current smokers had a RRR of 1.91 ($P < 0.001$) for being in the

TABLE 2. Association between hypogonadal status, age, comorbidity, and lifestyle factors

	RRR (95% CI)		
	Secondary hypogonadism	Primary hypogonadism	Compensated hypogonadism
Entire sample			
Age ^a (yr)	0.97 (0.86–1.09)	3.04 (2.13–4.32) ^d	2.41 (2.08–2.79) ^d
BMI \geq 25 and $<$ 30 kg/m ²	3.30 (2.13–5.12) ^d	1.82 (0.83–4.02)	0.77 (0.57–1.04)
BMI \geq 30 kg/m ²	8.74 (5.61–13.60) ^d	2.37 (1.01–5.58) ^b	0.73 (0.50–1.07)
Current smokers	0.91 (0.67–1.23)	0.69 (0.27–1.78)	1.91 (1.40–2.60) ^d
Alcohol intake \geq 5 d/wk	1.31 (0.99–1.73)	1.39 (0.77–2.49)	0.91 (0.67–1.25)
Comorbidity 1 or more	1.44 (1.11–1.87) ^c	2.25 (1.10–4.64) ^b	1.16 (0.87–1.54)
Excluding smokers			
Age ^a (yr)	0.95 (0.83–1.08)	3.15 (2.14–4.62) ^d	2.76 (2.30–3.31) ^d
BMI \geq 25 and $<$ 30 kg/m ²	3.11 (1.91–5.06) ^d	1.70 (0.73–3.97)	0.78 (0.55–1.12)
BMI \geq 30 kg/m ²	7.33 (4.47–12.00) ^d	2.39 (0.97–5.86)	0.70 (0.46–1.09)
Alcohol intake \geq 5 d/wk	1.31 (0.96–1.77)	1.21 (0.64–2.28)	0.94 (0.65–1.35)
Comorbidity 1 or more	1.55 (1.16–2.07) ^c	2.50 (1.13–5.53) ^b	1.11 (0.80–1.56)

Multinomial multilevel models taking account of the hierarchy of the design (individuals nested within centers). The RRR indicates the likelihood of being classified in one of the outcome categories of secondary, primary, or compensated hypogonadism compared with the referent eugonadal category in relation to independent variables (e.g. BMI). Thus, an RRR higher than 1 indicates an increased risk of hypogonadism vs. eugonadism as one independent variable changes while holding other variables in the model constant. For example, the RRR of 8.74 indicates that men with BMI of 30 kg/m² or higher are 8.7 times more likely to be in the secondary hypogonadism category than those with BMI less than 25 kg/m². Models were adjusted for center, and variance of random effect for both models was 0.04 (SE 0.03). The RRR resemble in their interpretation the OR given by logistic regression models.

^a Age effect: 10-yr increase.

^b $P < 0.05$; ^c $P < 0.01$; ^d $P < 0.001$ (reference was eugonadal group).

compensated hypogonadism group. However, exclusion of the 682 current smokers did not change the foregoing results using the entire sample (Table 2).

There was significant difference between centers in the prevalence of gonadal status ($P < 0.001$). However, after adjustment for age, BMI, comorbidity, and other variables (Table 2), the center random effect became nonsignificant.

Symptoms

Increased likelihood of sexual and physical symptoms was associated with secondary and primary hypogonadism (Table 3). After adjustments for age and other covariates, only poor morning erections and low sexual thoughts remained significant in secondary and primary hypogonadism, respectively (Table 3). Men in the primary hypogonadism group were more likely to have low sexual thoughts (OR = 3.68; $P < 0.01$), irrespective of age, due to a significant interaction effect between age and gonadal status (Table 3). Physical symptoms were associated with primary (in particular) and secondary hypogonadism; these relationships persisted after adjustment for age but not in the fully adjusted models.

The compensated hypogonadism group showed an increased likelihood of sexual and physical symptoms (Table 3). After adjustment for age and other covariates, the three physical but not sexual symptoms remained significant.

Discussion

We have previously reported that multilevel functional alterations in the hypothalamic-pituitary-testicular (HPT) axis are specifically linked to distinct risk factors that interact with chronological age in contributing to the lowering of T levels during male midlife transition (3). We now extend these observations to determine whether their application to the clinical setting can refine the assignment of LOH into distinct functional/anatomical diagnostic categories with different T and LH relationships. It has been suggested that measuring gonadotropins is of limited value in detecting hypogonadism in aging men in clinical practice (22). However, our results show that classification of middle-aged and older men with changes in T and/or LH into different categories highlights several distinguishing and important characteristics.

Secondary hypogonadism

The present study confirmed that the single most powerful predictor of low T is obesity (3, 23), with comorbidity also contributing. Not only are these men the youngest of the three categories of LOH, but also the prevalence of secondary hypogonadism did not increase with age. Although the negative effects of aging alone on testicular function can be moderated by increased LH compensation for a number of years (see below), obesity, irrespective of age, appears to be associated with hypothalamic/pituitary dysregulation for which there are no physiological com-

TABLE 3. Symptoms association (sexual and physical) with hypogonadal status

Dependent variables	OR (95% CI)		
	Secondary hypogonadism	Primary hypogonadism	Compensated hypogonadism
Sexual symptoms			
Unadjusted			
Decreased morning erections	1.57 (1.25–1.98) ^d	3.77 (2.14–6.64) ^d	2.17 (1.68–2.78) ^d
Erectile dysfunction	1.38 (1.08–1.77) ^b	3.83 (2.18–6.73) ^d	2.97 (2.30–3.83) ^d
Decreased frequency of sexual thoughts ^a	1.10 (0.85–1.44)	3.50 (2.03–6.02) ^d	2.14 (1.65–2.78) ^d
Adjusted for age			
Decreased morning erections	1.55 (1.21–1.98) ^d	1.85 (1.01–3.38) ^b	1.21 (0.92–1.58)
Erectile dysfunction	1.34 (1.01–1.77) ^b	1.39 (0.73–2.63)	1.35 (1.01–1.81) ^b
Decreased frequency of sexual thoughts ^a	0.97 (0.71–1.32)	3.78 (1.61–8.86) ^c	0.64 (0.39–1.06)
Adjusted for age, BMI, smoking status, alcohol intake, comorbidity, and marital/partner status			
Decreased Morning erections	1.42 (1.09–1.86) ^c	1.76 (0.93–3.32)	1.18 (0.89–1.56)
Erectile dysfunction	1.15 (0.85–1.56)	1.38 (0.71–2.70)	1.34 (0.99–1.82)
Decreased Frequency of sexual thoughts ^a	0.97 (0.70–1.35)	3.68 (1.44–9.42) ^c	0.63 (0.38–1.06)
Physical symptoms			
Unadjusted			
Unable to do vigorous activity	1.70 (1.32–2.19) ^d	3.38 (2.00–5.71) ^d	2.56 (1.98–3.33) ^d
Limited in walking >1 km	1.92 (1.29–2.86) ^c	4.42 (2.26–8.65) ^d	3.26 (2.26–4.70) ^d
Unable to bend	1.91 (1.26–2.92) ^c	2.55 (1.11–5.84) ^b	2.61 (1.74–3.91) ^d
Adjusted for age			
Unable to do vigorous activity	1.67 (1.28–2.17) ^d	1.58 (0.90–2.76)	1.47 (1.11–1.94) ^c
Limited in walking >1 km	1.88 (1.25–2.83) ^c	2.12 (1.05–4.26) ^b	1.93 (1.31–2.83) ^c
Unable to bend	1.89 (1.23–2.90) ^c	1.29 (0.55–3.04)	1.62 (1.06–2.47) ^b
Adjusted for age, BMI, smoking status, alcohol intake, and comorbidity			
Unable to do vigorous activity	1.26 (0.94–1.69)	1.37 (0.77–2.42)	1.45 (1.08–1.94) ^b
Limited in walking >1 km	1.15 (0.72–1.85)	1.81 (0.86–3.80)	1.77 (1.18–2.66) ^c
Unable to bend	1.06 (0.65–1.72)	1.13 (0.48–2.69)	1.63 (1.05–2.53) ^b

Multilevel (center-adjusted) logistic regression models with symptoms as outcomes.

^a Models include interaction between age and hypogonadal status, OR at mean age (60 yr).

^b $P < 0.05$; ^c $P < 0.01$; ^d $P < 0.001$ (reference was eugonadal group).

pensatory mechanisms to defer its unbridled effects. Increased aromatization of T to estradiol in adipose tissue (24), peripheral and central insulin resistance (25), and proinflammatory cytokine production (TNF- α and IL-6) from adipocytes (26) are all potential candidates for abrogating hypothalamic and downstream reproductive axis functions and reduced SHBG levels.

The increased sexual and physical symptoms in the secondary hypogonadism group were only moderately specific to low T after adjusting for BMI and other confounders. In the sense that it is independent of age, secondary hypogonadism, as defined in this analysis, is not, strictly speaking, late onset; it is associated with obesity and comorbid conditions at any age. A key message from the present study is that the hypothalamic/pituitary dysfunction associated with obesity in men considered to have secondary hypogonadism may potentially be reversible with weight loss (27), aromatase inhibitors or antiestrogens (28), thus offering rational therapeutic alternatives to symptomatic T replacement. We have excluded men with known pituitary disease and those receiving GnRH analogs for treatment of prostate cancer from the analysis

cohort. In the remaining men with T levels under 5 nmol/liter, secondary hypogonadism raises the possibility of occult pituitary disease (26). All nine such individuals were referred to their family physician for further assessment with a view to pituitary investigations if there were no plausible explanations for the apparent hypogonadotropic hypogonadism. Seven had active serious systemic illnesses (*e.g.* cancer, renal failure, or heart failure) considered sufficient to suppress the HPT axis; of these, two have since died. Two (with normal prolactin, thyroid function, and ferritin) did not have further pituitary investigations that were deemed unnecessary by their own physician.

Primary hypogonadism

A small minority (2.0%) of elderly men were at risk for primary hypogonadism. This may be a consequence of the age-related attrition of Leydig cells (29). These men probably represent the genuine form of LOH in that their relationship with age is the strongest, and they may be at the extreme end of the physiological spectrum of HPT axis

function encountered in aging (30), abetted to some extent by the age-associated increase in comorbidity.

Although men with primary hypogonadism showed a higher likelihood of sexual symptoms (low sexual thoughts), this relationship was independent of age, confirming the robust relationship between sexual function and T in men (31). The association between physical symptoms and primary hypogonadism remained significant after adjustment for age but did not persist after adjusting for other confounders. Primary hypogonadism comprised the oldest men (mean age 70.0 yr) in whom the increasing importance of lifestyle and comorbidity, as opposed to T decline, is highlighted by these results.

Secondary and primary hypogonadal groups both had lower mean E2 (Table 1) compared with the eugonadal group, which along with low T, may reflect Leydig cell dysfunction. This also suggests that central secondary hypogonadism is not associated with higher E2 despite its close relationship with obesity.

Compensated hypogonadism

A relatively large number of men (9.5%) were identified as having compensated hypogonadism (3, 9). The frequency of this condition showed a clear increase with age (Fig. 1, *inset*) forming the largest LOH category (21.1%) in the 70- to 79-yr age group. Although smokers are over-represented in compensated hypogonadism, there was no significant difference in total T, fT, or SHBG between smokers and nonsmokers in this group (data not shown). Excluding smokers from the analyses did not make any difference to the risk factor associations in any of the hypogonadal groups (Table 2). The explanation linking smoking with compensated hypogonadism remains unclear. Compensated hypogonadism was associated predominantly with physical symptoms. This is compatible with previous studies showing an inverse relationship between LH and muscle strength independent of T (10) and a lack of association between LH and libido (32). Although T levels in the compensated group remained above the thresholds for sexual symptoms, they may be insufficient to maintain previous levels of physical functions (33, 34). Given its wide normal range, it is possible that T had declined from previously high normal to current low normal levels in men with compensated hypogonadism. High LH may therefore be a biomarker for T decline within the reference range, indicating a readjustment of the HPT feedback set point in aging to compensate for deficiencies in testicular function and/or defective T feedback at the hypothalamic-pituitary level (35). A possible alternative explanation for the occurrence of physical symptoms in compensated hypogonadism may be the slightly lower mean fT in this group compared with eugonadal men (Ta-

ble 1 and Fig. 2). However, after stratifying this group into those with low (<230 pmol/liter) or normal fT, low fT levels were not associated with increased symptoms (sexual or physical) after adjusting for age and other confounders (data not shown).

Compensated hypogonadism may be analogous to sub-clinical hypothyroidism (high TSH and normal thyroid hormone levels) (36) where it is accepted that most patients will go on to develop overt hypothyroidism and T₄ replacement is indicated (37, 38). Our results suggest that elevated LH levels in compensated hypogonadism are not an isolated laboratory finding but significantly associated with physical symptoms. This lends support to the conclusion that it represents a genuine clinical subgroup of LOH. This condition may, therefore, be a forerunner of overt primary hypogonadism, being characterized by both elevated LH and higher age. Men with increased comorbidity and/or other as yet undefined factors may eventually progress from compensated to overt primary hypogonadism. The follow-up data in EMAS should provide verification to this hypothesized natural history of LOH.

The higher SHBG level in compensated hypogonadism could be an important proximal factor in the development of compensated hypogonadism and the higher E2 in the same group may be a potential mechanism. However, the present cross-sectional data cannot dissect out the complex but potentially important interrelationships, and more research on this aspect is warranted.

Symptoms of hypogonadism in eugonadal men

The prevalence of sexual (25–35%) and physical (5–21%) symptoms in eugonadal men is substantial (Table 1). This high symptom prevalence in apparently eugonadal men emphasizes the important point that factors other than T deficiency (especially age) are important causes of nonspecific LOH-like symptoms in older men and the apparent overlap between groups. Nevertheless, the relatively discrepant pattern in symptomatology between the three hypogonadal groups may be helpful in refining the diagnosis of LOH.

Strengths and limitations

EMAS is a large, population-based study that used standardized methods of clinical assessments and centralized hormone analyses including mass spectrometry measurement of T. There are, however, some limitations, which need to be highlighted. It is possible that men who participated in the study differed from those who did not, necessitating a cautious approach in interpreting our results, albeit they are based on internal comparisons of participants. However, this does not affect the main finding of our study on the differences between the three cat-

egories of hypogonadism. Given the cross-sectional design of the study, it was not possible to determine the directional or temporal nature of the observed relationships, for which prospective data are needed. Although only a single morning blood sample from each individual was analyzed, single measurements of T in large epidemiological studies, such as the EMAS, can provide consistent and reliable data (39). Finally, the results herein are based on the assessments of a relatively healthy, general population of European men, and extrapolation to other ethnic groups should be done with caution.

Summary and conclusions

This is the first study to show that secondary, primary, and compensated hypogonadism can be distinguished by hormone measurements, specific risk factors (especially age and obesity) and associated symptoms. Secondary hypogonadism is associated with obesity (and potentially reversible) independently of age, whereas primary hypogonadism (probably the genuine form of LOH) is strongly associated with age. Compensated hypogonadism represents a distinct clinical entity that warrants continued monitoring to prevent or preempt further deterioration. LOH is a complex clinical syndrome in need of additional research (7). Classification of symptomatic elderly men with different T and LH levels into different functional categories of LOH may provide a more precise (patho)physiological framework to refine the diagnosis and ultimately to improve management of this condition. Additional longitudinal studies are indicated to confirm the clinical significance of these different types of the age-related HPT axis dysfunction.

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