Rīgas Stradiņa universitāte

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PECULIARITIES OF THE DEVELOPMENT AND DIAGNOSIS OF LATE-ONSET HYPOGONADISM IN MEN IN THE CASE OF CHRONIC DISEASES – ARTERIAL HYPERTENSION, DYSLIPIDAEMIA, ADIPOSITY, METABOLIC SYNDROME, TYPE 2 DIABETES MELLITUS, CHRONIC OBSTRUCTIVE PULMONARY DISEASE – AND COMBINATIONS THEREOF

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The Doctoral Thesis is available in the RSU library of and at RSU webpage: www.rsu.lv.

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ABBREVIATIONS USED IN THE THESIS

T2CD	Type 2 diabetes mellitus
AIDS	acquired immune deficiency syndrome
AMS	Aging Males' Symptoms questionnaire
ANG-2	angiotensin-2
CAG	cysteine-adenosine-guanine triplet
CNS	central nervous system
CRP	C-reactive protein
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
FSH	follicle-stimulating hormone
HDL	high-density lipoproteins
BMI	body mass index (kg/m^2)
CHD	coronary heart disease
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular diseases
FEV 1	forced expiratory volume in one second
FVC	forced vital capacity
GnRH	gonadotropin-releasing hormone

HIV	human immunodeficiency virus
HPGA	hypothalamic-pituitary-gonadal axis
IIEF-5	International Index of Erectile Function
ISSAM	International Society for the Study of the Aging Male
LDL	low-density lipoproteins
LH	luteinising hormone
LOH	late-onset hypogonadism
MCP	monocyte chemotactic protein
NYHA	New York Heart Association
SARM	selective androgen receptor modulators
SHBG	sex hormone-binding globulin
SOX	sodium oxide
SSRI	serotonin reuptake inhibitors
TNF	tumour necrosis factor
TRT	testosterone replacement therapy

INTRODUCTION

Topicality of the Scientific Work

In recent years, much attention has been paid to the reproductive health of males of different ages. An important aspect of male health is an expressed impact of somatic diseases on male gonadal function. The issue of male late-onset hypogonadism, or LOH, is moving forward. It has been shown that with age, testosterone level gradually decreases even in a body of a completely healthy male. Moreover, this issue has hardly been studied in the context of comorbidities.

Testosterone fraction dynamics shall be studied in detail in the context of rather prevalent diseases, such as arterial hypertension, diabetes mellitus, dyslipoproteinemia, and metabolic syndrome. These diseases are featured by rather unfavourable prognosis regarding high risk of local vascular pathology, reducing the quality of life, and premature death. A pressing issue is the dynamics of testosterone fractions in the case of chronic obstructive pulmonary disease (COPD). In addition, it is important not only to study testosterone dynamics depending on the age, but also the characteristic clinical features of LOH, and the peculiarities of the above diseases.

Study Hypotheses

1. The diagnosis of LOH is more often confirmed in patients with signs of LOH in accordance with the Aging Males' Symptoms Questionnaire (AMS) data combined with arterial hypertension, dyslipidaemia, adiposity, metabolic syndrome, Type 2 diabetes mellitus, and chronic obstructive pulmonary disease compared to men without these pathologies.

2. Testosterone level in men with signs of LOH in accordance with AMS data and the aforementioned diseases are lower compared to men without these conditions.

3. In the case of each aforementioned disease, clinical manifestations of LOH are different, and the mean testosterone levels and/or ratios of testosterone sub-fractions are different.

Study Object

Studying the prevalence of late-onset hypogonadism in patients with comorbidity and/or simultaneously occurring pathology: COPD, metabolic syndrome, T2CD, dyslipidaemia in different general practitioners' and physicians sexologists' practices, and developing clinical and laboratory criteria regarding the impairment of gonadal function.

Aims of the Study

1. Evaluation of the clinical condition, and identification of the individuals with potential LOH in men over 40 years of age who have referred to general practitioner's offices with different health conditions, for preventive examinations, or have referred to sexologists with complaints of impaired sexual function, using Aging Males' Symptoms Questionnaire, or AMS Questionnaire data.
2. Determination of free and total testosterone blood level in men with an established hypogonadism in accordance with Aging Males' Symptoms Questionnaire data. Analysis and evaluation of comorbidities in this patient group.

3. Evaluation of free and total testosterone level in patients with arterial hypertension, adiposity, dyslipidaemia, Type 2 diabetes mellitus, metabolic syndrome, and COPD, who have had hypogonadism in accordance with Aging Males' Symptoms Questionnaire data.
4. Evaluation of free and total testosterone level in patients who have had hypogonadism in accordance with Aging Males' Symptoms Questionnaire data, but who have had no concomitant diseases listed above.
5. Revealing the laboratory-confirmed LOH prevalence in patients with signs of LOH in accordance with AMS questionnaire data and arterial hypertension, adiposity, dyslipidaemia, metabolic syndrome, Type 2 diabetes mellitus and COPD; revealing the laboratory-confirmed LOH prevalence in patients with signs of LOH in accordance with AMS questionnaire data and without the aforementioned diseases.
6. Investigating the effect of the aforementioned chronic diseases on the prospects for hypogonadism development; investigating the effect of these diseases on the total and free testosterone levels in patients with signs of LOH in accordance with AMS questionnaire data.
7. Revealing age-induced androgen deficiency-associated peculiarities of clinical features in the case of various clinical entities and the development of diagnostic criteria of androgen deficiency associated with the main somatic pathology.
8. Drawing up recommendations for general practitioners regarding LOH diagnostics in men over 40 years of age.

Novelty of the Study

1. Gonadal function screening in men over 40 years of age has been performed for the first time in Latvia.
2. Direct correlation between arterial hypertension, dyslipidaemia, adiposity, Type 2 diabetes mellitus, metabolic syndrome, COPD and the development of LOH symptoms has been established.
3. Metabolic syndrome, COPD, and dyslipidaemia have been found to affect the development of LOH the most. Up to now, no data on correlation between aforementioned diseases and LOH have been published in Latvia.
4. LOH diagnostic criteria in the case of a patient having metabolic syndrome, arterial hypertension, adiposity, dyslipidaemia, Type 2 diabetes mellitus, or COPD has been developed.

Personal Contribution

Analysis of literature, development of the study design and its harmonisation with the RSU Ethics Committee, selection of participants, the survey carried out by AMS questionnaire, physical examination of the participants of Male Sexual Health Questionnaire, explanatory work with the participants of the study regarding the correct completion of the questionnaire, sample delivery to the laboratory, analysis of the obtained results, drawing up publications, abstracts, and doctoral thesis.

Structure and Volume of the Thesis

The doctoral thesis is written in English. It contains 10 chapters: Introduction, Overview of Literature, Materials and Methods, Results, Discussion, Conclusions, Practical Recommendations, Acknowledgements, Literature References, Publications on the Subject of the Doctoral Thesis, and Annexes. The Doctoral Thesis contains 117 pages (excluding the annexes – 5 pages). It comprises 37 tables and 6 images. References to 281 literature sources have been used in the thesis.

1. MATERIAL AND METHODS

1.1. Object of the Study

1. Patients over 40 years of age with no complaints about sexual health condition who have referred to a general practitioner due to various reasons: acute illnesses, exacerbations of chronic diseases, and preventive examinations.
2. Patients over 40 years of age with complaints about sexual health who have referred to a sexologist with libido disorders, erectile dysfunction, and ejaculation disorder.

1.2. Inclusion Criteria of the Study

1. Age: $\geq$ 40 years of age.
2. Stage 1 to 3 arterial hypertension with high and very high risk of development of cardiovascular system complications without heart failure, or with concomitant chronic heart failure (≤ stage 1 according to the classification of the New York Heart Association) (Mancia et al., 2013).
3. Class 1 to 2 obesity (body mass index 30 to 39).
4. Compensated Type 2 diabetes (with glycated haemoglobin level up to 7 %).
5. Dyslipidaemia with elevated total cholesterol level above 5 mmol/l and/or LDL level above 3 mmol/l, triglyceride level above 1.7 mmol/l, HDL level below 1 mmol/l; or normal levels of cholesterol and its fractions in the case of taking statins.
6. Patients with metabolic syndrome.

7. Moderate COPD. GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines of 2013 have been used to evaluate the severity of COPD (Vestbo et al., 2013).

1.3. Exclusion Criteria of the Study

1. Age: < 40 years of age.
2. Arterial hypertension with class 2 to 4 heart failure according to NYHA classification.
3. Severe obesity (body mass index $\geq$ 40).
4. Severe, uncompensated Type 2 diabetes mellitus (glycated haemoglobin $\geq$ 8.5 %).
5. Dyslipoproteinemia with high cholesterol > 8.5 mmol/l and unadjusted lipid profile.
6. Mild to severe COPD, cardiovascular pathology with chronic heart failure exceeding class 1 by NYHA classification, stroke or myocardial infarction in medical history, grade 1 obliterating atherosclerosis of arteries in legs exceeding.
7. Sub-compensated or uncompensated somatic diseases, oncological or haematological pathologies, deterioration of intellectual and mental abilities subjectively evaluated during the visit to a physician and expressed as a patient's inability to understand the essence of the study and his disease, inability to understand information on investigation and treatment options, expressed memory impairment.

2. METHODOLOGY OF THE STUDY

2.1. Phases of the Study

The study design in time: cross-sectional study. It is based on a men's survey using Aging Males' Symptoms questionnaire, or AMS questionnaire, as well as on the assessment of the participants by means of clinical and laboratory methods. Aging Males' Symptoms questionnaire is recommended to be used in LOH diagnostics by the International Society for the Study of the Aging Male (ISSAM) (Morales, Lunenfeld, 2002). A permit from the RSU Ethics Committee has been obtained to conduct the study. Males over 40 years of age who had referred to general practitioners at nine general practitioner's offices in Latvia due to acute illnesses, exacerbations of chronic disease, or for preventive examinations, and who had agreed to take part in the study, were offered to complete the AMS questionnaire. Males over 40 years of age, who had referred to the physician-sexologist Anatolijs Požarskis' office, were offered to complete the same questionnaire. After the analysis of the AMS questionnaire data, a group of men with signs of LOH has been identified. These patients were offered to determine their blood testosterone and SHBG levels. In patients with LOH, established in accordance with laboratory and clinical indicators (clinical signs typical for LOH and lower limit, or reduced testosterone levels), symptoms of sexual dysfunction were analysed by completing Males' Sexual Health Questionnaire developed by us. 545 patients agreed to complete this questionnaire. Men's medical records filled in by the general practitioners have also been assessed, and chronic diseases identified in anamnesis of these patients have been recorded. The presence of the following data in participants' medical records for the last 6 months has been assessed: blood glucose, as well as a total cholesterol, triglycerides, HDL, and LDL

levels, and spirometry. If the data were present in a medical record, they were used in our study; if the data were not available, blood glucose, total cholesterol, triglycerides, LDL, and HDL levels were determined in patients. Physical examination were performed, and the following indicators determined: arterial blood pressure on both arms; height and weight, body mass index was calculated; measurement of waist circumference was performed.

The study group was comprised of patients in whom LOH had been established in accordance with the AMS questionnaire data, and the following diseases had been identified (n = 820): arterial hypertension, dyslipidaemia, adiposity, metabolic syndrome, Type 2 diabetes mellitus, COPD, and erectile dysfunction (if patients considered it a problem and referred to the physician with complaints of erection problems themselves).

The control group was comprised of patients in whom LOH had been established in accordance with the AMS questionnaire data, and in whom arterial hypertension, dyslipidaemia, adiposity, metabolic syndrome, Type 2 diabetes mellitus, and COPD had not been diagnosed, and who had no active complaints of erection problems (n = 402).

2.2. Diagnostic Criteria of Somatic Pathologies

Arterial hypertension. During the conduct of the study, we used the currently available hypertension classification system recommended by the European Society of Hypertension and the European Society of Cardiology (Mancia et al., 2013), where the optimal blood pressure (BP) level is considered < 120/80; normal BP: 120–129/80/84; high normal BP: 130–139/85–89; stage 1 hypertension: 140–159/90–99; stage 2 hypertension: 160–179/100–109; stage 3 hypertension: $\geq$ 180/$\geq$ 110.

Depending on blood pressure level, risk factors, asymptomatic organ impairment, and presence of concomitant clinical pathology, arterial hypertension has been divided into four risk groups of complications: low, moderate, high, and very high risk (Mancia et al., 2013).

Diabetes mellitus. During the study, diabetes mellitus was diagnosed on the basis of the following criteria: repeated measurements of fasting blood glucose levels are > 7.0 mmol/l (120 mg %), or > 11.1 mmol/l (200 mg %) two hours after 75 g glucose load.

Obesity. Obesity diagnosis was established in accordance with modern WHO classification principles depending on the body mass index. According to the body mass index, normal weight corresponds to 18.5–24.99 kg/m^2, overweight – to 25–29.99 kg/m^2, obesity – to 30–39.99 kg/m^2, severe obesity – $\geq$ 40 kg/m^2.

Dyslipoproteinemia. Dyslipoproteinemia was established according to the following metabolic parameters: total cholesterol concentration > 5.0 mmol/l, triglyceride level > 1.7 mmol/l, high-density lipoprotein cholesterol concentration < 1.0 mmol/l, and low-density lipoprotein cholesterol concentration > 3.0 mmol/l.

Metabolic syndrome. Metabolic syndrome was diagnosed if at least three of the following criteria had been established (Alberti, et al., 2009):

1. Arterial hypertension (characteristic values of arterial blood pressure > 130/85 mm/Hg, or patients with arterial hypertension taking antihypertensives).
2. Triglycerides > 1.7 mmol/l, or medical treatment of hypertriglyceridemia.
3. Fasting blood glucose level > 5.6 mmol/l, or medical treatment of hyperglycaemia.
4. HDL level < 1.0 mmol/l.

5. Men's waist circumference > 94 cm, which is a sign of abdominal obesity.

Chronic obstructive pulmonary disease. Moderately severe COPD was diagnosed according to the following criteria.

Anamnesis data (long-term smoking period, or long-term exposure to substances irritant to respiratory system), complaints (dyspnoea at physical exertion of moderate intensity, productive cough, periods with cough and high temperature), physical examination (vesiculotympanitic resonance to percussion, weakened respiration, dry noise to auscultation), instrumental examination (measurement of forced expiratory volume in one second (FEV1) 50 to 80 % of the normal at FEV1/FVC < 0.70, bronchodilation test – after the inhalation of salbutamol FEV1 increased on average by 7.6%, which is a sign of an irreversible bronchial obstruction).

2.3. Diagnostic Methods of Late-Onset Hypogonadism

Laboratory diagnosis of LOH was established by means of immunoenzymatic method using *Multiskan Plus* photometer test system at the wavelength 450 nm. During the diagnostics, total and free testosterone levels were established and divided into three categories: "normal value", "reduced to the threshold level", and "abnormally low". Following the recommendations of ISA, ISSAM, and EAU guidelines in 2006 (the year when our study was started), total and free testosterone level is considered normal > 3.46 ng/ml and > 72.00 pg/ml, reduced to the threshold level – 3.46–2.31 ng/ml and 65.00–72.00 pg/ml, and abnormally low < 2.31 ng/ml and < 65.00 pg/ml, respectively (Nieschlag et al., 2006).

2.4. Statistical Methods

Non-parametric (percentage and its 95 % confidence interval, cross-tabulation analysis) and parametric descriptive statistical methods (minimum, maximum, average, standard deviation, median) were used to describe the population. The Kolmogorov-Smirnov test was used to determine the normal distribution of parametric indicators.

The conditional odds ratio (OR) has been calculated using binary logistic regression to determine the independent influence of chronic diseases and age on hypogonadism. Binary logistic regression was also used to search for different associations between AMS symptoms and hypogonadism. Linear regression was used to determine the independent influence of chronic diseases and age on total and free testosterone levels.

To evaluate the significance of the differences between two sets of data, the Student's t-criterion was used. The difference between the parameters is statistically significant, if t-value is ≥ 2 (in this case, $p < 0.05$). Student's t-criterion was used to identify significant differences in quantitative parameters of investigated processes.

Statistical data processing was performed using the SPSS (Statistical Package for the Social Sciences) 20.0 software. MS Excel was used to create figures.

The level of significance chosen for this work (p) is 0.05, that is, the results are considered statistically reliable if $p < 0.05$.

3. RESULTS

3.1. Characterisation of Patients

The study comprised 820 patients. 648 (79.0 %) of these patients had no complaints about sexual health, and they were the patients of general practitioners who had completed the *AMS* questionnaire voluntarily. In addition, 172 men (21 %) referred to a sexologist due to sexual dysfunction. The following somatic and cardiac pathologies were recorded in patients:

- class 1 to 3 arterial hypertension with high or very high risk of complications (in 320 cases – 39 %);

- class 1 to 2 obesity (in 407 cases – 49.6 %);

- compensated (glycated haemoglobin level < 7 %) Type 2 diabetes mellitus (in 67 patients – 8.2 %);

- proatherogenic dyslipoproteinemia (in 681 patients – 83 %);

- metabolic syndrome (in 139 patients – 17 %);

- COPD (in 107 patients – 13 %).

The patients were in the age range of 40 to 70 years, and were distributed in the following age-defined patient groups: 40–45 years of age (81 patient, or 9.9 %), 46–50 years of age (93 patients, or 11.3 %), 51–55 years of age (372 patients, or 45.4 %), 56–60 years of age (157 patients, or 19.2 %), 61–65 years of age (85 patients, or 10.4 %), 66–70 years of age (32 patients, or 3.9 %) (see Table 3.1).

Table 3.1

Age and clinical characteristics of patients enrolled in the study

Age (years)	AH	ADPS	DM	Dyslp.	COPD	MS	Total
40–45	30	45	2	54	12	33	176
46–50	52	65	14	97	10	25	263
51–55	40	48	9	102	24	39	262
56–60	44	76	15	147	16	31	329
61–65	58	79	14	140	21	5	317
66–70	96	94	13	141	24	6	374

Abbreviations:
AH – arterial hypertension
ADPS – adiposity
DM– diabetes mellitus
Dyslp. – dyslipidaemia
ED – erectile dysfunction
COPD – chronic obstructive pulmonary disease
MS – metabolic syndrome

3.2. Characterisation of Testosterone Level in Men with and without Chronic Comorbidities

According to clinical and laboratory data, hypogonadism was found in 669 patients (54.7 % of 1222 study participants). In patient groups with chronic comorbidities, hypogonadism was found in 650 patients (79 % of 820 study participants). It was found in men without concomitant diseases in 19 cases (4.7 % of 402 participants in the group). The prevalence of hypogonadism is statistically significantly higher in the patient group with concomitant diseases ($p < 0.05$).

3.3. Age-Dependent Characterisation of Testosterone Level Dynamics in Men without Arterial Hypertension, Type 2 Diabetes Mellitus, Metabolic Syndrome, Dyslipidaemia, Adiposity, and COPD

402 men without any observed chronic concomitant disease were enrolled in the study. Male age characteristics were as follows: 40–45 years of age – 49 patients, 46–50 years of age – 51 patients, 50–55 years of age – 83 patients, 56–60 years of age – 68 patients, 61–65 years of age – 70 patients, 66–70 years of age – 81 patients.

For total and free testosterone level obtained in these subjects, the data has been represented in Table 3.2.

Table 3.2

Total and free testosterone level in healthy subjects of different age groups

Age (years)	Total testosterone			Free testosterone		
	median	mean value	SD	median	mean value	SD
40–45	4.80	4.97	1.06	7.40	7.09	10.19
46–50	4.70	4.75	0.56	72.35	74.79	7.74
51–55	4.60	4.72	0.67	72.30	74.28	7.63
56–60	4.70	4.73	0.52	72.30	73.47	5.61
61–65	4.60	4.67	0.47	72.30	73.05	5.14
66–70	4.70	4.72	0.34	72.30	72.70	2.82

Obtained results show that unambiguous total and free testosterone concentration dynamics has not been observed in serum. Moreover, a certain age-dependent trend of reduction of both forms of this hormone exists. The difference in the hormone level between the age groups is not statistically significant ($p > 0.05$). The reduction trend is characterised also by the indicator values of free testosterone concentration. However, this difference is not statistically significant ($p > 0.05$) either. Thus, healthy males are not featured by a particular tendency for reduction in free and total testosterone level with

increasing age. The summarised AMS questionnaire data presented by these men has been represented in Table 3.3.

Table 3.3

Results obtained by surveying men of different age without cardiac and respiratory system pathologies

Questionnaire item	Average score	Standard deviation	Median score
Decline in one's feeling of general well-being	1.89	0.47	2.00
Joint pain and muscular ache	1.41	0.65	1.00
Excessive sweating	1.76	0.59	2.00
Sleep problems	1.62	0.61	2.00
Increased need for sleep, often feeling tired	1.74	0.58	2.00
Irritability	1.75	0.59	2.00
Nervousness	1.80	0.60	2.00
Anxiety (feeling panicky)	1.80	0.63	2.00
Physical exhaustion/lacking vitality	1.85	0.57	2.00
Decrease in muscular strength	1.76	0.66	2.00
Depressive mood	1.74	0.73	2.00
Feeling that one has passed their peak	1.93	0.64	2.00
Feeling burnt out, having hit rock-bottom	1.78	0.64	2.00
Decrease in beard growth	1.57	0.59	2.00
Decrease in ability/frequency to perform sexually	1.01	0.12	1.00
Decrease in the number of morning erections	1.01	0.21	1.00
Decrease in sexual desire/libido	1.27	0.66	1.00

These results suggest poorly expressed changes to all parameters included in the questionnaire.

Therefore, in accordance with the AMS questionnaire data obtained by surveying men of different ages without somatic pathologies, the results can be characterised as mild deviation from normal values for all the parameters.

3.4. Characterisation of Age-Associated Androgen Deficiency in the Case of Different Comorbidities

The relationship between hypogonadism and chronic diseases and age has been investigated using a single and multiple factor analysis. The obtained results are shown in Table 3.4.

Table 3.4

Single and multiple factor analysis of the relationship between hypogonadism and chronic diseases and age

Independent characteristic		**mOR**	**95 % CI**	**p**	**cOR**	**95 % CI**	**p**
Dyslipidaemia	yes	16.90	12.72–22.46	< 0.001	15.80	10.64–23.46	< 0.001
	no	1			1		
Adiposity	yes	6.81	5.06–9.16	< 0.001	2.75	1.80–4.20	< 0.001
	no	1			1		
Arterial hypertension	yes	6.08	4.39–8.43	< 0.001	3.68	2.34–5.78	< 0.001
	no	1			1		
Metabolic syndrome	yes	8.99	5.01–16.10	< 0.001	4.66	2.33–9.32	< 0.001
	no	1			1		
COPD	yes	3.98	2.39–6.62	< 0.001	24.40	11.83–50.34	< 0.001
	no	1			1		
Type 2 diabetes mellitus	yes	2.03	1.18–3.50	0.01	1.47	1.24–1.92	0.03
	no	1			1		
Age		1.07	1.05–1.08	< 0.001	1.13	1.11–1.16	< 0.001

Abbreviations:
mOR – marginal *odds ratio*
cOR – conditional *odds ratio*
CI – confidence interval
p – level of significance
n – absolute number

As it is shown in Table 3.4, persons with dyslipidaemia have a 16.90-fold higher chance of developing hypogonadism, and this indicator is statistically significant ($p < 0.001$). Also, after having mapped with other chronic diseases and men's age, dyslipidaemia did not lose its significance. Namely, regardless of other factors studied, men with dyslipidaemia have a 15.80-fold higher chance of suffering from hypogonadism compared to men who do not have dyslipidaemia ($p < 0.001$).

Persons with adiposity have a 6.81-fold higher chance of developing hypogonadism, and this indicator is statistically significant ($p < 0.001$). Also, after having mapped with other chronic diseases and men's age, adiposity did not lose its significance. Namely, regardless of other factors studied, men with adiposity have a 2.75-fold higher chance of suffering from hypogonadism compared to men who do not have adiposity ($p < 0.001$).

Men with arterial hypertension have 6.08-fold higher odds of developing hypogonadism compared to men without this condition. This indicator is statistically significant ($p < 0.001$). After having mapped with other chronic diseases and men's age, arterial hypertension remained at same significance level. Namely, regardless of other factors studied, men with arterial hypertension have a 3.68-fold higher chance of suffering from hypogonadism compared to men who do not have this condition ($p < 0.001$).

Patients with metabolic syndrome have 8.99-fold higher odds of developing hypogonadism compared to men without metabolic syndrome. This indicator is statistically significant ($p < 0.001$). After having mapped with other chronic diseases and men's age, metabolic syndrome remained at same significance level. Namely, regardless of other factors studied, men with metabolic syndrome have a 4.66-fold higher chance of suffering from hypogonadism compared to men who do not have this condition ($p < 0.001$).

Patients with metabolic syndrome have 3.98-fold higher odds of developing hypogonadism. This indicator is statistically significant ($p < 0.001$).

After having mapped with other chronic diseases and men's age, this indicator is getting even higher. Namely, regardless of other factors studied, men with COPD have a 24.40-fold higher chance of suffering from hypogonadism compared to men without this condition ($p < 0.001$).

2.03-fold higher odds of developing hypogonadism has been established in patients with Type 2 diabetes mellitus, and this indicator is statistically significant ($p = 0.01$). After having mapped with other chronic diseases and men's age, a statistically significant association of T2CD with hypogonadism was found; namely, T2CD contribute about a 1.5-fold increase in the chance of developing hypogonadism ($p = 0.03$).

As regards the age of a person, we can see that its association with hypogonadism is also statistically significant ($p < 0.001$). Namely, regardless of whether a man has one of the chronic diseases, with an increase in age by one year, the chances for a patient to develop hypogonadism increases 1.13-fold, or by 13 %.

The study found that the dyslipidaemia and COPD increase the odds of developing hypogonadism the most (15.80- and 24.40-fold, respectively).

The median, mean value and standard deviation of testosterone depending on the status of chronic diseases has been studied. The results are shown in Tables 3.5 and 3.6.

Table 3.5

Median, mean value and standard deviation of total and free testosterone depending on the status of chronic diseases in persons without hypogonadism

Chronic disease		Total testosterone			Free testosterone		
		median	mean value	SD	median	mean value	SD
Dyslipidaemia	yes	3.90	4.21	1.17	78.00	81.25	12.25
	no	4.70	4.67	0.69	72.30	74.36	6.95
Adiposity	yes	3.90	4.21	1.22	76.90	80.95	12.53
	no	4.60	4.62	0.75	72.40	75.11	7.92
Arterial hypertension	yes	3.90	3.95	0.66	76.90	77.83	5.34
	no	4.60	4.64	0.83	72.40	75.63	9.10
Metabolic syndrome	yes	3.85	3.90	0.29	78.0	78.36	3.27
	no	4.60	4.59	0.84	72.40	75.78	8.92
COPD	yes	3.70	3.69	0.15	75.20	76.25	3.41
	no	4.60	4.60	0.83	72.40	75.83	8.97
Type 2 diabetes mellitus	yes	4.00	4.01	0.19	78.10	78.61	3.88
	no	4.60	4.59	0.84	72.40	75.74	8.95
No diseases		4.70	4.75	0.62	72.30	73.94	6.73

Table 3.6

Median, mean value and standard deviation of total and free testosterone depending on the status of chronic diseases in persons with hypogonadism

Chronic disease		Total testosterone			Free testosterone		
		median	mean value	SD	median	mean value	SD
Dyslipidaemia	yes	2.15	2.25	0.42	62.60	63.25	4.88
	no	2.55	2.68	0.59	65.88	64.57	5.35
Adiposity	yes	2.15	2.24	0.41	62.33	62.89	5.01
	no	2.35	2.41	0.53	64.68	64.06	4.91
Arterial hypertension	yes	2.15	2.22	0.40	62.80	62.49	4.44
	no	2.35	2.39	0.52	64.15	64.11	5.22
Metabolic syndrome	yes	2.05	2.09	0.30	59.88	60.98	4.92
	no	2.30	2.38	0.50	63.85	64.04	4.83
COPD	yes	1.95	2.12	0.41	61.45	63.61	3.80
	no	2.25	2.36	0.48	63.30	63.46	5.14
Type 2 diabetes mellitus	yes	2.13	2.29	0.55	62.68	62.50	6.26
	no	2.25	2.33	0.48	63.15	63.55	4.88
No diseases		3.45	3.55	0.30	60.75	62.24	6.05

As shown in the tables above, in both hypogonadal and eugonadal patients with dyslipidaemia, adiposity, arterial hypertension, metabolic syndrome, COPD and Type 2 diabetes mellitus both total and free testosterone levels are lower compared to the patients without these diseases ($p < 0.05$).

Using single and multiple factor analysis, the relationship between total testosterone and chronic diseases and age has been studied in this thesis. The results are represented in Table 3.7.

Table 3.7

Single and multiple factor analysis of the relationship between total testosterone and chronic diseases and age

Independent characteristic	**Regre-ssion coeffi-cient**	**95 % CI**	**p**	**Regression coefficient (condi-tioinal)**	**95 % CI**	**p**
Dyslipidaemia	– 1.64	– 1.53; – 1.75	< 0.001	– 1.18	– 1.06; – 1.30	< 0.001
Adiposity	– 1.12	– 0.97; – 1.26	< 0.001	– 0.36	– 0.24; – 0.48	< 0.001
Arterial hypertension	– 1.10	– 0.94; –1.25	< 0.001	– 0.47	– 0.35; – 0.59	< 0.001
Metabolic syndrome	– 1.18	– 0.96; – 1.40	<0.001	– 0.67	– 0.50; – 0.85	< 0.001
COPD	– 1.00	– 0.75; – 1.25	<0.001	– 1.18	– 1.01; – 1.36	< 0.001
Type 2 diabetes mellitus	– 0.56	– 0.25; – 0.88	0.001	0.007	– 0.22; 0.23	0.95
Age	– 0.03	– 0.03; – 0.04	<0.001	– 0.03	– 0.03; – 0.04	< 0.001

As shown in the table above, dyslipidaemia statistically significantly ($p < 0.001$) decreases the level of total testosterone by 1.64 units. After the mapping, the influence of dyslipidaemia on the level of testosterone slightly decreases, though remains statistically significant. Namely, regardless of other diseases and men's age, dyslipidaemia reduces the level of total testosterone by 1.18 units.

Adiposity statistically significantly ($p < 0.001$) decreases the level of total testosterone by 1.12 units. After the mapping, the influence of adiposity on the level of testosterone slightly decreases, though remains statistically significant. Therefore, regardless of other diseases and men's age, adiposity reduces the level of total testosterone by 0.36 units.

Arterial hypertension syndrome also statistically significantly ($p < 0.001$) decreases the level of total testosterone by 1.10 units. After the mapping, the influence of arterial hypertension on the level of total testosterone decreases, though remains statistically significant. Namely, regardless of other diseases and men's age, arterial hypertension reduces the level of total testosterone by 0.47 units.

Metabolic syndrome statistically significantly ($p < 0.001$) decreases the level of total testosterone by 1.18 units. After the mapping, the influence of metabolic syndrome on the level of total testosterone slightly decreases, though remains statistically significant. Namely, regardless of other diseases and men's age, metabolic syndrome reduces the level of total testosterone by 0.67 units.

Likewise, COPD statistically significantly ($p < 0.001$) decreases the level of total testosterone by 1.00 units. After the mapping, the influence of COPD on the level of total testosterone increases, and remains statistically significant. Namely, regardless of other diseases and men's age, COPD reduces the level of total testosterone by 0.18 units.

Type 2 diabetes mellitus has no statistically significant effect on the level of total testosterone ($p = 0.95$).

Concerning the men's age, it can be concluded that it also plays an important role in reducing the level of total testosterone. Namely, with an increase by one year of men's age, the level of total testosterone decreases by 0.03 units. In addition, this conclusion is statistically significant ($p < 0.001$).

Dyslipidaemia and COPD decreased the level of total testosterone the most: regardless of other diseases and men's age, these diseases decrease the level of total testosterone by 1.18 units.

The relationship between free testosterone and chronic diseases and age has been represented in Table 3.8.

Table 3.8

Single and multiple factor analysis of the relationship between free testosterone and chronic diseases and age

Independent characteristic	Regre-ssion coeffi-cient	95 % CI	p	Regression coefficient (condi-tioinal)	95 % CI	p
Dyslipidaemia	−5.86	−4.87; −6.85	< 0.001	−2.71	−1.64; −3.78	< 0.001
Adiposity	−4.53	−3.45; −5.60	< 0.001	−1.69	−0.57; −2.81	< 0.001
Arterial hypertension	−5.34	−4.20; −6.49	< 0.001	−2.52	−1.41; −3.64	< 0.001
Metabolic syndrome	−7.08	−5.49; −8.67	< 0.001	−6.77	−5.20; −8.34	< 0.001
COPD	−3.32	−1.49; −5.15	< 0.001	−4.58	−2.97; −6.19	< 0.001
Type 2 diabetes mellitus	−1.92	−4.20; −0.36	0.10	–	–	–
Age	−0.30	−0.25; −0.36	< 0.001	−0.34	−0.28; −0.39	< 0.001

Chronic diseases also influence free testosterone in a similar manner. As shown in the table above, dyslipidaemia statistically significantly ($p < 0.001$) decreases the level of free testosterone by 5.86 units. After the mapping, the influence of dyslipidaemia on the level of free testosterone decreases, though remains statistically significant. Namely, dyslipidaemia, regardless of other diseases and men's age, reduces the level of free testosterone by 2.71 units.

A similar effect of adiposity on free testosterone has been found. As shown in the table above, this disease statistically significantly ($p < 0.001$)

decreases the level of free testosterone by 4.53 units. After the mapping, the influence of adiposity on the level of free testosterone decreases, though remains statistically significant. Namely, adiposity, regardless of other diseases and men's age, reduces the level of free testosterone by 1.69 units.

Arterial hypertension statistically significantly ($p < 0.001$) decreases the level of free testosterone by 5.34 units. After the mapping, the influence of arterial hypertension on the level of free testosterone decreases, though remains statistically significant. Regardless of other diseases and men's age, arterial hypertension reduces the level of free testosterone by 2.52 units.

Metabolic syndrome also statistically significantly ($p < 0.001$) decreases the level of free testosterone by 7.08 units. After the mapping, the influence of metabolic syndrome on the level of free testosterone decreases, though remains statistically significant. Namely, regardless of other diseases and men's age, metabolic syndrome reduces the level of free testosterone by 6.77 units.

COPD statistically significantly ($p < 0.001$) decreases the level of free testosterone by 3.32 units. After the mapping, the influence of COPD on the level of free testosterone slightly increases, and remains statistically significant. Namely, regardless of other diseases and men's age, COPD reduces the level of free testosterone by 4.58 units.

Type 2 diabetes mellitus decreases the level of free testosterone by 1.92 units, but this indicator is not statistically significant. Since one-factor analysis of the influence of T2CD on testosterone level is not statistically significant, T2CD is not further included in the multiple factor analysis model.

Men's age also plays an important role in reducing the level of free testosterone. Namely, with an increase by one year of men's age, the level of free testosterone decreases by 0.34 units. In addition, this conclusion is statistically significant ($p < 0.001$).

3.5. Associations between Chronic Diseases and AMS Symptoms in Patients with Laboratory-Confirmed Hypogonadism

Using single and multiple factor analysis, the relationship between each symptom in the AMS questionnaire and chronic diseases and age in hypogonadal patients has been studied in this thesis.

A statistically significant association of the symptom "Decline in the overall well-being" with dyslipidaemia, metabolic syndrome, COPD and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, dyslipidaemia statistically significantly ($p < 0.001$) increases the likelihood of occurrence of the symptom "Decline in feeling of general well-being" almost 10 times. Metabolic syndrome increases these odds more than 6 times ($p < 0.001$), COPD – more than 3 times ($p < 0.001$), and T2CD – 2.5 times ($p = 0.001$). Patient's age has also a statistically significant role; after mapping with an increase in age by one year, the odds for the above symptom increase by 5 % ($p < 0.001$).

After the mapping with other diseases and the patient's age, a statistically significant association of the symptom "Joint pain and muscular ache" has been observed with dyslipidaemia only, namely, dyslipidaemia statistically significantly ($p < 0.001$) decreases the likelihood of occurrence of the symptom "Joint pain and muscular ache" more than 12 times (OR = 0.08).

A statistically significant association of the symptom "Excessive sweating" with dyslipidaemia, arterial hypertension, metabolic syndrome, and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, dyslipidaemia statistically significantly ($p < 0.001$) decreases the likelihood of occurrence of the symptom "Excessive sweating" about five times. Arterial hypertension increases these odds more than 33 times ($p < 0.001$), metabolic syndrome decreases the odds more than 250 times

($p < 0.001$), and T2CD decreases the odds more than 200 times ($p < 0.001$). The patient's age has no statistically significant association with this symptom.

A statistically significant association of the symptom "Sleep problems" with dyslipidaemia, arterial hypertension, COPD, and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, dyslipidaemia statistically significantly ($p < 0.001$) decreases the likelihood of occurrence of the symptom "Sleep problems" about five times. COPD increases these odds more than 20 times ($p < 0.001$), and T2CD – more than 112 times ($p < 0.001$). The patient's age has no statistically significant association with this symptom.

A statistically significant association of the symptom "Increased need for sleep, often feeling tired" with dyslipidaemia, arterial hypertension, COPD, and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, dyslipidaemia statistically significantly ($p < 0.001$) decreases the likelihood of occurrence of the symptom "Increased need for sleep, often feeling tired" about 7 times. COPD and T2CD increases the odds of occurrence of these symptoms: COPD increases them more than 111 times ($p < 0.001$), and T2CD – more than 83 times ($p < 0.001$). Patient's age has also a statistically significant role; after mapping with an increase in age by one year, the odds for the aforementioned symptoms increase by 5 % ($p = 0.03$).

A statistically significant association of the symptom "Irritability" with dyslipidaemia, arterial hypertension, metabolic syndrome, and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, dyslipidaemia statistically significantly ($p < 0.001$) decreases the likelihood of occurrence of this symptom about 2.5 times. Arterial hypertension and T2CD increases the odds of occurrence of this symptom more than 21 and 23 times, respectively ($p < 0.001$). Metabolic syndrome decreases the likelihood of occurrence of the symptom "Irritability" about 100 times ($p < 0.001$). The patient's age has no statistically significant association with this symptom.

A statistically significant association of the symptom “Nervousness” with dyslipidaemia, arterial hypertension, and metabolic syndrome has been observed after the mapping with other diseases and the patient’s age. Namely, dyslipidaemia statistically significantly ($p < 0.001$) decreases the likelihood of occurrence of the symptom “Nervousness” about 6.5 times. Arterial hypertension increases the odds of occurrence of this symptom more than 20 times ($p < 0.001$). Metabolic syndrome decreases the likelihood of occurrence of the symptom “Nervousness” 250 times ($p < 0.001$). The patient’s age has no statistically significant association with this symptom.

A statistically significant association of the symptom “Anxiety (feeling panicky)” with dyslipidaemia, arterial hypertension, and T2CD has been observed after the mapping with other diseases and the patient’s age. Namely, dyslipidaemia statistically significantly ($p < 0.001$) decreases the likelihood of occurrence of the symptom “Anxiety (feeling panicky)” about 10 times. T2CD increases the odds of occurrence of this symptom more than 375 times ($p < 0.001$). The patient’s age has also a statistically significant association with this symptom. Namely, with an increase in age by one year, the odds of a panic attack increase by 9 %, or 1.09 times ($p = 0.004$).

A statistically significant association of the symptom “Physical exhaustion/lacking vitality” with dyslipidaemia, adiposity, arterial hypertension, and metabolic syndrome has been observed after the mapping with other diseases and the patient’s age. Namely, arterial hypertension statistically significantly ($p < 0.001$) decreases the likelihood of occurrence of the symptom “Physical exhaustion / lacking vitality” about 10 times. Metabolic syndrome increases these odds more than 15 times ($p < 0.001$), dyslipidaemia – more than 2 times ($p = 0.003$), and adiposity – 1.5 times ($p = 0.01$). The patient’s age has no statistically significant association with this symptom.

A statistically significant association of the symptom “Decrease in muscular strength” with dyslipidaemia, arterial hypertension, metabolic

syndrome, COPD, and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, arterial hypertension statistically significantly decreases the likelihood of occurrence of this symptom about five times. Metabolic syndrome, COPD, and T2CD increase these odds more than 8.98, 6.55 and 19.97 times, respectively. Dyslipidaemia increases these odds more than 2 times ($p = 0.002$). The patient's age has no statistically significant association with this symptom.

A statistically significant association of depression with dyslipidaemia, arterial hypertension, metabolic syndrome, and COPD has been observed after the mapping with other diseases and the patient's age. Namely, arterial hypertension statistically significantly decreases the likelihood of occurrence of depression about ten times ($p < 0.001$). Metabolic syndrome and COPD statistically significantly ($p < 0.001$) increase these odds 15.30 and 4.25 times, respectively. Dyslipidaemia – more than 2 times. The patient's age also increases the probability of a symptom statistically significantly; with an increase in age by one year, the odds increase by 3 %.

A statistically significant association of the symptom "Feeling that you have passed your peak" with dyslipidaemia, adiposity, arterial hypertension, metabolic syndrome, and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, adiposity statistically significantly ($p < 0.001$) increases the likelihood of occurrence of the symptom "Feeling that you have passed your peak" more than 2.5 times. Metabolic syndrome increases these odds more than 8 times ($p < 0.001$), T2CD – more than 51 time ($p = 0.001$), dyslipidaemia – more than two times ($p = 0.008$); arterial hypertension decreases these odds about five times ($p < 0.001$). The patient's age has no statistically significant influence on the development of this symptom.

A statistically significant association of the symptom "Feeling burnt out, having hit rock-bottom" with arterial hypertension and metabolic syndrome has

been observed after the mapping with other diseases and the patient's age. Namely, arterial hypertension decreases the likelihood of occurrence of the symptom "Feeling burnt out, having hit rock-bottom" about five times ($p < 0.001$). Metabolic syndrome increases these odds almost 12 times ($p < 0.001$). With an increase in patient's age by one year, the odds of developing this symptom increases by 3 % ($p = 0.01$).

After the mapping with other diseases and the patient's age, a statistically significant association of the symptom "Decrease in beard growth" has been observed with arterial hypertension and adiposity only. Namely, arterial hypertension decreases the likelihood of occurrence of this symptom ten times ($p < 0.001$), and adiposity – about by half ($p = 0.02$). With an increase in patient's age by one year, the odds of developing this symptom increases by 4 % ($p = 0.002$).

A statistically significant association of the symptom "Decrease in ability/frequency to perform sexually" with dyslipidaemia, adiposity, arterial hypertension, metabolic syndrome, COPD, and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, dyslipidaemia increases the likelihood of occurrence of this symptom more than 5.5 times ($p < 0.001$), adiposity – more than six times ($p < 0.001$), arterial hypertension – almost three times ($p < 0.001$), COPD – almost 2.5 times. Metabolic syndrome and T2CD increase the odds of developing this symptom the most, about 33.5 and 25.5 times, respectively. With an increase in patient's age by one year, the odds of developing this symptom increases by 2 % ($p = 0.03$).

A statistically significant association of the symptom "Decrease in the number of morning erections" with dyslipidaemia, arterial hypertension, metabolic syndrome, COPD, and T2CD has been observed after the mapping with chronic diseases and the patient's age. Namely, dyslipidaemia increases the likelihood of occurrence of this symptom more than 5 times ($p < 0.001$), arterial hypertension – more than three times ($p < 0.001$), COPD – more than

four times. Metabolic syndrome and T2CD increase the odds of developing this symptom the most, about 7 and 16.6 times, respectively. With an increase in patient's age by one year, the odds of developing this symptom increases by 2 % ($p = 0.004$).

A statistically significant association of the symptom "Decrease in sexual desire / libido" with dyslipidaemia, adiposity, arterial hypertension, metabolic syndrome, COPD, and T2CD has been observed after the mapping with other diseases and the patient's age. Namely, dyslipidaemia increases the likelihood of occurrence of this symptom more than 7 times ($p < 0.001$), adiposity – more than 2 times ($p < 0.001$), arterial hypertension – almost 2 times ($p < 0.001$), COPD – almost 50 times ($p < 0.001$), metabolic syndrome – almost 12.5 times ($p < 0.001$), and T2CD – almost 16.5 times ($p < 0.001$). The patient's age has no statistically significant influence on the development of this symptom.

4. DISCUSSION

4.1. Early Diagnostic Criteria of Age-Associated Androgen Deficiency with an Underlying Pathology

Based on the results of our research, there is an opportunity to offer an algorithm for early and timely detection of men's LOH. We have divided early detection criteria of LOH into general and particular. General criteria are the total and free testosterone levels determined at laboratory; furthermore, in accordance with the obtained data, clinical manifestation of hypogonadism develops when total testosterone median level is 2.32 ng/ml and free testosterone median level is 65.4 pg/ml.

If a patient has such testosterone level, clinical manifestation of LOH is developing along with the studied somatic diseases. Particular criteria are LOH symptoms significantly affected by the patient's comorbidities.

- If a patient has arterial hypertension characterised by target organ damage, LOH has the following cardinal symptoms: sweating, irritability, anxiety, decreased libido, decrease of the frequency of sexual intercourses, decrease of the frequency of morning erection.
- In the case of obesity, cardinal symptoms of LOH are decreased libido, decrease of the frequency of sexual intercourses, decrease of the frequency of morning erection, increased feeling that "you have passed your peak", increased physical exhaustion/lacking vitality.
- In a patient with Type 2 diabetes mellitus, cardinal symptoms of LOH are worsening of general well-being, difficulties falling asleep and daytime somnolence, irritability, panic attacks, feeling that "you have passed your peak", decreased libido, decrease in the frequency of morning erection, and decrease in the frequency of sexual intercourses.

- In patients with dyslipidaemia the cardinal symptoms of LOH are decreased libido, decrease of the frequency of sexual intercourses, decrease of the frequency of morning erection, worsening of general health condition, increased physical exhaustion/lacking vitality, muscle weakness, depression, feeling that "you have passed your peak".
- With metabolic syndrome as comorbidity, LOH is characterised by the following symptoms: worsening of general well-being, physical exhaustion/ lacking vitality, decrease in muscular strength, depression, feeling that "you have passed your peak", feeling burnt out, having hit rock-bottom, decreased libido, decrease in the frequency of morning erection, and decrease in the frequency of sexual intercourses.
- In patients with COPD, cardinal symptoms of LOH are worsening of general health condition, insomnia, increased need for sleep, often feeling tired, muscle weakness, depression, decrease in the frequency of morning erection, decrease in the frequency of sexual intercourses, decreased libido.

4.2. Mutual Interaction of LOH and Comorbidities

With the age, men's body is undergoing changes that lead to the decrease in concentration of testosterone: decrease in the number of testosterone-synthesising Leydig cells in testes, decrease in the density of luteinising hormone receptors, impairments in the controlling communication of the hypothalamic-pituitary system, the enzyme that ensures testosterone metabolic synthesis pathway, and decrease in concentration and activity. With the reduction of testosterone level, chronic diseases start to develop in men's body (Lester, Mason, 2015; Isidori et al., 2005; Scweiger et al., 1999; Jockenhovel, 2004). On the other hand, chronic diseases can cause testosterone deficiency, or speed up its development. For example, in patients with visceral

adiposity, fat cells synthesise biologically active substances, which, being involved in metabolic processes, reduce testosterone synthesis as a result (*Butrova*, 1999; *Požarskis, Ērenpreiss*, 2010). In men with reduced libido or erectile dysfunction, the frequency of sexual intercourses is reduced, which, in turn, increases the testosterone deficiency even more. It forms a vicious circle: testosterone deficiency causes chronic concomitant diseases, and concomitant diseases increase the testosterone deficiency even more.

In this study, we focus directly on the question of which the clinical and biochemical peculiarities are observed in the case of diseases such as arterial hypertension, adiposity, dyslipidaemia, metabolic syndrome, Type 2 diabetes mellitus and COPD. We established hypogonadism in 79 % of these men. Until now, there were very little data on the prevalence of hypogonadism in men with each of these diseases. What is more, in men without aforementioned diseases, hypogonadism was found only in 4.7 % of all cases. Out of 1222 subjects (both with and without aforementioned diseases) we established hypogonadism in 54.7 % of these men. In the European Male Ageing Study (EMAS), LOH has been diagnosed only in 17 % of men aged 40 to 70 years. This difference may be linked to the fact that our study comprised men who referred to physicians mostly due to various diseases, but the EMAS study has investigated a general male population.

4.3. LOH and Arterial Hypertension

Arterial hypertension was established in 26 % of all the participants (n = 1222) and 39 % of the subjects with concomitant diseases (n = 820). Only 40 patients (3.3 % of all study subjects and 4.9 % of patients with concomitant diseases) had arterial hypertension as an isolated disease, while in the rest of the subjects, it was combined with other diseases studied. We have stated that

LOH is found in patients with hypertension more frequently than in normotensive patients. Men with arterial hypertension have 3.68-fold higher odds of developing hypogonadism compared to men without this condition. Regardless of other diseases and men's age, arterial hypertension decreases the level of both total and free testosterone by 0.47 and 2.52 units, respectively. Although the literature data give evidence on the connection of LOH in patients with metabolic syndrome and its components, i.e., adiposity or dyslipidaemia (Blaya et al., 2016), as well as the connection of testosterone deficiency with cardiovascular diseases and mortality risk (Lester, Mason, 2015), there have been too limited data on the prevalence of hypogonadism in patients with arterial hypertension until now. European Male Ageing Study (launched in 2003) has investigated health, chronic diseases, and the level of sex steroids in over 3000 men in the age group of 40 to 79 years. It was found that arterial hypertension was diagnosed in 28 % of the study participants (both hypogonadal and eugonadal). In patients with hypogonadism, systolic blood pressure was statistically significantly increased, but diastolic did not change (Tajar et al., 2012). Similar results have been obtained by the Massachusetts Male Aging study in the USA. In this study, arterial hypertension has been found in 36 % of all the patients. It was demonstrated that in patients with hypogonadism both systolic and diastolic blood pressure is higher than in patients with normal testosterone level (Feldman et al., 1994). In our study, arterial hypertension was observed almost as frequently as in the studies described above. Our study data are in line with the studies described above also in the section presenting evidence that testosterone deficiency is more frequently observed in patients with arterial hypertension compared with those without hypertension. The median value of total and free testosterone in men with hypogonadism and arterial hypertension in our study was 2.15 ng/ml and 62.80 pg/ml, respectively, which is low; with this testosterone level, the clinical features of LOH, especially the symptoms of sexual dysfunction, such as

decrease in sexual desire/libido, decrease in the frequency of sexual intercourses, and decrease in the number of morning erections, become broadly evolved. The presence of these symptoms markedly reduces the quality of life of the patients and leads to the secondary neurotic disturbances: adaptation impairment. World literature mainly describes arterial hypertension and LOH issues from the other point of view. For example, European Male Ageing Study results describe the average blood pressure in patients without hypogonadism, with moderate and severe hypogonadism, but the study does not focus exactly on the average testosterone indicators in all the patients with arterial hypertension and LOH. Our study describes the issue from this point of view for the first time: at which testosterone levels broad clinical features of LOH develop in the patients with arterial hypertension, and which AMS questionnaire symptoms are more common in these patients.

4.4 LOH and Obesity

Adiposity was diagnosed in 33 % of all study participants (n = 1222) and in 49.6 % of participants with concomitant diseases (n = 820). Adiposity as an isolated disease was not established in any patient; it was always combined with other studied diseases. We have discovered that LOH is observed more frequently in patients with adiposity than in those with normal weight. This is in line with the literature data. Several studies have demonstrated a direct correlation of testosterone deficiency with adiposity. For example, European Male Ageing Study has demonstrated that patients with LOH have an increased body mass index and/or waist circumference. In addition, a direct correlation between body weight and testosterone indicators has been revealed. If body weight has been decreased by more than 10 %, total testosterone level has increased by 2.9 nmol/L on average; if body weight has been increased by more

than 10 %, total testosterone level has decreased by 2.4 nmol/L on average. If body weight has been changed in the range of up to 10 %, the changes in testosterone level were not statistically significant (Lester, Mason, 2015). The connection of LOH with adiposity has also been referred to in other authors' publications. On the one hand, testosterone deficiency causes fat accumulation in the men's body; on the other hand, fat cells produce active substances that reduce the synthesis of testosterone (*Butrova*, 1999). As a result of this bilateral process, man's health condition is deteriorating progressively, and adiposity complications occur: metabolic syndrome, Type 2 diabetes mellitus, arterial hypertension, coronary heart disease (Phillips et al., 1994; Simon et al., 1997; Ohlsson et al., 2011). In our study we concluded that men with adiposity have a 2.75-fold higher chance of suffering from hypogonadism compared to men who do not have adiposity ($p < 0.001$). We also indicated that regardless of other diseases and men's age, adiposity statistically significantly ($p < 0.001$) decreases the level of both total testosterone by 0.36 units, and free testosterone by 1.69 units. In this part, our study data also coincide with the European Male Ageing Study, where a direct correlation between body weight and testosterone levels has been found.

In our study, we focus on the question at which testosterone indicators patients with adiposity develop clinical manifestation of LOH. In our study, the median total testosterone level in patients with LOH and adiposity was 2.15 ng/ml, and median free testosterone level was 62.33 pg/ml, that is sufficiently low to develop a broad spectrum of LOH symptoms. All symptoms of sexual dysfunction mentioned in the AMS questionnaire are often found in patients with adiposity: decreased libido, decrease of the frequency of sexual intercourses, decrease of the frequency of morning erection, which is the evidence of worsening of these men's quality of life. In earlier epidemiological studies, the values of body mass index and waist circumference in LOH patients have been outlined (European Male Ageing Study) in the case of

moderate and severe LOH, but the issue of the average testosterone values in patients with adiposity, as well as the peculiarities of clinical features of LOH in these patients have not been widely described. The research of these indicators is a strong point of our study; clinical and biochemical characteristics of LOH in men with adiposity have been investigated for the first time in Latvia. The proportion of adiposity in men aged 40–70 (33 %) in our study is similar to the study data from the clinical trials in Europe and in the United States. In these studies, obesity in men aged 40 years and older has been found in 23.9 % and 40 % of the cases, respectively. This may be explained by the fact that "western" eating habits are spreading increasingly in Latvia: more fast food is used.

4.5 LOH and Type 2 Diabetes Mellitus

As previously stated, Type 2 diabetes mellitus was diagnosed in 5.5 % of all study participants (both with and without comorbidities, n = 1222) and in 8.2 % of participants with concomitant diseases (n = 820). Our data are similar to the findings of European Male Ageing Study, where Type 2 diabetes has been stated in 6.6 % of men over 40 years of age. We diagnosed LOH in 67.2 % of the patients with Type 2 diabetes mellitus. A statistically significant association of T2CD with hypogonadism was observed ($p = 0.03$), namely, T2CD increases the odds of developing hypogonadism approximately 1.5 times, but no statistically significant influence of T2CD on the levels of total and free testosterone ($p = 0.10$, $p = 0.95$) was found. However, high proportion of LOH in T2CD patients is in line with the literature data mentioning that testosterone deficiency increases the risk of development of metabolic syndrome and Type 2 diabetes mellitus (Simon et al., 1997; Ohlsson et al., 2011). In a study, in which 103 male patients with Type 2 diabetes

mellitus were involved, Dhindsa with co-authors have found that hypogonadism had occurred in 33 % of men. A statistically significant correlation between body mass index and free testosterone level has been proven; the higher the BMI, the lower the free testosterone level (Dhindsa et al., 2004). Chandel with co-authors has studied the concentration of testosterone in 38 young men (mean age 26.45 ± 0.89 years) with Type 1 diabetes mellitus and 24 young men (mean age 27.87 ± 0.97 years) with Type 2 diabetes mellitus. Hypogonadism has been established in 58 % of patients with T2CD. In Type 1 CD patients, hypogonadism has been established in 8 % of the cases only. The authors concluded that the level of testosterone is lower in T2CD patients compared to Type 1 CD patients, and the prevalence of hypogonadism is very high in T2CD patients (Chandel et al., 2008). Similar results have also been obtained by Tomar with co-authors. The study comprised of 15 patients with Type 1 CD patients and 50 patients with Type 2 CD revealed that the levels of testosterone and free testosterone in patients with Type 1 CD were within the normal range, while in patients with Type 2 CD, total testosterone level was decreased in 48 % of the cases, and free testosterone level – in 26 % of the cases. Consequently, hypogonadism is common in T2CD patients, but not in men with Type 1 CD (Tomar et al., 2006).

The novelty of our study is the way we studied the average testosterone values when LOH manifests clinically in patients with Type 2 diabetes mellitus, as well as how we clarified the most specific symptoms of LOH in this patient group. Similarly as in patients with arterial hypertension and obesity, all the symptoms of sexual dysfunction are expressed in patients with Type 2 diabetes mellitus; moreover, panic attacks, a serious symptom of a psychiatric disorder, was denoted in this group of patients. This symptom may be both of organic nature caused by the diabetic angiopathy, atherosclerosis, and hypertensive encephalopathy due to impaired blood circulation in the brain,

and of psychological nature as a manifestation of adaptation impairment as a reaction to sexual dysfunction and worsening of general well-being. This is the evidence in patients with Type 2 DM and LOH, the quality of life is significantly reduced, and they may require special (psychiatric) treatment.

The fact that our study revealed no statistically significant influence of T2CD on total and free testosterone levels, which is different from other studies conducted elsewhere in the world, can be explained by a relatively small number of T2CD patients enrolled in the study.

4.6. LOH and Dyslipidaemia

Dyslipidaemia was diagnosed in 55.7 % of all study participants (both with and without comorbidities, n = 1222), and in 83 % of men with concomitant diseases (n = 820). In 157 cases, dyslipidaemia was an isolated disease, in other cases it was combined with other diseases studied. The figures of prevalence of dyslipidaemia are similar to the study data described in literature. In Massachusetts Male Aging Study, dyslipidaemia was diagnosed in 55 % of men aged 40 to 79 years. In European Male Ageing Study, dyslipidaemia has not been investigated separately; a group of patients with "One or more concomitant diseases", including CHD, arterial hypertension, dyslipidaemia and others, has been distinguished. Various study data reveal a direct correlation of hypogonadism with dyslipidaemia. For example, the Telecom Study and the Rancho Bernardo Study show that lower level of testosterone is associated with higher LDL and triglyceride levels, and lower HDL level (Simon et al., 1997; Laughlin et al., 2008). Other authors have also noted the relationship between dyslipidaemia, metabolic syndrome, and LOH in their publications, as well as TRT as an effective method of treatment of metabolic syndrome and its components (Winter et al., 2014).

In some smaller studies, the authors have not revealed the correlation between dyslipidaemia and LOH. For example, Ponholzer and co-authors have described a study that enrolled 247 patients with LOH of an average age of 75.8, and, although the trend toward lower levels of testosterone has been found in patients with cardiovascular risk factors, this difference was not statistically significant (Ponholzer et al., 2010). Perhaps this is due to the small number of participants in the study.

Our study data are in line with the large study data; dyslipidaemia has been observed more frequently in men with hypogonadism than in eugonadal patients. We established that, regardless of other chronic diseases and men's age, patients with dyslipidaemia have a 15.80-fold higher chance of suffering from hypogonadism compared to men who do not have dyslipidaemia ($p < 0.001$). We also proved that, regardless of other diseases and men's age, dyslipidaemia decreases the levels of both total and free testosterone by 1.18 and 2.71 units, respectively. Such a significant role of dyslipidaemia could be explained by its involvement in the pathogenesis of several pathological processes, for example, in the development of metabolic syndrome, or endothelial dysfunction.

The strength of our study is the way how we investigated clinical and biochemical peculiarities of LOH in men with dyslipidaemia. Median values of total and free testosterone levels in patients with dyslipidaemia and LOH were 2.15 ng/ml and 62.60 pg/ml, respectively. These indicators are quite low in order to develop clinical symptoms of LOH: decrease in sexual desire / libido, decrease in ability / frequency to perform sexually, decrease in the number of morning erection, depression, decrease in muscular strength, feeling burnt out, having hit rock-bottom, feeling that you have passed your peak, and decline in feeling of general well-being. These symptoms are not specific; however, they help to identify the patients with dyslipidaemia who shall be examined with regard to hypogonadism.

4.7. LOH and Metabolic Syndrome

We have revealed metabolic syndrome in 11.4 % of all the study participants (n = 1222), and in 17 % of participants with concomitant diseases (n = 820). Metabolic syndrome was found more frequently in patients with reduced testosterone levels than in eugonadal men. Data obtained in this part of our study data are in line with data described in literature. Wide epidemiological studies enrolling men over 40 years of age, e.g., Massachusetts Male Aging Study, European Male Ageing Study showed an increased prevalence of metabolic syndrome in men with testosterone deficiency (Feldman et al., 1994; Lester, Mason, 2015). Meta-analysis of the data of 20 studies indicate that metabolic syndrome is associated with LOH, and TRT has a positive effect on metabolic control and central adiposity (Corona et al., 2011). Although, these studies investigate the issue from the other point of view; for example, European Male Ageing Study has described the percent of males with moderate or severe hypogonadism, in which metabolic syndrome occurs. In our study, we focus on the question at which testosterone values patients with metabolic syndrome develop typical clinical features of LOH, and we studied the peculiarities. This is the novelty and the strength of our study. Symptoms that are most frequently found in patients with metabolic syndrome and LOH are as follow: decline in feeling of general well-being, physical exhaustion, decrease in muscular strength, depression, feeling that you have passed your peak, feeling burnt out, having hit rock-bottom, decreased libido, decrease in the frequency of morning erection, and decrease in the frequency of sexual intercourses.

The study revealed that metabolic syndrome decreases free testosterone level to the greatest extent compared to other diseases studied; by 7.08 units. After the mapping, the influence of metabolic syndrome on the level of free

testosterone decreases, though remains statistically significant. Namely, regardless of other diseases and men's age, metabolic syndrome decreases free testosterone level by 6.77 units. This can be explained by the fact that several pathogenetic mechanisms causing hypogonadism are enabled in patients with metabolic syndrome: both overweight, and lipid metabolism disorders, and glucose metabolism disorders. The evidence of correlation of these factors with testosterone deficiency is widely described in literature (Phillips et al., 1994; Simon et al., 1997; Laughlin et al., 2008; Ohlsson et al., 2011). Consequently, patients with metabolic syndrome shall be vigilant early, already at 40 years of age, concerning the possible development of LOH.

4.8. LOH and COPD

COPD was diagnosed in 8.8 % of all study participants (n = 1222) and in 13 % of men with concomitant diseases (n = 820). In patients with COPD, testosterone level was statistically significantly lower compared with patients without concomitant diseases. Compared to other diseases studied, COPD was found to increase the odds of development of hypogonadism to the greatest extent (24.4-fold); the total testosterone level decreases along with dyslipidaemia to the greatest extent (by 1.18 units), and is the second cause of decrease of free testosterone level after metabolic syndrome. COPD reduces the free testosterone level by 4.58 units. This is in line with the literature data. Karakou with co-authors compared testosterone level in 69 patients with COPD and the control group; testosterone level in patients with COPD was statistically significantly lower (Karakou et al., 2013). Similar results have been obtained by Vertkin with co-authors. In addition, a direct correlation between testosterone level and the severity of COPD has been observed: the lower the testosterone level is, the more severe the symptoms of COPD are (Vertkin,

2013). In a study comprising 70 patients with COPD, the Turkish researcher Kahraman with co-authors has discovered prevalent erectile dysfunction and lower testosterone level, but the difference in testosterone level was not statistically significant compared with the control group (Kahraman et al., 2013). Meta-analysis of 2918 patients has shown that in 9 studies involving patients with COPD, testosterone concentration was lower compared with the control group. However, these studies did not involve a large number of participants (Atlantis et al., 2013). In their review article, Balasubramanian and Naing note that hypogonadism is found in COPD patients in 22–69 % of the cases, and is associated with other systemic problems: osteoporosis, depression, and muscle weakness. Such a significant importance of COPD in developing hypogonadism and decreasing testosterone levels may be due to hypoxia caused by this disease, which in turn interferes with the supply of oxygen to both the testicles and the CNS, and harms the synthesis of testosterone.

However, some recent studies, according to the author's data, provide controversial information on the aforementioned facts. The difference in results may be related to the small number of participants in the study, and the selection criteria. Data on the efficacy of TRT in COPD patients are controversial and need to be further explored (Balasubramanian, Naing, 2012). After studying 140 COPD patients with an average age of 67.4 ± 10.1 years, Mousavi and co-authors found that hypogonadism occurred in 58.6 % of men. The researchers have proved that there is a correlation between testosterone level and the severity of COPD: the lower the testosterone level is, the more severe COPD is (Mousavi et al., 2012).

In large epidemiological studies involving men over 40 years of age, such as Massachusetts Male Aging Study, European Male Ageing Study, the prevalence of COPD and its association with testosterone deficiency has not been studied.

In our research we explored not just the prevalence of COPD in Latvian patients over 40 years of age at several general physicians' and physicians-sexologists' practices, but also the mean values of testosterone, at which the clinical manifestation of LOH occurs, as well as the peculiarities of clinical manifestation in these patients for the first time. The effect of COPD on hypogonadism and on total and free testosterone level has also been studied. Symptoms typical in patients with COPD and LOH are not specific; however, they worsen men's quality of life and show the necessity to ensure them high-quality medical care.

5. CONCLUSIONS

1. Late-onset hypogonadism was laboratory-diagnosed in 79 % of patients with signs of late-onset hypogonadism in accordance with the "Male Aging Questionnaire" and with concomitant diseases (arterial hypertension, adiposity, dyslipidaemia, metabolic syndrome, Type 2 diabetes mellitus, COPD).
2. Late-onset hypogonadism was diagnosed in 4.7 % of patients with signs of late-onset hypogonadism in accordance with the "Male Aging Questionnaire" and without the aforementioned concomitant diseases.
3. In patients with arterial hypertension, dyslipidaemia, obesity, metabolic syndrome, or COPD, serum testosterone levels were found lower in comparison to the control group. In addition, the most significant decrease was observed in cases of dyslipidaemia, metabolic syndrome, and COPD. Namely, dyslipidaemia and COPD decreased total testosterone concentration by 1.18 units ($p < 0.001$), while the decrease in free testosterone levels was most commonly caused by metabolic syndrome and COPD: by 6.77 and 4.58 units, respectively. No statistically significant effect of Type 2 diabetes mellitus on testosterone concentration was found.
4. Arterial hypertension, dyslipidaemia, obesity, metabolic syndrome, COPD, and Type 2 diabetes mellitus increase the odds of developing hypogonadism.
5. For each disease – arterial hypertension, dyslipidaemia, adiposity, metabolic syndrome, Type 2 diabetes mellitus, and COPD – different AMS questionnaire symptoms were typical; yet, the common symptoms of all clinical entity studied were connected with sexual dysfunction ($p < 0.001$).

6. Mean and median AMS questionnaire score in persons with dyslipidaemia, adiposity, arterial hypertension, COPD, metabolic syndrome, and T2CD is lower compared to the persons without chronic diseases ($p < 0.05$).

6. PRACTICAL RECOMMENDATIONS AND IMPLEMENTATION

1. Patients aged 40 years or over, having arterial hypertension, or adiposity, or dyslipidaemia, or metabolic syndrome, or Type 2 diabetes mellitus, or COPD, shall perform the screening of gonadal function condition and of its worsening, in order to prescribe a corrective testosterone replacement therapy, if necessary.
2. Treatment and prevention of men's adiposity shall be dealt with actively; reduction of body weight will help to avoid the development of LOH.
3. General physicians shall pay special attention to patients with metabolic syndrome, dyslipidaemia, and COPD, as these patients belong to a group with a high risk of development of an expressed LOH syndrome.
4. Diagnostics of age-induced androgen deficiency shall be based not just on determining the level of testosterone, but also on the analysis of clinical features. Clinical symptoms of age-induced androgen deficiency are specified by patients' comorbidities.
5. LOH diagnostic criteria with arterial hypertension, adiposity, dyslipidaemia, metabolic syndrome, Type 2 diabetes mellitus, and COPD as comorbidities have been developed.
6. These criteria are necessary to use in general practitioners' practices, thereby improving the medical care for men with somatic pathology.

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