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ORIGINAL ARTICLE



## Prevalence of testosterone deficiency among aging men with and without morbidities

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### ABSTRACT

In this cross-sectional study 1852 men aged 40–70 years attending primary health care were invited to fill out the aging male symptoms (AMS) scale. Out of these, 1222 men were found positive for the AMS and agreed to provide blood samples for the general blood test, lipid profile, glucose levels, and assessment of both total and free testosterone (T) levels. Men were screened for the following morbidities and syndromes: dyslipidemia, arterial hypertension, obesity, type II diabetes, metabolic syndrome, and chronic obstructive pulmonary disease (COPD). Testosterone deficiency was diagnosed if total T  $\leq 3.46$  ng/mL or free T  $\leq 72$  pg/mL. Among all 1222 men with positive AMS, decreased blood testosterone levels were detected in 669 men (55%). A total of 402 men were found healthy and 820 men were detected with different morbidities. Out of 669 men with testosterone deficiency, only 2.8% had no co-morbidities and 97.2% were men with co-morbidities. Testosterone levels were found significantly higher among healthy men (median 4.7 ng/mL) as compared to the men with morbidities (median 2.55 ng/mL,  $p < .001$ ), adjusted for age. Testosterone deficiency was detected in significantly lower proportion of 402 men without co-morbidities as compared to the 820 men with co-morbidities: in 19 men (4.7) and in 650 men (79.3%,  $p < .05$ ), respectively.

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## Introduction

Late onset hypogonadism (LOH) is a clinical and biochemical syndrome, associated with advancing age in men, and characterized by typical symptoms and decreased testosterone levels [1,2]. According to the data from the *European Male Aging Study (EMAS)*, LOH can be diagnosed if at least three sexual symptoms are present (decreased libido, decreased frequency of morning erections, and erectile dysfunction), and total and/or free testosterone levels are below 3.2 and 63 pg/mL, respectively [3].

It has been reported that after the age of 40 the levels of testosterone in men are decreasing approximately for 1–1.6% per year, levels of sex hormone binding globulin (SHBG) are increasing approximately for 1.3% per year, and levels of free testosterone are decreasing for approximately 2.8% per year [4–6].

There is no consistency in data on the prevalence of the LOH among aging men. It has been reported that it affects 7–30% of aging men in some early studies [7,8]. Later on, it has been reported that the overall

prevalence of testosterone deficiency syndrome varies from 6 to 12% in community-dwelling men aged 40–70 years, and rises to 15–30% in diabetic or obese men [9,10]. The results from the *EMAS* study showed that biochemical testosterone deficiency can be detected in 17% of the community-dwelling men aged 40–70 years, but testosterone deficiency plus clinical symptoms – only in 2% of these men [3]. It has been also reported that LOH is more common in aging men suffering from obesity and chronic diseases like diabetes, hypertension, chronic obstructive pulmonary disease (COPD), arthritis, and chronic stress [1,9,10].

The aim of this study was to evaluate the prevalence of testosterone deficiency in aging men with different chronic diseases, as compared to the aging men without morbidities.

## Materials and methods

A total of 1852 men aged 40–70 years (median 57 years) attending primary health care in 2007–2015

were invited to participate in this prospective study. All men were given to fill out the aging male symptoms (AMS) scale [11]. Out of these 1852 men, 1340 men had positive AMS (27 points and more). They were invited to deliver a blood sample to assess the testosterone levels, and 1222 men agreed and were enrolled. The permission of the ethical committee was obtained for the study.

All 1222 men provided morning (8.00–11.00) fasting blood samples for general blood test, lipid profile, glucose levels, and assessment of both total and free testosterone (T) levels. T levels were assessed by immune-fermentative method, using photometric test system *Multiskan Plus* with a wavelength 450 nm. Testosterone deficiency was diagnosed if total  $T \leq 3.46$  ng/mL or free  $T \leq 72$  pg/mL [12]. As suggested by the ISSAM recommendations [12,13], men with testosterone levels above 3.46 ng/mL must be regarded as eugonadal, while those men with testosterone levels below 2.32 nmol/L and men with borderline testosterone levels of 2.3–3.46 nmol/L and positive LOH symptoms can be regarded as hypogonadal. Since in our study only men with positive AMS were included, a cut of level of 3.46 ng/mL was chosen.

All men were also investigated by general practitioner. Following morbidities have been distinguished among the study participants:

1. Arterial hypertension stage I–III according to the recommendations of the European Associations of Hypertension and Cardiology (2013), or stage  $\leq$  I according to the recommendations of the New York Association of Cardiology [14].
2. Obesity: body mass index (BMI) 30–39
3. Dyslipidemia: total cholesterol  $>5$  mmol/L, and/or LDL  $>3$  mmol/L, triglycerides  $>1.7$  mmol/L, and high-density lipoprotein (HDL)  $<1$  mmol/L
4. Metabolic syndrome – when at least three of the following criteria were met: arterial hypertension  $>130/85$  mm/Hg, fasting glucose  $>5.6$  mmol/L, triglycerides  $>1.7$  mmol/L, HDL levels  $<1.0$  mmol/L, and waist circumference  $>94$  cm [15].
5. Compensated diabetes type II (glycosylated hemoglobin  $<7\%$ ).
6. COPD with *FEV1* 50–80% with the ratio of *FEV1*/*FVC*  $<0.70$  [16].

For statistical analyses the following methods were employed: for the description of the study population descriptive non-parametric and parametric data were used. For the evaluation of the distribution of the parametric data, Kolmogorov–Smirnov test was used.

Binary logistic regression analysis was used to calculate odds ratios to assess the impact of the age and chronic diseases on testosterone deficiency. To calculate the impact of chronic diseases on the levels of total and free testosterone, linear regression analysis was used. Differences were deemed statistically significant if  $p < .05$ . Statistical Package for the Social Sciences (SPSS) version 20.0. software (SPSS Inc., Chicago, IL) was used to process the data.

## Results

Out of 1222 investigated men, 402 men were found healthy and 820 men were detected with different morbidities (Table 1). As can be seen from Table 1, in most of the cases men had a combination of several morbidities. Isolated morbidities were detected in small numbers of the analyzed men: arterial hypertension in 40 men, dyslipidemia in 156 men, and COPD in 41 men. Dyslipidemia was detected in 55.7% of all 1222 investigated men, arterial hypertension – in 22%, obesity – in 33%, type II diabetes – in 5.5%, metabolic syndrome – in 11.4%, and COPD – in 8.8% of all men.

Among all 1222 men, testosterone deficiency was detected in 669 men (55%). Out of these 669 men, only 2.8% had no co-morbidities and 97.2% were men with co-morbidities.

Testosterone levels were found significantly higher among healthy men (median 4.7 ng/mL) as compared to the men with morbidities (2.55 ng/mL,  $p < .001$ ), adjusted for age. Testosterone deficiency was detected in significantly lower proportion of 402 men without co-morbidities as compared to the 820 men with co-morbidities: in 19 men (4.7) and in 650 men (79.3%,  $p < .05$ ), respectively.

All 19 men without co-morbidities diagnosed for the T deficiency had normal total testosterone levels but decreased free testosterone levels. Out of 650 men with co-morbidities and testosterone deficiency, 62 men (9.5%) had decreased free testosterone levels but normal total testosterone levels (other 90.5% of men had decreased total testosterone levels alone or

**Table 1.** Distribution of different morbidities detected in 820 men out of the 1222 investigated men.

Morbidity	Number of men	Percentage (%)
Hypertension	320	39
Dyslipidemia	681	83
Obesity (BMI $> 30$ )	407	49.6
Type II diabetes	67	8.2
Metabolic syndrome	139	17
COPD	107	13

COPD: chronic obstructive pulmonary disease.

**Table 2.** Univariate and multivariate analyses of odds ratios for different morbidities and age to have the testosterone deficiency.

Factor (moridity)	OR	95% CI	p	adOR	95% CI	p
Dyslipidemia	16.90	12.72–22.46	<.001	15.80	10.64–23.46	<.001
Obesity	6.81	5.06–9.16	<.001	2.75	1.80–4.20	<.001
Hypertension	6.08	4.39–8.43	<.001	3.68	2.34–5.78	<.001
Metabolic syndrome	8.99	5.01–16.10	<.001	4.66	2.33–9.32	<.001
COPD	3.98	2.39–6.62	<.001	24.40	11.83–50.34	<.001
Type II diabetes	2.03	1.18–3.50	.01	1.47	1.24–1.92	.03
Age	1.07	1.05–1.08	<.001	1.13	1.11–1.16	<.001

OR: unadjusted odds ratios; adOR: odds ratios adjusted for other factors (morbidities and age); CI: confidence interval.

in combination with decreased free testosterone levels).

Odds ratios for men with different morbidities to exhibit testosterone deficiency are shown in Table 2. After adjusting for other morbidities and age, the highest risk for hypogonadism was demonstrated in men with COPD (OR = 24) and dyslipidemia (OR = 16) (Table 2). In men with obesity, hypertension, metabolic syndrome, and type II diabetes odds ratios for testosterone deficiency were also significant, ranging from 1.5 to 4.7. Also advancing age was found to be an independent risk factor for the testosterone deficiency (OR = 1.13): possibility to acquire the hypogonadism showed an increase of 13% per year with advancing age.

## Discussion

Out of the 1852 men aged 40–70 years that filled out the AMS questionnaire, 72% (1340 men) were found positive for the AMS (27 points and more by the AMS scale). Out of the 1222 men with positive AMS, 55% men were diagnosed with LOH (testosterone deficiency). Many symptoms included into the AMS scale are not specific for the hypogonadism (like muscle pain, increased sweating, fatigue, anxiety, panic attacks, etc.) that can explain why only about the half of the aging men with positive AMS had actually low testosterone levels. These findings go in line with the EMAS that showed that only sexual symptoms are actually specific for the LOH [3].

The most important finding of our study was a very low prevalence (5%) of testosterone deficiency in aging men (40–70 years), which were positive by the AMS scale but were deemed healthy upon laboratory and physical investigations. Thus, most of the men with positive AMS but otherwise healthy upon clinical and laboratory investigations were found to have normal testosterone levels. It once again proves that AMS scale includes many symptoms not specific for the

testosterone deficiency which seems fails to diagnose hypogonadism in aging men with no somatic morbidities. On the other hand, testosterone deficiency was found to be very frequent (79%) among aging men with different morbidities and positive AMS – and that is the most important message from our study. Most of the previous studies that have investigated community-dwelling aging men from general population showing the prevalence of LOH in 2–12% of such men [3,9,10]. Our findings showing that 5% of aging men without morbidities exhibit decreased testosterone levels go into line with these data. Also, our findings of frequency of hypertension (22%), dyslipidemia (56%), obesity (33%), type II diabetes (5.5%), metabolic syndrome (11.4%), and COPD (8.8%) among aging men were in concordance with the data from the other studies, including Massachusetts male aging study and EMAS [3,7,17,18].

The association of the COPD and low levels of testosterone has been demonstrated also in other studies [19–21], albeit not in all studies [22]. Several studies have also demonstrated an association between dyslipidemia and testosterone deficiency [6,23,24], although some studies failed to show a direct relationship [25]. In our study, we have found that aging men with COPD and dyslipidemia exhibit very risk for LOH. Patients with COPD exhibited the highest risk (OR = 24) for testosterone deficiency when adjusted for other morbidities and age. Also, dyslipidemia was found as a very significant risk factor (OR = 16) for the LOH.

Somewhat lower but still significant risk for hypogonadism (OR = 1.5–4.7,  $p < .05$ ) exhibited also other morbidities as similarly demonstrated in previous studies: arterial hypertension [7,26,27], obesity [9,10,28], type II diabetes [6,29,30], and metabolic syndrome [26,31–33].

The limitation of this study was unavailability of the testosterone levels for the 512 (28%) out of the 1852 aging men who were negative by the AMS scale. They could serve as more appropriate control group of the healthy aging men as compared to the men with positive AMS but no morbidities employed in our study. We can speculate that proportion of men with testosterone deficiency among these men should have been even lower than 5% that we found among men with no morbidities but positive for the AMS, especially since EMAS study has demonstrated the proportion of 2% of men with hypogonadism among community-dwelling aging men [3].

In conclusion, we have demonstrated that AMS scale is not very specific tool to diagnose LOH in

aging men but still can be used because 55% of men positive for the AMS exhibited testosterone deficiency. Most importantly, we have demonstrated that all aging men suffering from different morbidities like arterial hypertension, COPD, type II diabetes, metabolic syndrome, or even altered lipid profiles, or obesity – should be tested for the testosterone levels to diagnose LOH since testosterone deficiency can be detected very frequently among such men.

### Compliance with an ethical standard

Study follows the principles of the Declaration of Helsinki.

### Disclosure statement

The authors declare that they have no conflict of interest.

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