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MEN'S HEALTH PROBLEMS IN CARDIOLOGY

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Men's health problems in cardiology

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**The physician should have the sight of a falcon,
the hands of a girl, the wisdom of a snake,
and the heart of a lion.**

*Avicenna (980–1037 AD)
philosopher, physician and scientist*

Table of contents

Abbreviations	VII
Introduction.....	1
Chapter 1. Men's health as an important factor in the demographic situation.....	5
Chapter 2. Metabolic risk factors as a link in men's health issues	11
Chapter 3. Erectile dysfunction as an interdisciplinary issue	29
Chapter 4. Androgen deficiency in men: the systemic effects of hormone replacement therapy.....	45
Chapter 5. Consensus on the diagnosis and treatment of erectile dysfunction, androgen deficiency and CVD	69
Conclusion	81
Appendix 1. 10-year prognosis for developing fatal cardiovascular events; European SCORE (Systematic COronary Risk Evaluation) Scale	83
Appendix 2. Scale for determining erectile function (International Index of Erectile Function)	85
Appendix 3. Questionnaire for the assessment of androgen status in men (AMS Questionnaire).....	97

Abbreviations

AO	Abdominal Obesity
AHA	American Heart Association
BP	Blood Pressure
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
ED	Erectile Dysfunction
FSH	Follicle-Stimulating Hormone
HDL Cholesterol	High-Density Lipoprotein Cholesterol
IGT	Impaired Glucose Tolerance
IHD	Ischaemic Heart Disease
IIEF	International Index of Erectile Function
IR	Insulin Resistance
LDL Cholesterol	Low-Density Lipoprotein Cholesterol
LH	Luteinizing Hormone
MetS	Metabolic Syndrome
PDE5	Phosphodiesterase Type 5
PSA	Prostate-Specific Antigen
SHBG	Sex Hormone Binding Globulin
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
WHO	World Health Organization

Introduction

According to the *World Health Organisation* (WHO), male life expectancy in Russia is 63 years, 12 years less than female life expectancy. Thirty seven percent of the total mortality among men relates to complications from cardiovascular disease (CVD). Russian men have the highest mortality from CVD among European countries. This is largely due to the socio-economic situation in Russia and delays in the detection and management of risk factors. To date, nearly 200 cardiovascular risk factors have been identified, which are divided into several groups: behavioural, biological and environmental. There are seven important risk factors which make the greatest contribution to the development of CVD: hypertension, hypercholesterolemia, smoking, obesity, alcohol, diabetes, and sedentary lifestyle. In general, these risk factors contribute both to the development of CVD and other non-communicable diseases. In addition, these risk factors tend to be coalesce. In 1988, an American scientist, Gerald Reaven, theorized on the relationship between arterial hypertension, dyslipidaemia and impaired glucose tolerance (IGT). According to Reaven, insulin resistance (IR) / hyperinsulinemia is a binding link between these disorders. In recent years, publications regarding the connection between metabolic syndrome (MetS), erectile dysfunction (ED) and androgen deficiency have started to appear. On the one hand, low testosterone levels when accompanied by ED and reduced libido are associated with IR, abdominal obesity, and lipid metabolism disorders. In particular, patients with hypogonadism, when compared with individuals with obesity and normal weight, have significantly increased IR / hyperinsulinemia. On the other hand, in men with ED and MetS,

when compared with those with ED and without MetS, total testosterone levels are four times lower. A similar pattern is observed in free testosterone levels. Stepwise regression analysis shows that metabolic risk factors occupy a dominant position among the main risk factors in the progression of ED.

Thus, metabolic risk factors act as a link between the development of CVD, ED and androgen deficiency.

However, according to the *Institute of Preventive Medicine* at the University of Lisbon, 76% of general practitioners do not consult on sexual disorders or their treatment. Similarly, 32% of doctors say that there is no time, and 24% do not have the appropriate knowledge.

In 2012, the *American Heart Association* (AHA) issued guidelines on sexual activity and CVD. These guidelines were prepared by experts using published articles, the *Princeton Consensus (Expert Panel)* recommendations, and guidelines on physical activity from the *European Society of Cardiology*. In the AHA guidelines, the acute cardiovascular effects of sexual activity were examined. The possibilities and limitations of sexual activity within CVD were presented, covering conditions such as stable angina (Stable Ischemic Heart Disease), unstable angina, post-myocardial infarction, heart failure, heart valve disease and hypertrophic cardiomyopathy. The impact of cardiovascular medications on sexual function, as well as the possibility of using Phosphodiesterase Type 5 (PDE5) inhibitors in combination with cardiac medications, were also explored.

In general, to prevent complications in these diseases, it is necessary to develop interdisciplinary algorithms for integrated diagnosis and treatment of individuals at high cardiovascular risk, and metabolic disorders, and sexual dysfunction and / or hypogonadism.

This publication takes a first step in bringing together the pathologies which traditionally occur in cardiology, endocrinology and urology.

The guidance in this book covers the demographic situation in the male population of Russia, the role of CVD, diseases of the prostate, sexual dysfunction and androgen deficiency in reducing quality of life and life expectancy. It provides current views on MetS, the role of lifestyle changes and strategies for medical management. ED is presented as an interdisciplinary problem, with contemporary views on the role of cardiovascular risk factors in its development, diagnostic

algorithms, and the use of PDE 5 inhibitors, including people at cardiovascular risk. There is a detailed explanation of the prevalence, clinical picture of androgen deficiency and its connection with other medical conditions. A meta-analysis of clinical studies on the systemic effects of hormone replacement therapy with the use of testosterone is included, and questions of how safe it is in long-term use are explored. A separate chapter is devoted to a consensus approach on the diagnosis and treatment of ED, androgen deficiency and CVD. We also present the results of our epidemiological and clinical studies. In the appendix there are three scales: the European SCORE scale to determine the 10-year prognosis for development of fatal cardiovascular events, a scale of erectile function (International Index of Erectile Function (IIEF)), and a questionnaire to assess androgen status in men (AMS Questionnaire).

This publication is aimed at cardiologists, urologists, andrologists, endocrinologists, general practitioners, family physicians and clinical interns.

I would like to thank my friends, Anna and Richard Williams, for the preparation of the English version of this book.

The author gratefully accepts all suggestions and comments by email: mmamedov@mail. A PDF version of the book is available at www.cardioprogress.ru

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Chapter 1

**MEN'S HEALTH AS AN IMPORTANT FACTOR
IN THE DEMOGRAPHIC SITUATION**

Currently, global demographics, including within Russia, are increasingly discussed, and it is not without good reason. For the past 20 years, disability and mortality among people of working age have grown notably. This applies principally to demographics among men [1]. According to the WHO, male life expectancy in Russia is 63 years old, 12 years less than female life expectancy. A meta-analysis of epidemiological studies conducted in six countries (Japan, USA, Mexico, Argentina, Hungary, Russia) shows that the greatest number of deaths among men at different ages occur in Russia (Table 1.1). At the age of 65–74 years and 75–84 years, the numbers are 6,292 and 11,920 per 100,000 men, which is two times higher than in Japan and the United States [2]. If we look at the distribution of mortality rates over time (by years) for Russia since 1985, there have been significant fluctuations in total and CVD mortality, depending on external factors

**Table 1.1. All-cause mortality among men in 6 countries
(based on 100,000 people)**

Countries	65–74 years	75–84 years
Japan	2387	6930
Mexico	3133	6715
USA	3191	7116
Argentina	3880	8506
Hungary	5590	11612
Russian Federation	6292	11920

(similar for both men and women). The collapse of the Soviet Union and the subsequent socio-economic reforms of the early 1990s, and the economic recession in 1998, led to a significant exacerbation of psychosocial stress, drastic impoverishment of the general population, an increase in alcohol consumption and, consequently, the growth of total and cardiovascular mortality (Figure 1.1) [3]. WHO experts predict an increase in the incidence of non-communicable diseases of 40–50%, mainly from CVD (myocardial infarction and cerebral stroke) (Figure 1.2), largely due to high cardiovascular risk [4]. In general, Russia is a country of high cardiovascular risk and, at the current time, the number of individuals with high cardiovascular risk is 36 million (20% of the total population). 37% of total mortality among Russian men results from complications of CVD which, of course, is one of the determining factors of life expectancy and quality of life (Figure 1.3) [5].

In recent decades a new terminology of sexual medicine has emerged. This primarily includes diseases related to sex and the sexual characteristics of various diseases. Traditionally, the concept of men's

Figure 1.1. Trends in mortality in Russia between 1985-2003

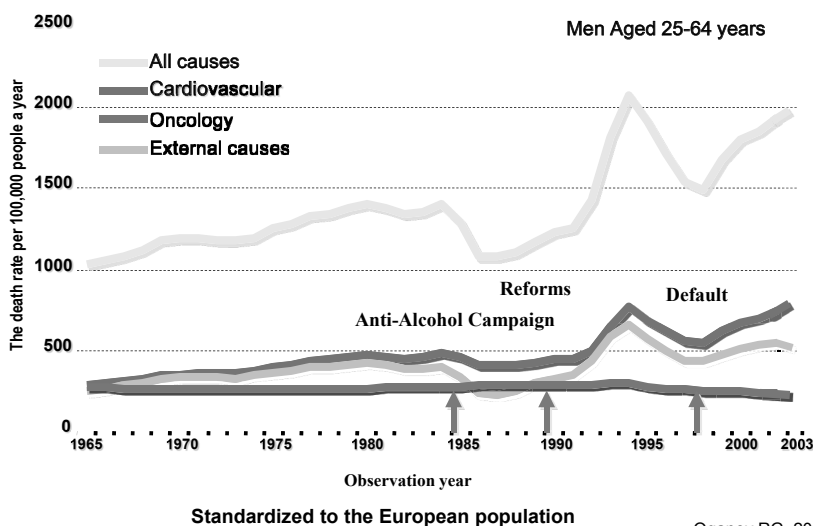
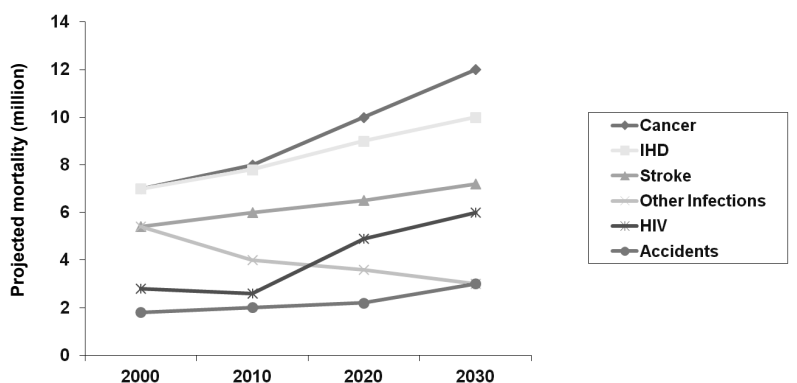


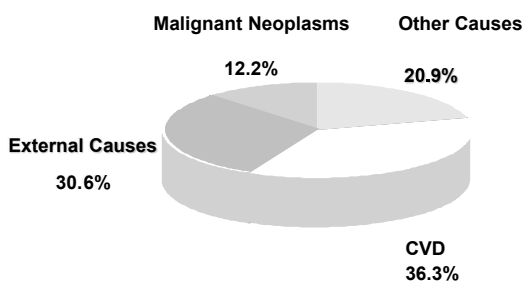
Figure 1.2. Projected increase in mortality associated with different diseases (2002-2030)



World Health Statistics, 2007

health is associated with the condition and the various diseases of the genitourinary system, which include infectious and inflammatory diseases of the prostate, hyperplasia and malignant neoplasms of the prostate, sexual dysfunction and androgen deficiency [6, 7]. In the Russian literature, epidemiological and clinical studies on the prevalence of diseases of the genitourinary system are limited. However, the available evidence suggests that this problem is highly relevant and requires the development of preventive activities. According to the Russian clinical academic, Professor Tatyana Potyomina, 40% of

Figure 1.3. Causes of mortality among Russian men of working age



Oganov RG, 2006

447 men attending for infertility problems are in the 26–30 years age group. In general, the cause of infertility among 47% of men can be determined. Every second man suffers from chronic prostatitis, 15% from varicocele, while 14% are diagnosed with endocrine disorders [8]. Recently there has been an increase of prostate diseases from 229 to 427 per 100,000 of population. Hyperplasia of the prostate is diagnosed in 31.9% of men older than 50 years [9, 10]. Sexual disorders that have a direct impact on the reproductive health of men of working age are also one of the most common disorders. Thus, among a sample of 869 men aged 34–57 years, ED occurred in 31% of cases, while 14% experienced a total lack of erection [11].

At the turn of this century, there has been a significant increase in non-communicable diseases among men of working age, which has a direct impact on life expectancy and quality of life. However, this problem should not be considered solely an issue within medical science as it is, above all, social in nature, and thereby has an impact on the very fabric of a country.

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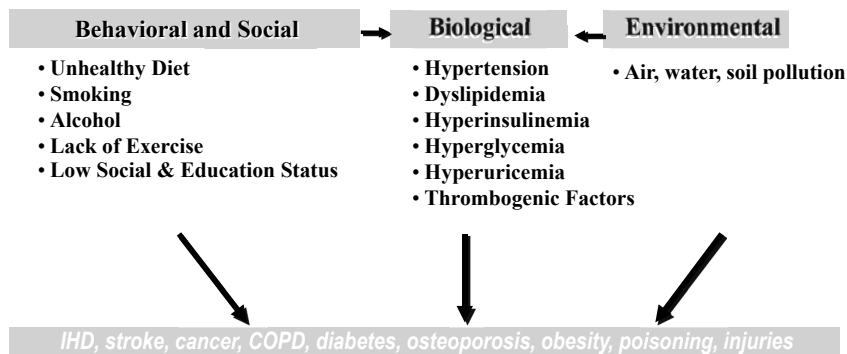
Chapter 2

METABOLIC RISK FACTORS AS A LINK IN MEN'S HEALTH ISSUES

It is known that in the development of various diseases the presence of risk factors plays an important role. By risk factors we mean different characteristics which promote the development and progression of certain diseases. The concept of risk factors was introduced in the late 1940's. To date, there are more than 200 risk factors, and their number increases every year. Risk factors are divided into several groups: behavioural (poor diet, smoking, excess alcohol consumption, inadequate physical activity, low social and educational status), biological (hypertension, dyslipidaemia, hyperinsulinemia, hyperglycaemia, hyperuricemia, thrombogenic factors) and environmental (air, water and soil pollution). A meta-analysis of prospective studies indicates that these risk factors play an important role in the formation of common non-communicable diseases such as ischaemic heart disease (IHD), stroke, cancer, chronic obstructive pulmonary disease (COPD), diabetes, osteoporosis, obesity, injuries, etc. (Figure 2.1) [1].

According to the international INTERHEART study, 9 risk factors play an important role in the development of acute myocardial infarction: lipid metabolism disorders, smoking, diabetes, stress, hypertension, obesity, low fruit and vegetable consumption, lack of physical activity and alcohol abuse. The Russian epidemiological study PRIMA, which randomly sampled men ($n = 619$) aged 30–69 years, has looked at the prevalence of 20 risk factors for CVD. The results of the study show a high prevalence of 10 main risk factors among men of working age. The most common are hypercholesterolemia, overweight / obesity,

Figure 2.1. Risk factors for non-infectious diseases

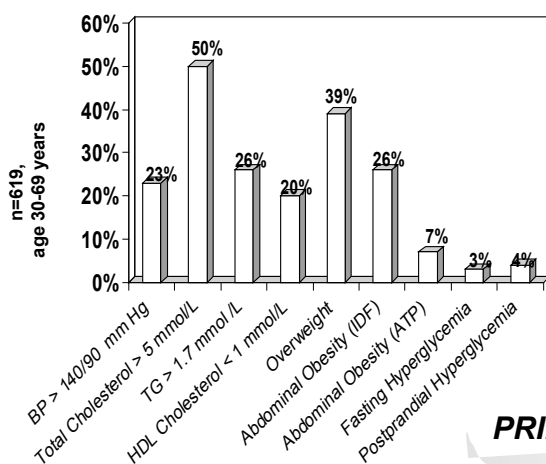


Oganov RG, 2006

hypertriglyceridemia, hypertension and low high-density lipoprotein cholesterol (HDL cholesterol) (Figure 2.2). Moreover, the majority of men of working age have a sedentary lifestyle, smoke, and drink alcohol regularly, while 30% consume too much alcohol (Figure 2.3).

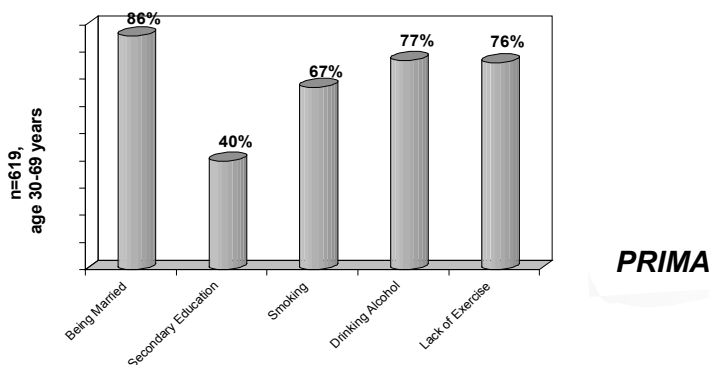
It has been established in many epidemiological studies that cardiovascular risk factors tend to coalesce [2]. According to a clinical

Figure 2.2. Prevalence of modifiable risk factors among men in a single city of the Volga Federal District (Cheboksary)



PRIMA

Figure 2.3. Social status and behavioral risk factors in a random sample of men in a single city of the Volga Federal District (Cheboksary)



study conducted in the National Research Center for Preventive Medicine among 500 men with the presence of arterial hypertension for at least 5 years, only 8% of cases suffered from hypertension only, 22% had a combination of hypertension and hypercholesterolemia or overweight (or obesity), 31% of patients had a combination of three risk factors (hypertension, hyperlipidaemia, overweight or obesity), and 39% of patients had MetS [3]. Therefore, metabolic disorders are the dominant risk factors in men at a high risk of cardiovascular complications.

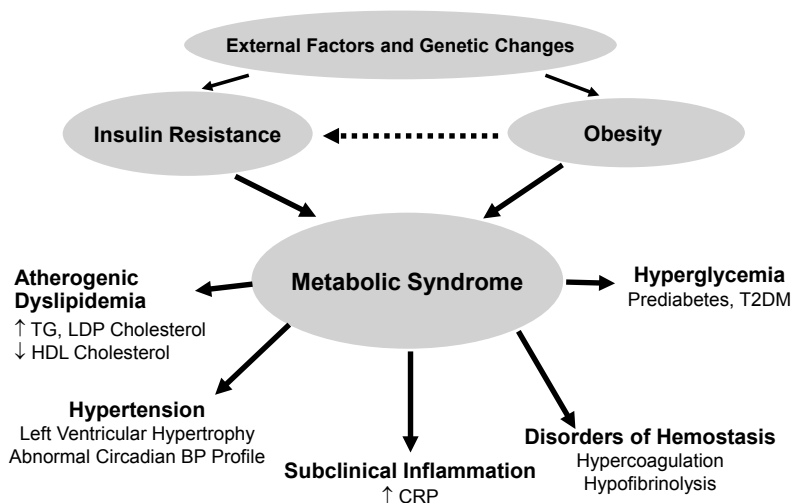
Metabolic syndrome: definition and risk of cardiovascular complications

The theory of MetS had a complex evolution during the Twentieth Century. According to European sources, in 1923 a Swedish physician, Eskil Kylin, was the first to describe the syndrome, known as «hypertension-hyperglycaemia-hyperuricemia» [4]. At the same time, a Soviet scientist, G.Lang, noted the close connection between hypertension and obesity, impaired glucose metabolism and gout [5]. Such descriptions, in different variations, could be found until the 1970s. By the mid-Twentieth Century, the first suggestions about the cause of the relationship between these seemingly different disorders were presented. Thus, Terry Smith, in his book «Insulin and atheroma»,

offered a hypothesis about the role of insulin in the development of atherosclerosis and related diseases [6]. In 1988, an American scientist, Gerald Reaven, theorized about the relationship between hypertension, dyslipidaemia and IGT. According to Reaven, IR / hyperinsulinemia is a binding link between these disorders [7].

In 2005, the International Diabetes Federation produced a new definition of MetS, according to which MetS comprises a combination of abdominal obesity, IR, hyperglycaemia, dyslipidaemia, hypertension, disorders of haemostasis and chronic subclinical inflammation (Figure 2.4) [8].

Figure 2.4. Metabolic syndrome: a modern view



Grundy S, 2005

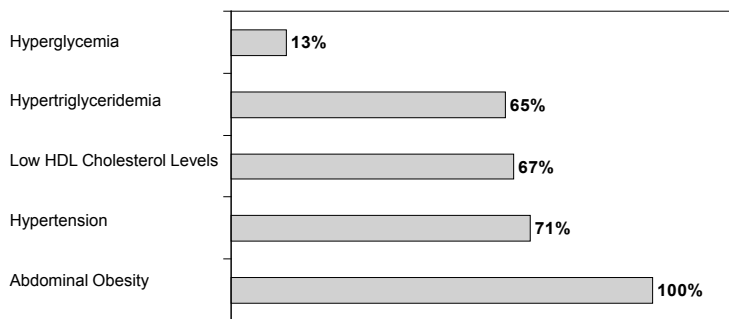
- Abdominal obesity has a high correlation with other components of MetS. Initially, waist circumference was considered as a marker for abdominal obesity in combination with body mass index (BMI) or hip circumference ratio. It has now been demonstrated that an increase in waist circumference has a strong correlation with abdominal fat deposition.
- IR and compensatory hyperinsulinemia are present in most patients with MetS, and are a predictor of IHD. However, currently IR markers are not defined for the diagnosis of MetS, except for the differential

diagnosis of MetS with other disorders, or with a combination of risk factors.

- Hyperglycaemia implies having prediabetes in a patient (IGT and / or high fasting glucose), which can in 40–50% of cases within 5 years convert into type 2 diabetes mellitus (T2DM). On the other hand, prediabetes, especially IGT, is an independent risk factor for CVD. With the advent of the theory of MetS, diagnosis and correction of prediabetes have become relevant. A sufficient number of studies have now accumulated on the role of lifestyle changes and antihyperglycemic therapy in the prevention of diabetes at the stage of prediabetes.
- Atherogenic dyslipidaemia in MetS is characterized by increased levels of triglycerides (TG), small, low-density lipoprotein cholesterol (LDL cholesterol) particles and reduced HDL cholesterol levels. Thus, in MetS there are quantitative and qualitative changes in the basic parameters of lipid metabolism. In the literature, the combination of these disorders refers to the lipid triad, which has a high atherogenicity.
- In most cases patients with MetS have stage I–II hypertension. However, the formation of hypertension involves several mechanisms, including activation of the sympathoadrenal system, renin-angiotensin system, impairment of renal tubular sodium reabsorption. Hemodynamic disorders are characterized by abnormal circadian blood pressure (BP) profile due to lack of BP dipping at night.
- MetS is related to chronic subclinical inflammation. One of the main markers of subclinical chronic inflammation is an increase in the C-reactive protein (CRP) level of blood (> 3 mg/L).
- Haemostatic disorders are characterized by hypercoagulability (an increase in the concentration of fibrinogen, VII coagulation factor) and a decrease of fibrinolytic activity (an increase in the concentration of plasminogen activator inhibitor-1).

Over the past 15 years there have been more than 20 epidemiological studies showing that the prevalence of MetS in an adult population can range from 10% in China to 24% in the U.S. It has been found that age, postmenopausal status in women, behavioural factors (sedentary lifestyle, a high carbohydrate diet), and socio-economic status play an

Figure 2.5. Prevalence of metabolic syndrome components among men aged 30-69 years

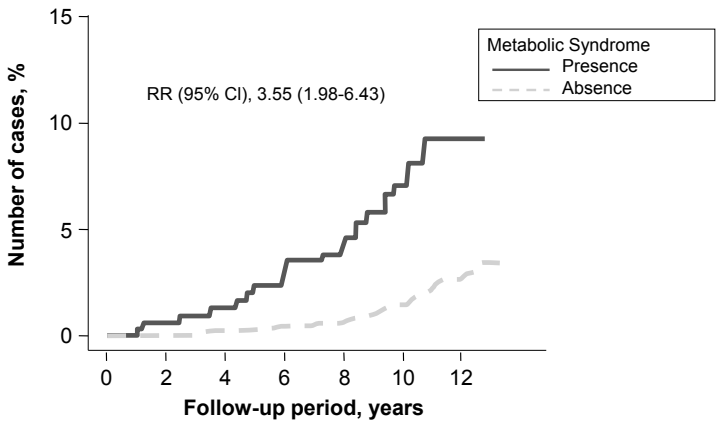


PRIMA

important role in the development of MetS [9]. In 2006, the results of a Russian study conducted in a random sample of 1,800 adults in the city of Cheboksary, confirmed this pattern. It was shown that 20.6% of people of working age have MetS. In the age group 30–39 years, 1% were found to have MetS, 3.6% aged 40–49 years, 9% aged 50–59 years, and 7% aged 60–69 years [10]. We performed a sub-analysis of the prevalence of MetS among men and, among 619 men of working age, MetS was diagnosed in 17%. The dominant elements of MetS in the representative population of men were abdominal obesity, hypertension, hypertriglyceridemia and low HDL cholesterol (Figure 2.5). In addition, it was shown that in the male population other biological and behavioural risk factors were quite common, and this explains the high morbidity, early disability and mortality due to CVD and other non-communicable diseases.

One of the reasons for interest in MetS is the atherogenic potential or high risk for cardiovascular complications. According to the Kuopio Ischaemic Heart Disease Risk Factors Study of MetS patients it was found that the risk for developing IHD was 2.9–4.2 times higher, death rate from IHD was 2.6–3.0 times higher, and all-cause mortality was 1.9–2.1 times higher than for patients without metabolic disorders [11] (Figure 2.6). The ARIC study showed that patients with MetS had two times more cases of ischemic stroke (men's risk was 1.9 and women's risk was 1.52 higher) than the control group, and the risk

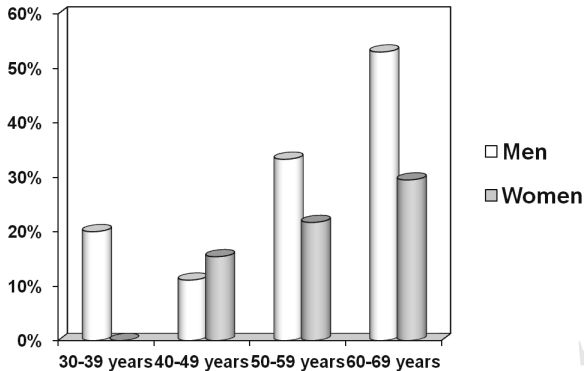
Figure 2.6. Mortality due to cardiovascular disease



Lakka HM, et al. JAMA. 2002;288:2709-2716.

for ischemic stroke was more pronounced in men than in women (1.9 and 1.52, respectively) [12]. The Russian cross-sectional PRIMA study also examined the association between CVD and MetS. It was shown that approximately 40% of patients at the time of MetS diagnosis had different clinical manifestations of atherosclerosis, with a large number having IHD. In men aged 30–39 years, 50–59 years and 60–69 years, IHD is more common than in women of the same age (Figure 2.7).

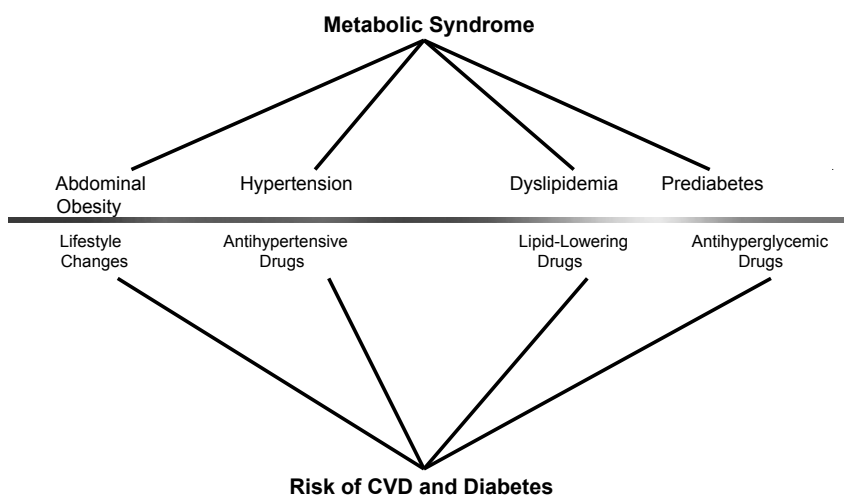
Figure 2.7. Prevalence of IHD in patients with metabolic syndrome depending on their age and sex



Modern principles in correcting metabolic syndrome

Correction of MetS requires a systematic approach because it is multidimensional. It is possible that, at the beginning of the development of MetS, one factor serves as a dominant component, which is often abdominal obesity. Other factors join sequentially and, the combination of factors, contributes to a multiplicative intensity. By the age of 40–50 years, a patient has fully developed MetS. By the time of their first visit to a doctor in primary care, the patients with MetS may have been diagnosed with various significant cardiovascular risk factors and, in one third of cases, may even have CVD detected. In this situation, to the question of what treatment needs to be initiated to correct MetS, there is only one answer: a comprehensive treatment taking into account the various manifestations of MetS and their intensity. In other words, there is no panacea for the treatment of MetS. Often, to achieve target levels in main cardiovascular risk factors, a combined antihypertensive, lipid-lowering and anti-hyperglycemic therapy is required (Figure 2.8). Among antihypertensive medicine

Figure 2.8. Main principles for correction of the manifestations of metabolic syndrome



for correction of hypertension in MetS there are ACE inhibitors, angiotensin receptor blockers, calcium channel antagonists and, in some cases, selective beta-blockers in medium therapeutic doses. If the target levels of BP have not been achieved, then a combination of two or more antihypertensive drugs should be prescribed. Among the lipid-lowering drugs, statins are the drugs of choice (with the detection of any degree of hypercholesterolemia) and fibrates (with evidence of hypertriglyceridemia). In recent years, the feasibility of antihyperglycemic drugs in patients with MetS at the stage of prediabetes has been increasingly discussed. It has been demonstrated that the use of acarbose (a drug to reduce postprandial hyperglycemia), metformin and rosiglitazone (drugs to reduce insulin resistance) at the early stages of carbohydrate metabolism disorders reduces the risk of diabetes from 31% to 68% [13] (Table 2.1).

However, we also state that at all stages of the development of MetS there should be lifestyle change. The results of clinical and prospective studies indicate that a change in food habits, good diet and regular physical activity have systemic metabolic effects and at the same time can reduce the intensity of all symptoms of MetS by 10–15%. At initial stages of MetS, lifestyle changes may be the method of choice. At late stages of MetS lifestyle changes are recommended as a part of combined therapy which, in some cases, can help to reduce the dose of drugs. Thus, the selection of drug and non-drug interventions in MetS depends on the intensity of the symptoms.

There have been intense debates in recent years around the theory of MetS. Some scientists have questioned the existence of MetS and argue that it should be considered as a mechanical combination of risk factors. These statements appeared after «sensational» proposals by the International Diabetes Federation regarding the criteria for determining MetS. In contrast to previous criteria, the presence of abdominal obesity is now a main diagnostic criterion of MetS. Also, its cut-off points were reduced. In the definition of ATP III NCEP (USA, 2001), a criterion for abdominal obesity was considered to be waist circumference for men > 102 cm and women > 88 cm. But, in the new definition, the figures are > 94 cm and > 80 cm, respectively. Scientists have not reached a consensus on the definition of MetS. Some take a classic approach. In particular, one of the most reputable

Table 2.1. **Description of medications used to correct metabolic syndrome**

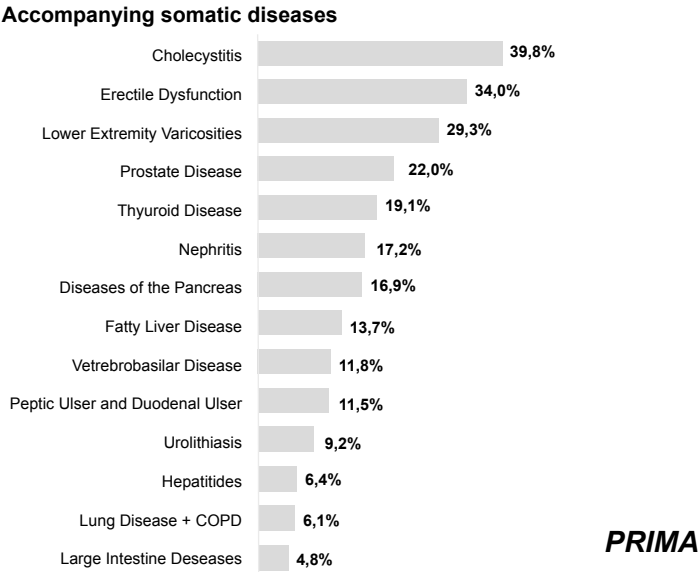
Groups of Medications	Effects
Antihypertensive drugs	
ACE inhibitors	↓ BP, slightly positive or neutral metabolic effects, organ protection
Angiotensin II receptor antagonists	↓ BP, slightly positive or neutral metabolic effects, organ protection
Imidazoline receptor agonists	↓ BP, positive metabolic effect
Selective beta blockers	↓ BP, heart rate, blocking peripheral sympathoadrenal system, neutral metabolic effect
Calcium antagonists	↓ BP, antiischemic, atherosclerotic and neutral metabolic effects
Thiazide-like diuretics	↓ BP, neutral metabolic effect, organ protection
Lipid-lowering drugs	
Statins	Dose-dependent ↓ of cholesterol up to 55%, triglycerides up to 30%, pleiotropic effects
Fibrates	Primarily ↓ of triglycerides and ↑ in HDL cholesterol, additional metabolic effects
Antihyperglycemic drugs	
Metformin	↓ Insulin resistance, hepatic glucose production, body weight and additional metabolic effects
Rosiglitazone (pioglitazone)	↓ Insulin resistance, anti-inflammatory and additional metabolic effects
Acarbose	↓ Postprandial glucose level, body weight, additional metabolic effects
Antiplatelet drugs	
Aspirin	↓ Platelet aggregation and adhesion, antiatherosclerotic effect

scientists in the world, S. Grundy, believes that the tightening of criteria leads to over diagnosis and increased health care costs. Most epidemiological studies have been conducted using ATP III NCEP criteria. Also, in a comparative study, American criteria were found to be the best predictors of CVD. Supporters of the new criteria suggest that abdominal obesity, as one of the manifestations of IR, contributes to

the development of different metabolic disorders, and the tightening of criteria will provide a separate risk group for CVD and other diseases. There are currently ongoing studies with hard endpoints using the latest criteria of MetS. Despite the debate about the criteria, MetS should be treated as a combination of risk factors that have a pathogenic or cause-and-effect relationship. This has been confirmed in the new European guidelines on diabetes, prediabetes and CVD, in which MetS is considered as a separate disorder.

To date, MetS has been beyond the scope of interest for a good number of cardiologists and endocrinologists. In clinical studies it has been demonstrated that this high atherogenic condition is associated with steatosis, a purine metabolism disorder and polycystic ovary syndrome, which provides a reason for considering it as an interdisciplinary issue. In the PRIMA trial, the association of MetS with other medical conditions was examined. The results of the trial showed that more than 60% of patients with MetS have different disorders: chronic cholecystitis, ED, varicose disease of the lower extremities, chronic prostate diseases and others (Figure 2.9).

Figure 2.9. Clinical picture of individuals with metabolic syndrome



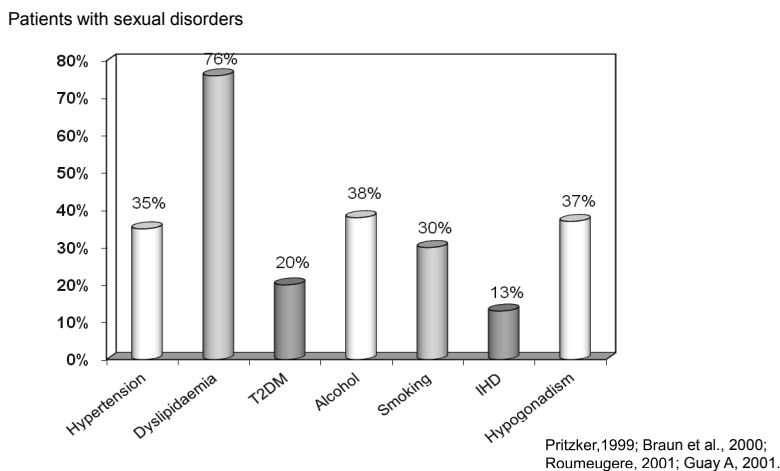
Relationship between metabolic syndrome and men's health problems

A few years ago, there were some publications on the relationship between MetS with ED and androgen deficiency in men [14–17]. In other words, scientists believe that there is a cause-and-effect relationship between these states. Is this true? We present the results of several studies supporting this hypothesis.

A meta-analysis of three clinical studies has shown that 35% of patients with ED have hypertension, 76% have lipid metabolism disorders, 20% have diabetes, and approximately 30% smoke and consume too much alcohol (Figure 2.10). Interestingly, 37% of patients with ED have been diagnosed with hypogonadism [15, 17]. According to Russian researchers, ED occurs in 51.2% of patients with MetS, whereas 46.4% of men with ED have major components of the MetS [18]. In general, men with ED are two times more likely to have major risk factors such as hypertension, hypercholesterolemia, depression and diabetes than men without ED.

On the other hand, metabolic dysfunction is one of a group of disorders in male androgen deficiency. In the 1970s, GB Phillips for the first time demonstrated the relationship between sex hormones

Figure 2.10. Association of cardiovascular risk factors and sexual disorders



and glucose, insulin levels and lipid metabolism parameters in men with myocardial infarction [14]. Several studies have shown that low testosterone levels are associated with an increase in some cardiovascular risk factors, such as a disordered lipid profile and coagulation factors, impaired glucose metabolism, obesity, and hypertension. In particular, according to the Telecom Study, men with low testosterone levels had higher levels of TG, LDL cholesterol and apolipoprotein B, as well as levels of fasting and two-hour plasma glucose, than men with normal testosterone levels [19]. In the Tromso Study, among 1,548 men examined in a subgroup of individuals with hypertension, the testosterone levels were low in all age groups [20].

In several large epidemiological and clinical studies, results have shown that low testosterone levels precede the development of T2DM and IHD (Table 2.2). According to the data from prospective studies, low testosterone levels precede the development of abdominal obesity, MetS and diabetes. In particular, Laaksonen et al. have demonstrated that in patients with low levels of total testosterone, after adjustment for BMI, the risk of developing MetS is 1.7 times higher [21]. In the Rancho Bernardo Study (294 elderly men were observed

**Table 2.2. Prospective epidemiological studies:
focus on the relationship among androgen deficiency
and metabolic disorders**

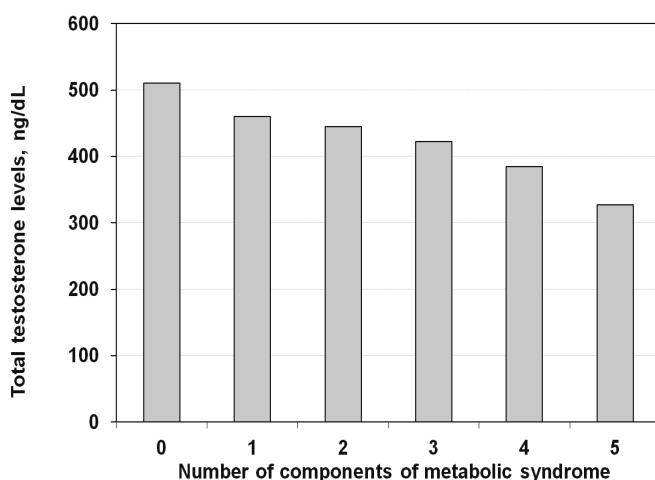
Source	Number of responders	Age	Results
Stellato et al, 2000	n=1156	40–70	Low testosterone levels precede T2DM in adult men
On et al, 2002	n=294	55–89	Low testosterone levels precede insulin resistance and T2DM in adult men
Laaksonen et al, 2004	n=702	42–60	Low testosterone levels precede MetS and T2DM in men
Muller et al, 2003	n=400	40–80	High testosterone levels increase insulin sensitivity and reduce the risk of MetS
Kupellian et al, 2002	n=1709	40–70	Low testosterone levels precede MetS in adult men with a BMI < 25 kg/m ²

for up to 8 years), it was shown that low testosterone levels increase the risk of diabetes (odds ratio 2.7, 95% CL: 1.1–6.6) [22].

But there is also a view that there is an inverse correlation between MetS and total testosterone. In other words, while components of MetS accumulate, total testosterone decreases (Figure 2.11).

In the literature, there is increasing evidence that hypogonadism is an independent risk factor for IHD [23]. In a clinical study involving 129 men, a correlation between testosterone levels and the stage of IHD was found. In the Rotterdam study among 1,032 men and women aged 55 years and over, a possible association between endogenous testosterone levels and atherosclerosis of the aorta was studied. Calcification of the aorta was diagnosed by radiography at baseline and after 6.5 years. The authors found an association between low testosterone levels and the progression of atherosclerosis of the aorta. In women, high levels of testosterone also had a correlation with evident atherosclerosis [24]. In the South Yorkshire Study a high prevalence of hypogonadism in men with IHD (23.4%) was shown,

Figure 2.11. Total testosterone levels among men with one, two, three or more components of the metabolic syndrome (n = 864, average age of 52 years)



where the presence of atherosclerosis was verified by using coronary angiography. A positive correlation was found between hypogonadism and hypertension [25].

According to results of a Russian study where 298 men aged 35 to 75 years with risk factors and CVD were examined, androgen deficiency was identified in the majority of patients with cardiovascular pathology in contrast to healthy men of the same age. Men without cardiovascular pathology were diagnosed with hypogonadism in only 10% of cases, but in the presence of hypertension, hypogonadism occurred in 17% of cases. In men with a combination of two or more risk factors, particularly with metabolic disorders, the probability of androgen deficiency was high: among individuals with hypertension and obesity – 55.3%, hypertension and T2DM – 75%, hypertension and IHD – 68.8% of cases. Almost all men (96.8%) with multiple disorders (hypertension, T2DM, obesity and IHD) had all signs of hypogonadism. These patients had severe clinical manifestations of hypogonadism and ED [26].

Thus, a sufficient quantity of scientific data has accumulated to show that there is some pathogenetic link and / or association between ED and MetS and between androgen deficiency, ED and MetS. To clarify the nature of this relationship an analysis of current ideas on the classification, pathogenesis, clinical presentation, diagnostic criteria, as well as on the principles of treatment of ED and androgen deficiency is required.

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Chapter 3

ERECTILE DYSFUNCTION AS AN INTERDISCIPLINARY ISSUE

ED is one of the most widely discussed problems of medicine, which has progressed beyond the scope of urology. The problem, being of the medical and social character, has a direct impact on the quality of life and fertility in men of reproductive age. In recent years, it has been called the «barometer of men's health» and «tip of the iceberg» of a systemic vascular disorder [1–3].

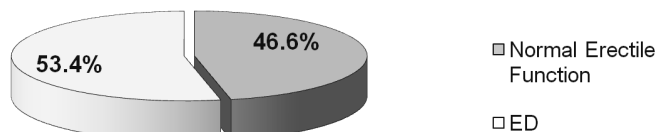
The prevalence of erectile dysfunction

Worldwide, 150 million men suffer from ED. In the U.S. the figure is 34 million. There is a linear relationship between age and incidence of ED. The MALES study showed that the frequency of ED in men aged 60–69 years was twice as much as in men aged 40–49 years (30% vs. 15%) [4]. In the CANSED study they have demonstrated that in outpatient practice about 50% of men aged 40–88 years suffer from ED [3].

In 2013, the first Russian epidemiological study was completed to evaluate erectile function in men of reproductive age. It is necessary to emphasize that that was the first project in the area of Eastern Europe and the CIS. The cross-sectional epidemiological study was conducted in the city of Cheboksary (Volga Federal District). The study randomly included 1050 men aged 30–69 years. 967 men fully completed the study. Erectile function was assessed using the International Index of Erectile Function (IIEF) questionnaire. In general, during the study ED was diagnosed in 53.4% of men of reproductive age (Figure 3.1).

Figure 3.1. Prevalence of erectile dysfunction in a random sample of men of reproductive age

967 men were surveyed out of randomly selected 1050 respondents.



Evdokimova AA, Mamedov MN, 2013

Table 3.1. Severity of erectile dysfunction in a random sample of male population

Severity of ED according to IIEF	IIEF points	The absolute number of men	% of the total population (n = 967)	% of men with ED (n = 516)
Mild	17–21	239	24.7%	46.3%
Moderately Mild	12–16	151	15.6%	29.3%
Moderate	8–11	39	4.03%	7.6%
Severe	5–7	87	9%	16.9%

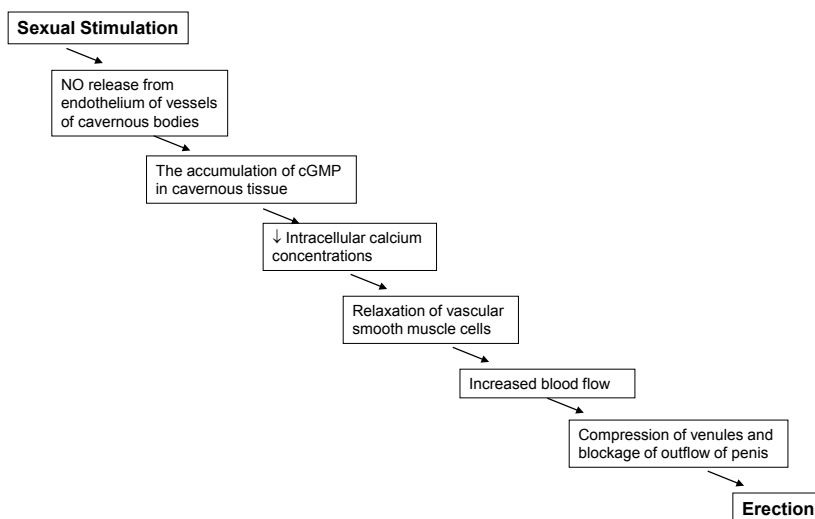
There was found the relationship between the incidence of ED and the age, that is, in older age groups the prevalence of ED was higher in comparison with groups of young men. The detailed analysis showed that one in four men in the population had a mild degree of ED, moderately mild ED was diagnosed in 16% of men, moderate ED was found in 4%, while the severe degree of ED was found in 9% of cases (Table 3.1).

A definition of ED given by the National Institutes of Health in the US is an inability to get and / or keep an erection sufficient for sexual activity. This term was proposed to replace the old «impotence» [2].

Physiology of erection

Erection is an increase in the volume of the penis with a sharp increase in its elasticity, which is caused by stretching and filling the

Figure 3.2. Physiology of erection

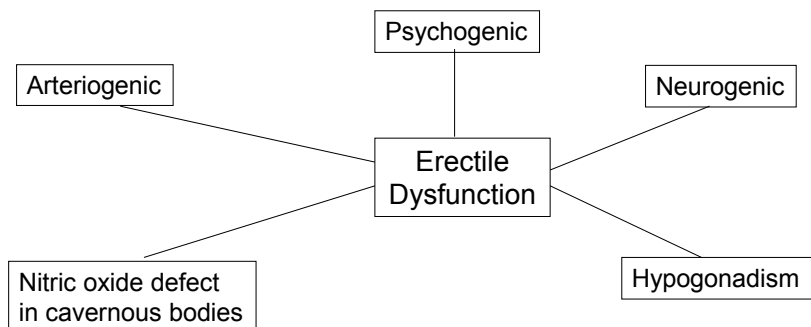


cavernous bodies during sexual stimulation. Erection can be considered as a complex neurovascular phenomenon, and sexual stimulation plays a role in the nature of it. Physiology of erection is shown in Figure 3.2. During the activation of the parasympathetic nervous system there is a release of neurotransmitters, in particular, nitric oxide from endothelium of vessels of the cavernous bodies, which leads to accumulation of cyclic guanosine monophosphate in the cavernous tissue and relaxation of the arteries and cavernous bodies. Filling of the lacunae with arterial blood causes the compression of the venules and blocking the outflow of blood from the penis [5]. Thus, the development of ED can be associated with the lack of vasodilation due to endothelial dysfunction, vascular resistance to the cyclic guanosine monophosphate, the lack of compression of the penile veins or a combination thereof.

The aetiology of erectile dysfunction: association with cardiovascular risk factors and disease

In general, there are psychogenic and organic types of ED, the latter is divided into hormonal, neurogenic and vascular (arterial

Figure 3.3. Pathogenesis of erectile dysfunction



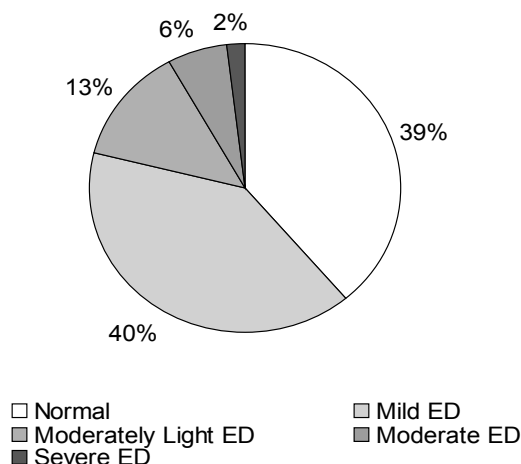
insufficiency, veno-occlusive dysfunction). Some authors refer to a mixed type of ED, although in almost all cases there are multiple disorders [6]. For example, there is a psychogenic component in organic primary ED (Figure 3.3).

In actual practice, the main cause of ED in the majority of men (80%) is vascular disease, which includes atherosclerosis, hypertension, diabetes, hormonal dysfunction, chronic kidney disease, COPD, etc. At the same time, smoking, alcohol abuse, lack of exercise and taking certain medications contribute to the development of ED (some antihypertensive drugs, antidepressants, tranquilizers, narcotic drugs, H2-blockers, hormones). In the table 3.2 there is a meta-analysis of

Table 3.2. **Vascular genesis of erectile dysfunction: contribution of CVD risk factors**

CVD risk factors	Contribution to the development of ED	Source
Hypercholesterolemia (↑ by 1 mmol/L)	— ED development by 1.32 times	Wei M et al. Am J Epidemiol 1994; 140: 930–937.
Hypertension (↑ BP by 10 mm Hg)	↑ ED incidents by 10%	Grimm RH et al. Hypertension 1997; 29: 8–14
Smoking	↑ Risk of ED by 1.7 times	Parazzini F et al. Eur Urol 2000; 37(1): 43–49.
Physical activity (↑ energy consumption by 300–400 kcal a day)	↓ Risk of ED by 15–20%	Derby CA et al. Urol 2000; 56: 302–306
Hyperglycemia (↑ HbA1c by 1%)	↓ Total IIEF score by 2–3 units	Romeo J et al. J Urol 2000; 163: 788–91

Figure 3.4. Erectile dysfunction in men with high cardiovascular risk



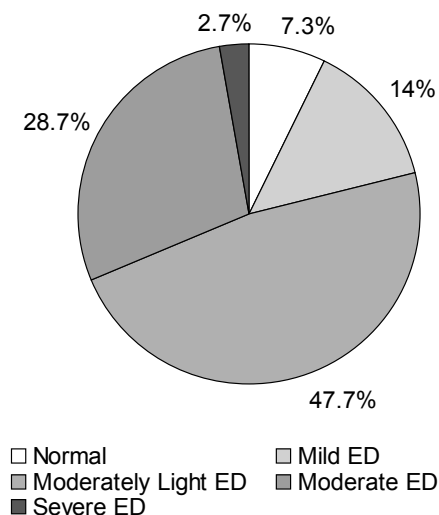
Mamedov MN, Sharvadze GG, 2010

several large studies, and according to them the main risk factors for CVD make a large contribution to the development of ED. An increase in the intensity of certain cardiovascular risk factors enhances the risk of ED from 15% to 70%. According to our data, ED, among men with high cardiovascular risk on the SCORE scale ($n = 500$) due to the presence of hypercholesterolemia, hypertension and smoking without clinical manifestations of CVD, was detected in 61% of cases (Figure 3.4), whereas ED, among 300 men with the presence of IHD, stable angina (with or without a history of myocardial infarction), was diagnosed in 92.7% of cases (Figure 3.5). Patients with IHD have more evident ED in contrast to the cohort of men with high cardiovascular risk.

These data confirm again the importance of vascular origin in the development of ED [7–9].

In recent years, a group of scientists has actively promoted a hypothesis that ED is an early marker or a precursor of CVD. In particular, Montorsi P has showed in two prospective studies involving 350 men that in 90–100% of cases ED precedes the development of acute coronary syndrome, IHD and stable angina (Table 3.3). And the interval among these events is on average 12–36 months. This is because the

Figure 3.5. Erectile dysfunction in men with IHD



Mamedov MN, Didigova RT, 2012

Table 3.3. Interval between the development of erectile dysfunction and IHD

	Patients (n=)	Type of IHD	Prevalence of ED (%)	ED prior IHD (%)	The interval between ED and IHD (months)
Montorsi F. Eur Urol 2003	300	Not Differentiated	49	67	38.8 (1-168)
Montorsi P. Circulation 2005	249	Acute Coronary Syndrome	41	100	24 (12-36)
Montorsi P. Eur Heart J 2006	95	Stable Angina	67	93	28±36
Foroutan SK Urol J 2007	401	Not Differentiated	46	42	23 (10-36)

Table 3.4. Why does ED precede other vascular disorders?

Arteries	Diameter
Penile	1-2 mm
Coronary	3-4 mm
Carotid	5-7 mm

penile arteries are 2–3 times smaller in diameter than the coronary vessels, and 3–4 times smaller than the carotid arteries (Table 3.4). Thus, in the presence of risk factors there is primarily functional and organic damage in smaller arteries [10, 11].

A team of European experts (G. Jacson, N. Boon, M. Kirby, J. Dean, G. Hackett, P. Montorsi, F. Montorsi, M. Miner) summarizing the data of evidence-based medicine have created a consensus that ED is a predictor of IHD [12]. The following are the main clauses of the consensus taking into account the grades of recommendation and levels of evidence:

- The majority of men with ED have an early development of IHD, and the affection of their coronary arteries is more pronounced as compared to men without ED (recommendations 1, the evidence A).
- ED is associated with higher total mortality due to increased cardiovascular complications (Recommendation 1, the evidence A).
- Treatment of risk factors by doing exercises and losing weight also leads to an improvement of erectile function (recommendations 1, the evidence A).
- Stabilizing the patient's cardiovascular system is the main objective of the treatment rather than correcting ED in men with comorbid conditions. PDE5 inhibitors are the first-line therapy in patients with IHD and ED with or without diabetes (recommendations 1, the evidence A).

Identification of ED in clinical practice

Diagnostics of ED is carried out on the basis of history, physical examination, laboratory and instrumental investigations.

There are a number of questionnaires to determine ED, which can be used not only for mass screening, but also in clinical practice. The International Index of Erectile Function (IIEF) is the most widely used questionnaire, consisting of 15 questions that allow evaluating 5 components of sexual function (erection, orgasm, sexual desire, intercourse satisfaction and overall sexual satisfaction) (Appendix 2) [13]. In domestic practice the scale of «Men's copulatory function» is also used, which is designed to analyse sexual dysfunction of organic origin.

There are some limitations of this scale (the presence of a permanent sexual partner, friendly relationship, etc.) [14].

In 1998, Goldstein I and co-authors suggested a four-point scale for measurement of erection (Erection Hardness Score):

- 1 – Penis is increased, but not hard;
- 2 – Penis is hard, but not enough to penetrate;
- 3 – Penis has a hardness to penetrate, but not completely hard;
- 4 – Penis is completely hard and rigid.

This scale is good for assessing the effectiveness of an undergoing therapy. The validity of this scale has been tested in a double-blind, placebo-controlled trial [15–17].

Laboratory studies for ED are used to identify its cause or association with other disorders. For this purpose, testosterone levels, glucose, lipids, prolactin and prostate-specific antigen (PSA) are measured. There are several instrumental methods for identifying the nature and degree of ED. Monitoring of spontaneous nocturnal erections (the RigiScan device) is performed to exclude psychogenic ED. Doppler ultrasound of the penile arteries helps evaluate the microcirculation (in mode B it is possible to determine structural changes, fibrosis, and Peyronie's disease). A research is more informative in a comparative analysis of data obtained at rest and during erection (visual stimulation or drug test, the use of PDE5 inhibitors). The test of intracavernous vasoactive drug injection (alprostadil) can detect vascular ED. In some cases, procedures (cavernosometry and cavernosography) to assess the condition of the cavernous bodies and the veins, and neurophysiological tests can be done [11, 18].

Principles of treatment of ED: current views

The principles of ED treatment can be roughly divided into two periods: before the advent of a new group of drugs – PDE5 inhibitors – and after, the use of which has encouraged to diagnose ED and opened up new prospects for its correction. The elimination of reversible causes of ED is certainly relevant. They include lifestyle changes and correction of main diseases, including drug therapy and surgery [6].

Up to the 1990s of the last century (in some cases up to now!) in the treatment of ED biogenic stimulants, adaptogens, vitamins, herbal

remedies (Tentex, Yohimbine, etc.) and sedatives were commonly used. However, it was later shown that the effectiveness of such a treatment strategy was slightly better than placebo and was 30%. During that time, other very effective methods for correcting sexual disorders were developed which found their place in the modern algorithms for the treatment of ED. First of all, they include intracavernous and intraurethral introduction of some drugs (phentolamine, papaverine, prostaglandin E1), vacuum-constriction therapy, vascular surgery (creation of anastomoses), and, finally, penile prosthetic surgery (the latter method of correction is used when other interventions are not effective) [19].

PDE5 inhibitors for ED are the same as statins are for atherosclerosis. PDE5 inhibitors enhance the relaxing effect of nitric oxide by inhibiting the homonymous enzyme and increasing the concentration of cyclic guanosine monophosphate during sexual arousal, by increasing this way the blood flow to the cavernous body and helping to get and keep a physiological erection [20]. Effect of PDE5 inhibitors is reversible.

Currently in clinical practice there are four drugs from the group of PDE5 inhibitors: sildenafil (Viagra, Pfizer), tadalafil (Cialis, Lilly) and vardenafil (Levitra, Bayer Schering / GlaxoSmithKline), and udenafil (Zydena, Dong-A Pharmaceutical Co., Ltd.) [21, 22]. In the table 3.5 there is a comparative analysis of these three drugs from the group of PDE type 5.

Sildenafil was the first PDE5 inhibitor approved in 1997 for the clinical use in the United States. Clinical efficacy and safety of sildenafil have been studied in more than 100 double-blind, placebo-controlled clinical trials. The absorption of sildenafil slows down when it is used after fatty foods and alcohol.

The pharmacokinetic profile of tadalafil significantly differs from sildenafil, since the elimination half-life of tadalafil is longer than the corresponding figures of sildenafil. Clinical efficacy of tadalafil persists for 36 hours after taking the drug, so that a couple can more freely choose the time to get intimate.

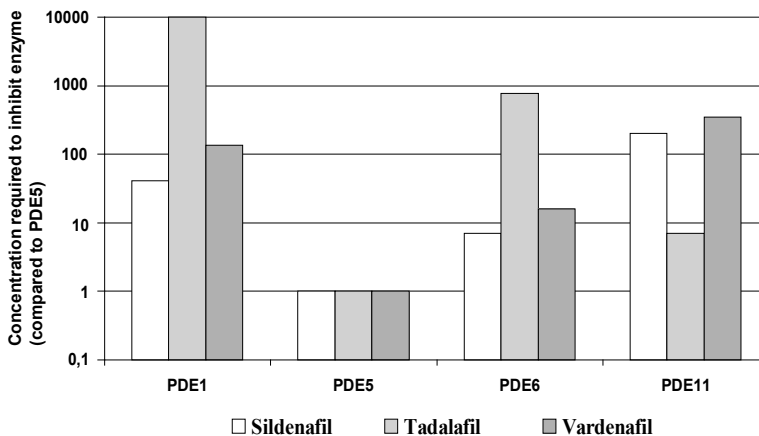
In a study *in vitro* it has been shown that vardenafil in comparison with other PDE5 inhibitors act more selectively on a subgroup of PDE type 5 than on other known types of phosphodiesterase. Moreover,

Table 3.5. Comparative characteristics of three drugs from the group of PDE type 5

Indicator	Vardenafil	Sildenafil	Tadalafil
A rapid onset of action	+	–	–
Multiple dosing	+	+	–
<i>Side effects</i>			
Muscle pain and back pain	–	+	+
Blurred vision	–	+	+
Hot flashes	+	+	+
High efficacy	+	+	+
Lack of impact of food and alcohol consumption	+	–	+
Extended duration of action	–	–	+

vardeafil has less effect on PDE6 – isozyme contained in the retina of the eye, by blocking which there are some disturbances of color perception – than sildenafil, and has a smaller impact on PDE1, contained in the testicle, than tadalafil and sildenafil, and therefore, does not inhibit spermatogenesis [23] (figure 3.6 and table 3.5).

Figure 3.6. Comparative selectivity of PDE5 inhibitors



In the general population the efficacy of all three drugs of PDE5 inhibitors is comparable [21, 22]. There are a small series of studies looking into a comparative analysis of the efficacy and safety of three PDE5 inhibitors [21]. In a multicenter, randomized, cross-over and open-label study led by leading experts in the world, Eardley I, Mirone V, Montorsi F, Ralph D and others, the efficacy of sildenafil and tadalafil has been examined. The study included 367 men at the average age of 54 with the presence of ED. After the conducted therapy the successful penetration was achieved by 82% (sildenafil 50–100 mg) and 85% (10–20 mg tadalafil) of men with ED. The successful sexual intercourse had 72% of men after treatment with sildenafil and 77% of men after treatment with tadalafil. After the stage of active treatment patients took part in the open-label stage of the study, in which 29% of men preferred further therapy with sildenafil and 71% with tadalafil.

However, the efficacy of drugs in some groups and comorbid conditions is different. In the literature, there have been published some data comparing the efficacy of the three PDE5 inhibitors. In particular, SI Gamidov showed that in men (average age of 50 years) with MetS and ED (duration of 3 or more years) the efficacy of vardenafil was 78.2%, of sildenafil – 69.6% and of tadalafil – 63.5%. In general, the presence of metabolic disorders requires using higher doses of the drugs [23]. In this study with 532 men taking PDE5 inhibitors for 6 months, a survey of the preference of certain PDE5 inhibitors has been carried out. Every fifth of the patients preferred sildenafil, every third – tadalafil, and 50% of men preferred vardenafil. The main reasons of choosing sildenafil were its relatively good tolerability and sufficient efficacy. Among patients who chose tadalafil, the majority (mostly young patients at an average age of 39 ± 5 years) preferred it because it had longer duration of action. Patients chose vardenafil primarily for its efficacy, rapid onset of its action and a possibility of combining it with eating and drinking alcohol.

A team of scientists from Columbia University in New York and the University of Minnesota have conducted a meta-analysis of studies on the efficacy of vardenafil in patients with hypertension and ED. For the analysis they used data from studies with duration of more than 12 weeks in men who had ED for more than 6 months. Among men with ED ($n = 2427$) in 36% of cases hypertension was detected. Treatment

with vardenafil helped increase the IIEF-EF domain score (the erectile function domain of the International Index of Erectile Function) by an average of 8.9 points. A detailed analysis of the results showed that in the main group the index increased by 15.4–26.1 points, whereas in the placebo group it was 11.3–17.8 points. In addition, vardenafil increased the frequency of successful intercourse by an average of 32.4% (individual values at the same time were 57.2–92.2% in the group of vardenafil, 32–66.9% in the placebo group). The researchers came to a conclusion that vardenafil was as effective in patients with ED and hypertension as in patients with ED and without hypertension [25].

For a long time there was a belief that there was a high risk of sudden death in patients with CVD during sexual intercourse. However, further studies have shown that these representations are exaggerated. Due to the emergence of new highly effective methods of ED treatment, most men have had an opportunity to resume their sexual life, including patients with CVD. To standardize the medical approach to the problem of sexual activity and cardiovascular risk the Princeton consensus has been developed. According to the new guidelines for the treatment of sexual dysfunction in patients with CVD patients are divided into three groups (Table 3.6). In low-risk patients the resumption of sexual activity or sexual dysfunction treatment is considered safe, patients with average risk need further examination before resuming sexual activity, whereas high-risk patients need first a correction of CVD [26, 27]. In the clinical study conducted by Thadani and colleagues it was shown that the intake of vardenafil 10 mg per day by patients with IHD and ED did not aggravate the symptoms of stable angina and did not affect myocardial blood supply and its effects were comparable to placebo.

There are two characteristics that have to be considered when prescribing these drugs to patients with the presence of cardiovascular pathology. First, they reduce BP by an average of 8 mm Hg. However, this is not a contraindication for using them in hypertensive patients taking antihypertensive drugs. Second and more important point is the interaction of PDE5 inhibitors with nitrates. In a series of randomized, placebo-controlled studies it has been demonstrated that in patients with IHD who take nitrates of various forms (spray, sublingual tablets or long-acting nitrates), the use of PDE5 inhibitors contributes

Table 3.6. Algorithms for determining the risk of sexual activity in cardiovascular disease (Princeton consensus)

Degree of risk	Cardiovascular disease	Guidelines on the management of patients
Low	Asymptomatic, < 3 factors of IHD, controlled hypertension, stable angina, FC (functional class) I-II heart failure, condition after successful coronary revascularization, uncomplicated heart attack, light valve damage, heart failure CI (circulatory insufficiency) I	Sexual relations or treatment of sexual dysfunction are possible; reassessment is carried out once over every 6–12 months
Average	> 3 risk factors of IHD, stable angina, heart attack happened from 2 to 6 weeks ago, FC II heart failure, other vascular manifestations of atherosclerosis	Conduct exercise ECG test and echocardiogram on the basis of which a patient is referred to a high or low risk group
High	Unstable or refractory angina, uncontrolled hypertension, FC III-IV heart failure, heart attack or stroke happened less than 2 weeks ago, life-threatening arrhythmias, hypertrophic obstructive cardiomyopathy, severe valve damage	Sexual relations or treatment of sexual dysfunction are deferred until stabilization

to a drastic reduction in BP from 36/12 mm Hg (nitroglycerin) to 52/29 mm Hg (mononitrates). In this regard, the AHA adopted the following resolution, «if a patient with an angina attack takes a PDE5 inhibitor, then it is prohibited to take nitrates for 24 hours.» [28].

Contraindication to the use of PDE5 inhibitors is a simultaneous intake of nitrates (24 hours before and 48 hours after the intake of a PDE5 inhibitor). The development of an angina attack due to the intake of PDE5 inhibitors is also a contraindication to the use of nitrates. In unstable cardiovascular events the drugs of this group are also used with caution [21, 27].

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Chapter 4

ANDROGEN DEFICIENCY IN MEN: THE SYSTEMIC EFFECTS OF HORMONE REPLACEMENT THERAPY

Testosterone is the main sex hormone in men. The chemical structure of testosterone was decoded in 1935 by Leopold Ruzicka, who was awarded, together with Adolf Butenandt, the Nobel Prize in 1939. Testosterone is produced mainly by the testicles from cholesterol (95%), much less – by the adrenal cortex. Only a small amount of testosterone is deposited in the testicles. Daily volume of discharge of testosterone into blood is approximately 6 mg, and a complete turnover of testosterone in blood happens about 200 times [1, 2].

The synthesis of testosterone is controlled by hypothalamic-pituitary-ovarian axis. The hypothalamus releases gonadotropin-releasing hormone, which stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (gonadotropins; FSH) by the hypophysis. LH stimulates the production of testosterone by the Leydig cells and contributes to the development of the testicles, and FSH together with testosterone regulates spermatogenesis and sperm maturation. At the same time FSH increases the activity of LH and testosterone [3]. In turn, testosterone regulates the release of these gonadotropins by negative feedback of the hypothalamus and hypophysis. The release of FSH is selectively inhibited by inhibin-polypeptide which is produced by the Sertoli cells, found in the testicles, and is stimulated by activin.

Testosterone entering the bloodstream is transported in plasma by globulin binding sex hormones or bound to albumin, only a small part of it remains in free form in dynamic equilibrium with bound

fractions. Circulating in plasma testosterone is largely converted into dihydrotestosterone in target tissues under the influence of the enzyme 5 alpha-reductase. Testosterone is also metabolized to estradiol by means of the aromatase enzymes in the testicles, adipose tissue and the brain. In many tissues, the activity of testosterone depends on its restoration to dihydrotestosterone, which, in turn, binding with androgen receptors, leads to changes on the cellular level [1].

Androgens, including testosterone and its metabolite dihydrotestosterone, have different functions in different periods of life:

- during embryonic development androgens play a key role in the differentiation of male sex organs – the prostate, seminal vesicles, penis and the scrotum;
- during pubertal period androgens are responsible for starting the process of sexual maturation. Testosterone is involved in the formation of sperm, the development of male secondary sex characteristics (body hair growth, increased throat, thickening of the vocal ligaments). Testosterone is necessary to stimulate sexual behaviour and sexual functions;
- in adulthood androgens are necessary to maintain reproductive function and male secondary sex characteristics. Testosterone acts on muscle mass and strength, fat distribution, bone mass, erythropoiesis, potency and libido. Moreover, androgens can have a non-specific effect on overall metabolism, spiritual and medical states [1, 2].

Thus, endogenous androgens not only play an important role in the growth and development of young man, but also participate in maintaining men's health in adulthood. At the same time the regulation of hormones' production by the testicles and the mechanisms of hormonal influence at the early stages, beginning from the early embryonic development and ending at old age, are the same.

Androgen deficiency (hypogonadism): definition and relationship with CVD. Hypogonadism is insufficient secretion of testosterone by the testicles in conjunction with relevant symptoms. This state of reduced testosterone secretion is a result of disturbances at different levels of the hypothalamic-pituitary-gonadal system [4]. Hypogonadism may be congenital or acquired. Depending on the level of the lesion there are (Table 4.1):

Table 4.1. Clinical manifestations of hypogonadism in men, depending on the period of puberty

Signs	Clinical presentation before puberty	Clinical presentation after puberty
Sexual development	Eunuchoidism Aspermia	
Testicular volume	Reduction of less than 6 cm ³	Normal or slightly reduced (10 cm ³)
Penis size	Small - less than 5 cm	Normal size
Voice	High-pitched	Normal
The presence of gynecomastia	Present	Present
Infertility	Present	Present
Libido	Absent	Reduced
Bone density	Reduced	Reduced
Anemia	Mild – normochromic, normocytic	Mild – normochromic, normocytic
The amount of facial and body hair	Decrease	Decrease
Muscle mass and strength	Decrease	Decrease
Obesity markers	Increase in BMI and abdominal obesity	Increase in BMI and abdominal obesity
Psychosomatic condition		Depression, feeling down Hot flashes, «tides»

– primary or hypergonadotropic hypogonadism is due to dysfunction of the Leydig cells. Insufficient secretion of sex hormones by the testicles (low testosterone levels and deterioration of spermatogenesis) leads to an increase in tropic hormones of the hypophysis by negative feedback mechanism;

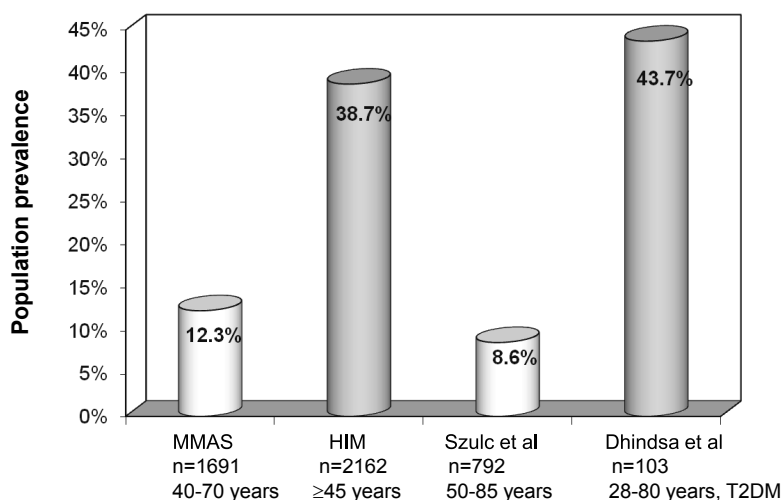
– secondary or hypogonadotropic hypogonadism is due to dysfunction of the hypothalamus or hypophysis, and accompanied by a reduced secretion of pituitary gonadotropins, which results in reduction in the secretion of hormones of the Leydig cells. Also the signs of hypogonadism develop through resistance of target organs to androgens or 5- α reductase deficiency. In addition, the secondary hypogonadism is conditioned by the disturbance of activity of enzymes, which involved in the synthesis of testosterone, or by the defects of LH receptors. [5]

In 2005, the International Society for the Study of the Aging Male proposed a new term «age-related hypogonadism», which is characterized by a gradual decline in testosterone production. And there is no change in gonadotropin secretion. The highest concentration of androgens is observed in men aged 25–30 years. In healthy men over 60 years the concentration of testosterone in the body is reduced to 35–50%. It has been found that with age the response to the impulses, received from peripheral receptors, in the cerebral cortex is reduced, the number of androgen receptors in the tissue of the penis decreases and there is reduced penile sensitivity. Testicular genesis of decreased androgen levels is confirmed by the age decrease in the number of the Leydig cells, by vascular changes that lead to hypoxia and reduced testosterone production, and also by reducing the ability of the testicles to produce a required amount of testosterone in response to chorionic gonadotropin. In addition, there is an increase with age in sex hormone binding globulin (SHBG) levels, and that further contributes to the reduction of free testosterone. However, in some disorders and chronic diseases this process is accelerated. In particular, SHBG in plasma increases in hyperthyroidism, steatosis, cirrhosis of the liver, and HIV infection. On the other hand, obesity enhances the aromatization of androgens, stimulates an increase in oestrogen levels, and as a consequence, provokes an inhibition in production of LH. As a result of two parallel processes the amount of testosterone available to target cells (free and albumin-bound) decreases. Some medications (glucocorticoids, spironolactone, oestrogens, cimetidine, carbamazepine), excessive use of alcohol and drugs also lead to a decrease in testosterone levels [6].

Thus, most forms of hypogonadism diagnosed in adults, are acquired, and most often it develops as a result of obesity, systemic diseases and intake of certain medications.

According to experts, in recent years the number of men with low testosterone levels has been steadily growing. Meta-analysis of a number of epidemiological studies shows that in population of working age men low testosterone occurs from 8.6% to 38.7% [7–9] (Figure 4.1). In particular, the HIM study, conducted in the United States, the prevalence of hypogonadism has been estimated (total testosterone < 300 ng/dL) in men older than 45 years. In the study,

Figure 4.1. Meta-analysis of the prevalence of hypogonadism in 4 populations of men *



* Data are presented on the basis of total testosterone levels

together with the assessment of hormonal status, demographics and associated diseases were assessed. Among 2,162 men, in 836 (38.7%) hypogonadism was identified, while only a small part of them had been receiving testosterone replacement therapy. It was shown that the probability of detection of hypogonadism was significantly high in men with the following medical conditions and disabilities: hypertension (1.84), hyperlipidaemia (1.47), diabetes (2.09), obesity (2.38), prostate disease (1.29) and the COPD (1.40) [8].

Interestingly, hypogonadism has been found during doctor appointments for the following reasons: 61.6% of general inspection, 12% of CVD, 8% of respiratory diseases, 6.5% diseases of the musculoskeletal system, and 12.1% of others. Indeed, among men with hypogonadism compared to eugonadal men the risk factors and somatic disease are often significant (Table 4.2).

We have also conducted a clinical study to identify the age-related hypogonadism in men with high cardiovascular risk according to the European SCORE scale. The study examined 239 men aged 30–59 years with the presence of CVD risk factors and high cardiovascular risk $\geq 5\%$ according to the European SCORE scale for the high-risk

Table 4.2. **Combination of systemic diseases with hypogonadism**

Condition	Hypogonadal Patients (n=836)	Eugonadal Patients (n=1326)	Significant Difference
Hypertension	547 (65.4%)	678(51.1%)	<0.001
Hyperlipidemia	506 (60.5%)	670 (50.5%)	<0.001
Diabetes Mellitus	258 (30.9%)	237 (17.9%)	<0.001
Obesity	270 (32.2%)	225 (17%)	<0.001
Prostate Disease	165 (19.7%)	226 (17%)	0.121
Chronic Pain	155 (18.5%)	211 (16%)	0.113
Sleep Disorders	129 (15.4%)	185 (14%)	0.342
Asthma / COPD	102 (12.2%)	118 (8.9%)	0.013
Headaches	70 (8.4%)	125 (9.4)	0.405
Rheumatoid Arthritis	28 (3.3)	29 (2.2)	0.101
Osteoporosis	15 (1.8)	15 (1.1)	0.199

countries, which corresponded to the presence of more than two of the following risk factors:

- hypertension (according to the criteria of the European Society of Hypertension, 2009)
- high levels of total cholesterol > 5 mmol/L and LDL cholesterol > 3 mmol/L
- smoking

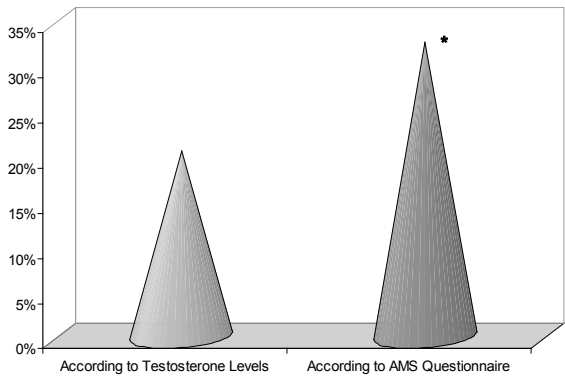
At the same time the presence of other risk factors (hypertriglyceridemia, low HDL cholesterol levels, prediabetes, and obesity, including central obesity) was considered.

The exclusion criteria were diabetes, CVD, chronic alcoholism, primary hypogonadism, and pelvic surgery.

Androgen deficiency or hypogonadism was diagnosed with the presence of the symptoms listed below:

- clinical symptoms of hypogonadism
- a score of 37 or higher by the AMS questionnaire (Appendix 3)
- total testosterone < 12 nmol/L and / or free testosterone < 0.225 nmol/L.

Figure 4.2. Androgen deficiency identified using two criteria in men with high cardiovascular risk



* $p < 0.05$ significant difference in androgen deficiency prevalence defined by two methods

Among 239 men with high cardiovascular risk, the clinical signs of hypogonadism were found in 32.5%, according to the AMS questionnaire, and hypogonadism was diagnosed in 20.5% of men according to the levels of total and free testosterone (Figure 4.2).

The study also determined the prevalence of androgen deficiency in three age ranges of men with high cardiovascular risk. For this reason, patients were divided into three age groups: 30–39, 40–49 and 50–59 years (Table 4.3). Among patients aged 30–39 years there were no cases of hypogonadism, whereas among patients aged 40–49

Table 4.3. Prevalence of androgen deficiency according to total and free testosterone levels in men with high CV Risk in three age groups

Age	30–39 years n/%	40–49 years n/%	50–59 years n/%
Patients with Hypogonadism	0	10/17.2%	14/26.4%
Patients without Hypogonadism	6 (100%)	48/82.8%**	39/73.6%**

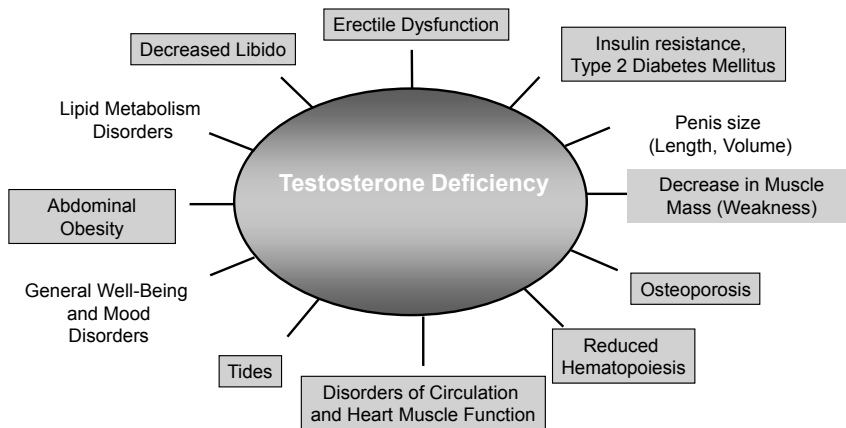
** $p < 0.01$ significant difference between groups of patients with and without hypogonadism

years hypogonadism was diagnosed in 17.2%, and those aged 50–59 years – in 26.4% of cases. Thus, one in five men with high cardiovascular risk is diagnosed with androgen deficiency, and with age its prevalence increases.

Clinical symptoms of age-related hypogonadism

The clinical symptoms of hypogonadism are numerous, and it is due to the effects of testosterone and its metabolites [5, 10, and 11]. The main symptoms are: androgenic, reproductive, anabolic, and psychotropic and an impact on hemopoiesis. There are the following groups of disorders (Figure 4.3):

Figure 4.3. Clinical manifestations of testosterone deficiency in men



Oettel M Naturwissenschaften 91: 66-76 (2004)

1. Disorders of sexual function:

- Decrease in libido
- Erectile dysfunction
- Disorders of orgasm and ejaculation
- Infertility

2. Somatic disorders:

- Decrease in muscle mass
- Obesity, abdominal, in particular
- Decrease in bone density

- Breast enlargement (gynecomastia)
- Decrease in the amount of hair on the face and body
- Thinning of the skin
- Disturbances in lipid and carbohydrate metabolisms
- Cardiovascular disease

3. Vegetative-vascular and psycho-emotional disorders

- Feelings of heat and redness of the face
- Dizziness
- Shortness of breath
- Irritability, fatigue
- Decrease in memory and attention
- Sleep disorders
- Decrease in capability to work

Diagnosis of hypogonadism is conducted on the basis of specific complaints, the general clinical examination (BMI, skin condition, the ratio of muscle and adipose tissue, skeletal proportions, the presence and degree of gynecomastia) and andrological examination (size and consistency of the testicles, scrotum, penis, hair growth on the face and body). According to the recommendations of the Endocrine Society Clinical Practice Guidelines in the diagnosis of androgen deficiency it is encouraged to consider a combination of clinical symptoms with decreased testosterone levels.

For a complex evaluation of various symptoms associated with androgen deficiency there are some widely used questionnaires. In Russia, as well as in other countries, the questionnaire AMS (Aging Male Symptoms) is used. This accessible and approved method is suitable for screening, and for assessing the efficacy of treatment (Appendix 3) [12].

The main diagnostic criterion of hypogonadism is the determination of hormones, in particular, total testosterone. Until now, there have been discussions about cut-off points and units to establish androgen deficiency. Total testosterone levels less than 12 nmol/L are seen as a sign of androgen deficiency. Since testosterone has circadian rhythms (oscillation goes up to 35% during the day, the peak of secretion is observed in the morning), it is recommended to determine its level at 8–9 in the morning. Men older than 60 years have disrupted circadian rhythm of testosterone; therefore, strict adherence to these rules is not

required. In some cases, it is reasonable to check free and bioavailable testosterone. To determine the levels of free testosterone, a method for calculating special graphs, nomograms, is widely used. There are some calculators to estimate free testosterone that are based on determination of total testosterone, SHBG and albumin. The levels below 0.255 nmol/L of free testosterone (the method of Vermeulen) are also an indication for further diagnostic research. To determine the nature of hypogonadism (primary and secondary), levels of SHBG, LH and FSH are also determined. In primary testicular failure it is desirable to conduct karyotyping to exclude Klinefelter's syndrome [11, 13, and 14]. In table 4.4 there is a comparative analysis of the hormonal status in hypogonadal and eugonadal men.

Table 4.4. Hormonal status in eugonadal and hypogonadal men

Laboratory Results	Hypogonadal Men	Eugonadal Men	Significant Difference
Total Testosterone ng/dL	245.6±4.12	439.9±3.52	< 0.001
Bioavailable Testosterone ng/dL	86.1±2.4	108.8±1.3	< 0.001
Free Testosterone ng/dL	47.9±1.03	63.9±0.53	< 0.001
Sex Hormone Binding Globulin	43.7±0.74	68.3±0.87	< 0.001

In patients, suspected of having secondary hypogonadism, the examination on the hypophysis (neoplastic processes), prolactin (hyperprolactinemia) and the determination of hemoglobin levels (hemochromatosis) are carried out [15]. The following belong to the group of androgen deficiency risks:

- Diseases of the sella turcica area
- Patients treated with the drugs that affect the metabolism of testosterone
- Chronic renal failure
- COPD
- Infertility
- Osteoporosis
- HIV infections
- Erectile dysfunction

Hormone replacement therapy

Natural testosterone, if given orally, intramuscularly or sublingually, is rapidly absorbed and destroyed, and to maintain its physiological levels is quite difficult [16]. Therefore, effective androgen therapy requires either the use of medications, to ensure constant release of testosterone, or its chemical analogues. Currently, there are several forms of testosterone, including oral, injection (both short-acting and long-acting), and transdermal forms of androgen replacement therapy in men [17, 18] (Table 4.5).

For oral or sublingual use there are some 17 α -alkyl derivatives of testosterone. They are metabolized in the liver more slowly than natural testosterone; they must be taken several times a day. Their androgenic properties are low or variable. Alkylated androgens can be hepatotoxic.

Transdermal patches can provide a slow delivery of testosterone into the bloodstream. These systems provide physiological testosterone levels in plasma mimicking the circadian rhythm. In some cases, patches may cause irritation, burning sensation, mild forms of erythema. In some cases, the patch is attached to the scrotum, which leads to some increase in the level of dihydrotestosterone (DHT) and testosterone metabolism.

Recently transdermal testosterone gels have been considered as one of the optimal forms of hormone replacement therapy. In a double-blind, randomized study of 227 men with hypogonadism, testosterone replacement therapy at a dose of 5 and 10 grams per day could increase the level of testosterone in most participants to the values which were typical for men with preserved function of the gonads, and could maintain those levels throughout the treatment. Thus, after application of a transdermal gel with the dosage of 5 g per day, the average daily testosterone levels became normal in 87% of patients on the 30th day, in 78% on the 90th, and in 89% on the 180th day. During the studies the data showed a reduction in intensity of bone reabsorption and an increase in bone mineral density of the thigh bone and the vertebrae. The change in the body parameters was observed: decreased total mass and the body fat percentage and increased muscle mass. The therapy resulted in an increased percentage of full

Table 4.5. **Drugs used for treatment of androgen deficiency**

Medications	Brand name	Dose	Benefits	Disadvantages
<i>Parenteral administration</i>				
Testosterone Cypionate	Depo Testosterone, Testosterone Cypionate	75–100 mg per week or 150–200 mg every 2 weeks, intramuscularly	Long-term effect, affordable	Sudden fluctuations in testosterone levels
Testosterone Enanthate	Delasteril Testoviron Depo-Testosterone			
Testosterone Ester Mixture	Sustanon 250	250 mg every 3 weeks, intramuscularly	Effect on the second day after administration	
Testosterone Undecanoate	Nebido	1000 mg every 10–12 weeks, intramuscularly, 4 injections per year	Long-term effect, maintenance of the physiological levels of Testosterone in blood	In some cases there is pain at the injection site
<i>Oral administration</i>				
Testosterone Undecanoate	Andriol		Not metabolized by the liver	Effective with initial manifestations
<i>Transdermal administration</i>				
Testosterone Patches	Androderm Testoderm	2.5–7.5 mg per day 10–15 mg per day	Good efficacy Ease of use	Allergic reactions
Testosterone Gel	Androgel Testogel	25–50 mg per day	Painless, no skin reactions, good efficacy	Development of adverse effects (hirsutism) on gel contact with a partner

erection and increased libido (and, also, sexual activity). Transdermal gels are applied to the skin of the shoulder, upper arm or abdomen. Local reactions using a gel happen in no more than 5% of patients.

The gel should not be applied to the genital area. It is better to avoid skin contact with the skin of another person, as there is a high probability of virilization. Patients are advised to cover the application site of the gel with clothing, and it is recommended to wash their hands with soap afterwards [19].

Intramuscular injections of depo-testosterone, esters, in an oil suspension are widely used in replacement therapy. Esterification of testosterone increases its solubility and slows down its release into the bloodstream. Usually, these drugs increase testosterone levels in plasma to the upper limit of normal in a few days after injection, which subsequently reduce to an average point at the end of the interval between injections.

Among testosterone medications, testosterone undecanoate have been widely used. It is a depot drug with a delayed release of active substance, and it is used four times a year [20]. A single injection of testosterone undecanoate helps stably maintain physiological testosterone levels within 12 weeks, while the use of a usual form of testosterone requires 22 injections a year. Testosterone undecanoate is an ester of natural testosterone, which, gradually releasing, is hydrolyzed to produce testosterone and undecanoic acid. An increase in serum testosterone is usually observed on the next day after injection. The half-life is 34 days. And its pharmacotherapy is identical to the physiological effects of testosterone. Tens of clinical studies have been conducted on the efficacy and safety of testosterone undecanoate. A stable maintenance of normal testosterone levels has been shown in studies with duration of 6–24 months, along with that there has been a gradual but steady decline in levels of not only estradiol and SHBG, but also pituitary hormones. A moderate increase in serum hemoglobin has been noticed. Hormone-modulating effect of testosterone undecanoate was accompanied by the restoration of sexual function, improved mood, a decrease in body fat and increase in muscle mass of patients, decreased levels of total cholesterol and TG and an increase in the bone mineral density. Importantly, patients previously taking other testosterone drugs reported an ease of use of testosterone undecanoate and improved adherence to treatment [21–23].

The effectiveness of androgen replacement therapy should be evaluated according to the dynamics of clinical symptoms of the

underlying disease. As a result of the effective therapy there are an increase in sexual satisfaction, loss of vegetative-vascular and mental disorders, increased bone density, and the positive dynamics of metabolic disorders.

The field of testosterone application expands primarily due to comorbid conditions, which include the treatment of sexual disorders, diabetes and MetS, osteoporosis and CVD in combination with androgen deficiency [5, 6].

One of the discussed issues, related to the prescription of hormone replacement therapy with testosterone drugs, is their effect on the prostate gland. It was believed that therapy with testosterone drugs could lead to prostate cancer. In 2002 PL Zhang published results of the study where it was shown that endogenous testosterone levels were lower in patients with prostate cancer. In recent years, several large studies have been conducted to demonstrate the safety of testosterone therapy, particularly, the testosterone undecanoate therapy. The detection rate of new cases of prostate cancer due to testosterone therapy statistically was not significantly different from that in the placebo group [24].

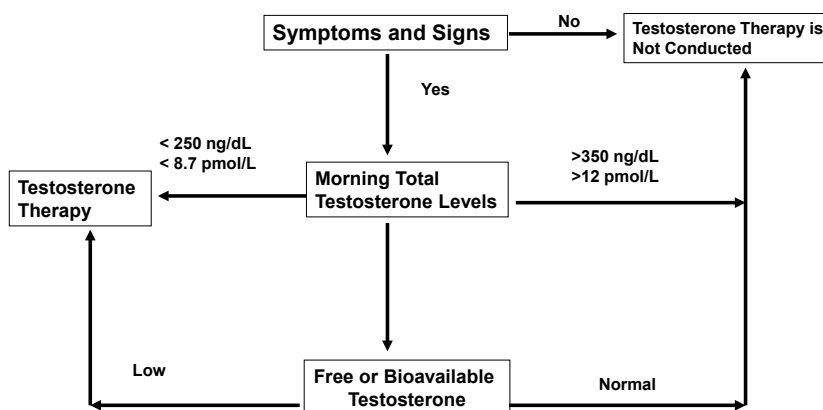
The *International Committee of Androgen Therapy* in 1995 presented a guideline for the testosterone therapy in men. According to it before prescribing the testosterone therapy it is necessary to exclude the fact that patient has prostate cancer, and in future to examine him periodically in case its manifestations appear. It is mandatory to conduct a rectal examination and to check the PSA level in blood. If there is a reason to suspect the presence of prostate cancer (rectal examination or PSA level is higher than 3 ng/mL), further examination is to be done in order to exclude prostate cancer. If palpable changes have been detected, an increase of PSA level is more than 3 ng/mL or PSA level doubles within 3 ng/mL during 1 year, then the testosterone therapy discontinues and prostate biopsy is conducted. The absolute contraindications of replacement therapy are: prostate cancer (prostate adenocarcinoma), breast cancer, severe urinary tract obstruction, and planned parenthood (decrease in formation of sperm). Relative contraindications include benign prostatic hyperplasia, polycytosis, gynecomastia, and sleep apnoea syndrome. One of the necessary conditions for long-term testosterone replacement therapy is the functional

state of the liver. By using the testosterone undecanoate therapy, liver enzymes levels do not change. It is important to remember that in decompensated IHD and heart failure the drug should be taken with caution [3, 13].

Summarizing the results of major studies, the *Endocrine Society* of developing practice guidelines (*Endocrine Society Clinical Practice Guidelines*) proposed in 2006 guidelines for the use of testosterone therapy in men with androgen deficiency [25]. The following are the main statements of these guidelines:

- diagnosis of androgen deficiency is established in men with clinical signs of this condition;
- evaluation of the morning total testosterone levels is a component part of the diagnosis. To verify the diagnosis it is necessary to repeat the tests, and in some cases it is also necessary to determine the levels of free and bioavailable testosterone;
- hormone replacement therapy with testosterone is prescribed to men with clinical signs and symptoms of androgen deficiency and with low testosterone levels to improve somatic state, sexual activity, increase the muscle mass and bone density (Figure 4.4);
- one of the aims of testosterone replacement therapy is to maintain the level of testosterone in the mid-normal range;

Figure 4.4. Diagnostic algorithms for use of hormone replacement therapy



- testosterone therapy is contraindicated in individuals with prostate cancer, with an increased PSA level > 3 ng/mL, erythrocytosis (hematocrit > 50%), prostatic hyperplasia (according to the IPSS scale > 19), sleep apnoea syndrome, and in patients with NYHA functional class heart failure III–IV.
- men receiving testosterone therapy should be regularly monitored according to the standard plan.

Metabolic effects of hormone replacement

Recent studies have clearly demonstrated that high testosterone levels enhance insulin-stimulated glucose disposal and reduce the risk of developing MetS. Protective effect of testosterone does not depend on changes in obesity markers. In 2007 the results of the comparative DIMALITE study were published, which examined the efficacy of testosterone in men aged 35–70 years with T2DM and MetS with low levels of free testosterone < 40%. In a 12 week study the dynamics of metabolic risk factors on the background of two types of treatment, the first group of men received advice on lifestyle changes, and the second group of men along with that was assigned to receive 50 mg of testosterone per day, were studied (Table 4.6). In general, both groups received positive and significant changes. However, in the second group the metabolic effects were more pronounced, in particular, free testosterone levels increased to normal (40–60%), which was combined with a reduction in BMI by 17%, waist circumference by 10%, levels of glycated haemoglobin by 16%, TG by 48%, and HDL cholesterol by 20% [26]. This data has been confirmed by the results of a series of clinical studies using injectable forms of testosterone undecanoate. Thus, normalization of total testosterone levels (Figure 4.5) in 24 men over 30 years old with diabetes and testosterone levels less than 12 nmol/L was combined with a significant reduction in IR (HOMA IR). In general, the use of hormone replacement therapy reduced insulin requirements on average by 7 ± 1.9 units per day. Along with that, there was a decrease in waist circumference by 6 cm, a considerable reduction in TG levels by 50% and LDL cholesterol levels in blood by 20%. According to Zitzmann M and co-authors, an injectable

Table 4.6. **DIMALITE STUDY**
(Diabetes Management by Lifestyle and Testosterone)

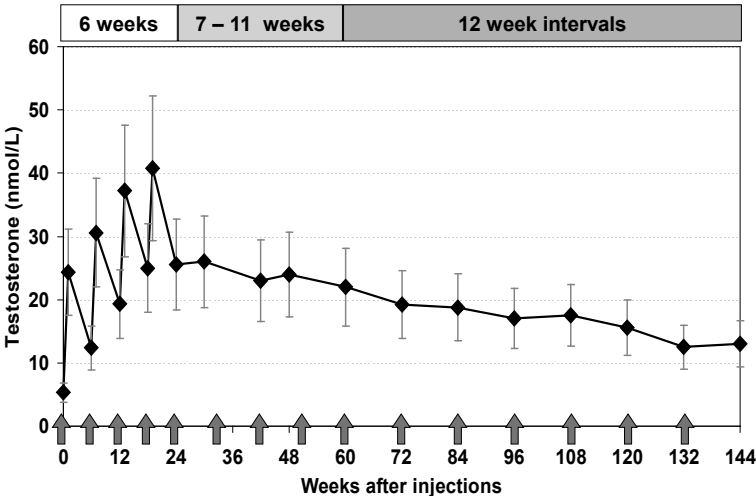
Men aged 35–70 years with type 2 diabetes mellitus (metabolic syndrome), and FAI levels (T / SHBG) < 40%.

Indicators	Lifestyle changes		Lifestyle changes + + testosterone (50 mg/day)	
	Before Study	After 12 months	Before study	After 12 months
FAI (T/SHBG)	28.6	36.7*	29.3	48.2*
BMI	33.6	29.4*	32.7	27.2*
Waist Circumference	107.4	102.6*	106.8	95.7*
HbA1c	7.6	6.82*	7.49	6.28*
Triglycerides	271	168*	286	149*
HDL cholesterol	38.6	43.7*	38.2	46.5*

* p < 0.05 significant difference compared to initial values

Heufelder et al, 2007

Figure 4.5. Dynamics in total testosterone levels of testosterone undecanoate injections every 12 weeks in patients with hypogonadism



von Eckardstein S et al. J Androl 23: 419 – 425 (2002)

Table 4.7. Effect of testosterone undecanoate on metabolic risk factors in men with hypogonadism and type 2 diabetes

Indicators	Initially	After 90 Days
HbA1c	7.4%	– 0.3%
Waist Circumference, sm	106 sm	– 6 sm
BP	132/90 mm Hg	– 5%
Total Cholesterol, mmol/L	6.3 mmol/L	– 17%
HDL Cholesterol, mmol/L	1.23 mmol/L	7%
Triglycerides, mmol/L	2.81 mmol/L	– 40%

European Journal of Endocrinology (2006) 154 899-906
Zitzmann M et al. Endo 2005 Abstract Book: 306

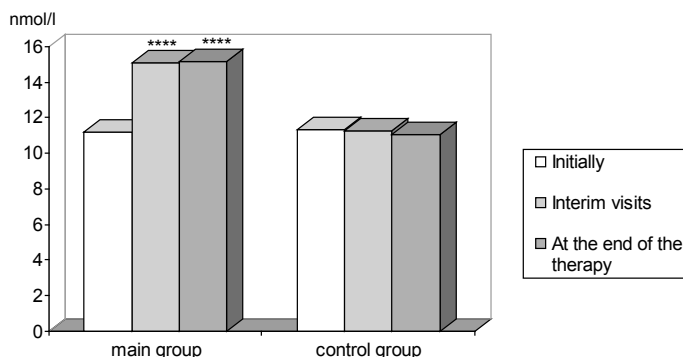
form of testosterone undecanoate helps reduce BP by an average of 5% (Table 4.7).

At the National Research Center for Preventive Medicine a clinical trial was conducted to study the efficacy and safety of hormone replacement therapy in men with high cardiovascular risk (without clinical manifestations of CVD) and confirmed androgen deficiency. For this purpose, 40 men were randomly divided into two groups:

The first (control) group of men (n = 20) continued to receive prior therapy, which had been carried out before the study (in most of the cases it was the antihypertensive therapy).

The second (main) group on the background of the prior therapy received a drug (1000 mg testosterone undecanoate). The drug was administered intramuscularly in a phased manner (4 injections): first injection was 0 point of the start of therapy, a second injection was after 6 weeks, the intervals before the third and fourth injections were 12 weeks. The study duration was 30 weeks. The initial levels of total testosterone in the main and control groups were comparable. However, during the intermediate stage, we observed an increase in total testosterone levels in the main group patients, which was significantly higher than in the control group of patients (Figure 4.6). At the endpoint, there was the retention of that tendency in both groups of men with hypogonadism and high CV risk. A conducted course of

Figure 4.6. Assessment of the impact of testosterone undecanoate on testosterone levels in men with high cardiovascular risk and hypogonadism



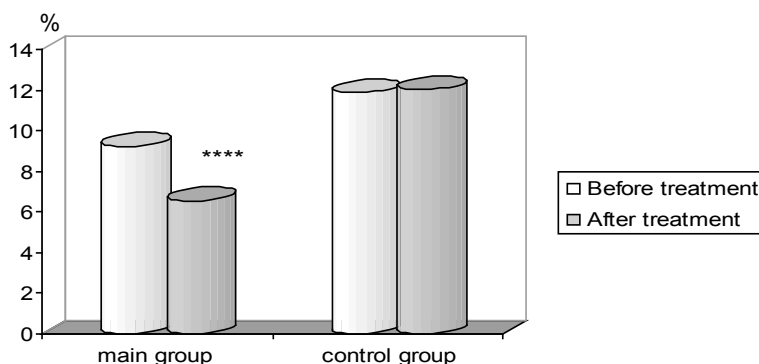
**** $p < 0.0001$ significant difference compared with initial levels and control group

treatment contributed a significant increase in total IIEF score by 12%, whereas in the control group the averages did not have any statistical fluctuations.

One of the trial objectives was to determine the effect of hormone replacement therapy on cardiovascular risk factors, including metabolic disorders. The course of hormone replacement therapy helped reduce BP by 10% (initially, patients had grade 1–2 hypertension), the body weight by 2.8 kg, waist circumference by 1.7 cm, levels of total cholesterol by 11%, LDL cholesterol by 12%, TG by 22%, and the IR index. All these changes as compared with the control group were statistically significant. The course therapy with testosterone undecanoate resulted in a decrease in the total CV risk by 30%, which was significant when compared with the initial level in the main group, and also with a control group (Figure 4.7). However, the average figures of the total CV risk after hormone replacement therapy (HRT) were still in the range of high risk.

An important objective of the trial has been to study how safe the testosterone undecanoate therapy is in patients with androgen deficiency and high cardiovascular risk. For this purpose we studied the dynamics of a set of indicators, including the levels of hemoglobin, hematocrit, liver enzymes activity, renal parameters, prostate ultrasound and determination of PSA. The study found that the levels of bilirubin, hemoglobin, erythrocytes, hematocrit, alanine transaminase

Figure 4.7. Effect of hormone replacement therapy on the level of total cardiovascular risk according to SCORE scale



**** $p < 0.0001$ significant difference compared to baseline and control group

(ALT), aspartate transaminase (AST), creatinine, and urea increased compared with the initial levels and the control group. However, these changes were not more than 5% and did not exceed the normative values (Table 4.8). PSA and prostate volume also increased transiently, but after the therapy they returned to their original levels.

Thus, the use of hormone replacement therapy in patients with age-related hypogonadism and high cardiovascular risk not only normalizes the levels of total and free testosterone, but also positively affects the main CVD risk factors, and it is a relatively safe treatment.

In the literature there are also discussions about the effect of hormone replacement therapy on clinical symptoms of angina and chronic heart failure. According to some authors hormone replacement therapy with testosterone improves angina symptoms in men with IHD, in particular, the time of onset of ST segment depression is reduced by 1 mm [27–29]. The results of a series of studies have shown that testosterone improves myocardial blood flow in men with IHD, in particular, the diameter of the coronary arteries and the blood flow are increased, and there is an increase in the time of onset of ST segment depression by 1 mm and in exercise tolerance. The efficacy of testosterone therapy has been also studied in men with chronic heart failure. In a double-blind, placebo-controlled study of 76 men with moderate chronic heart failure the testosterone therapy improved

Table 4.8. Dynamics of safety parameters in relation to testosterone undecanoate therapy

	Parameters initially	Interim visit parameters	Parameters after treatment
<i>Hemoglobin, g/L</i>			
Main Group	143.90±2.21	148.65±2.06 ****	148.70±1.63 ****
Control Group	145.75±2.82	145.80±2.39	145.60±2.37
<i>Bilirubin, mkmol/L</i>			
Main group	14.57±0.86	16.67±0.67 ****	16.15±0.73 ****
Control group	13.72±1.09	14.17±1.00	13.99±1.10
<i>Creatinine, mkmol/L</i>			
Main group	91.68±2.75	94.65±3.59*	93.84±2.88*
Control group	79.55±3.52	83.85±3.00	82.55±2.40

*p < 0.05 significant difference compared with control group;
 ***p < 0.001 significant difference compared with control group

exercise tolerance [30]. Thus, testosterone improves the function of the myocardium and also reduces cardiovascular risk. On the other hand, the results of a systematic review of the literature suggest that there are no randomized, placebo-controlled studies of the impact of testosterone replacement therapy on cardiovascular endpoints in young hypogonadal men. A meta-analysis of randomized trials indicates that in elderly hypogonadal men the incidence of cardiovascular events is comparable to the placebo group.

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Chapter 5

CONSENSUS ON THE DIAGNOSIS AND TREATMENT OF ERECTILE DYSFUNCTION, ANDROGEN DEFICIENCY AND CVD

We once again ask the question. Is there a direct link between ED, hypogonadism and MetS?

The accumulated facts and arguments of the leading experts suggest that:

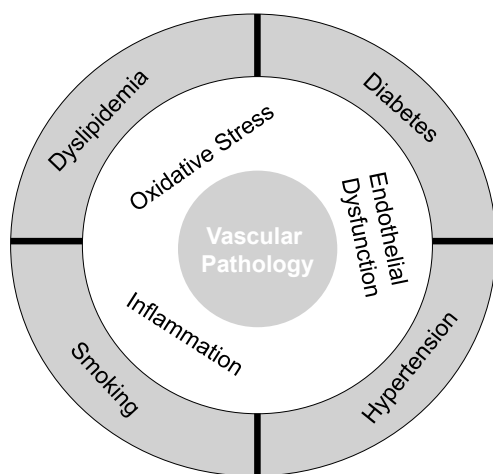
- Many components of MetS are risk factors for ED. According to domestic researchers, among 7 main risk factors (high cholesterol, overweight, hypertension, family history of CVD, IR / hyperinsulinemia, hypertriglyceridemia, T2DM) the highest correlation with ED has IR / hyperinsulinemia, hypertriglyceridemia and T2DM – in other words, the main metabolic disorders [1]. It has been shown in large studies that not only ED may precede the development of MetS, but also there is a high probability of developing ED in men with MetS [2].
- Hypogonadism is associated with MetS. According to Pagotto U et al., the immunoreactive insulin levels and markers of IR in patients with hypogonadism were significantly pronounced in comparison with a group of men with obesity and normal weight. In the population-based San Antonio Heart Study of CVD and diabetes a positive correlation between testosterone levels and metabolic risk factors has been established. High testosterone levels in men were associated with low atherogenic index and insulin levels [3];
- Hypogonadism is one of the reasons for ED. This hypothesis has been proven in many studies. Among men with ED and MetS in

comparison with men with ED and without MetS, the number of individuals with low testosterone levels occurs 5 times more often [1, 4–6].

Thus we can assume that, in a combination of all three disorders, first place belongs to the common mechanisms of vascular disorders. In experimental studies it has been shown that a combination of risk factors contributes to the development and interaction of the three mechanisms: endothelial dysfunction, oxidative stress and chronic inflammatory process, and that leads to the development of various organic changes of the arteries of different calibres (Figure 5.1). According to De Angelis and co-authors in patients with diabetes and ED in comparison with patients with diabetes and without ED there is a statistically significant increase in the level of specific markers of endothelial dysfunction, hypercoagulability and decrease in blood fibrinolytic activity, and also inflammatory cytokines such as thrombomodulin, P-selectin, intercellular adhesion molecule 1 (ICAM-1), plasminogen activator inhibitor-1 (PAI-1) [7, 8].

It is obvious that metabolic risk factors, in particular MetS, act as a unifying link between development of CVD, ED and androgen deficiency, all of which affect the length and quality of life in men of working age.

Figure 5.1. Risk factors and vascular pathology: a single mechanism

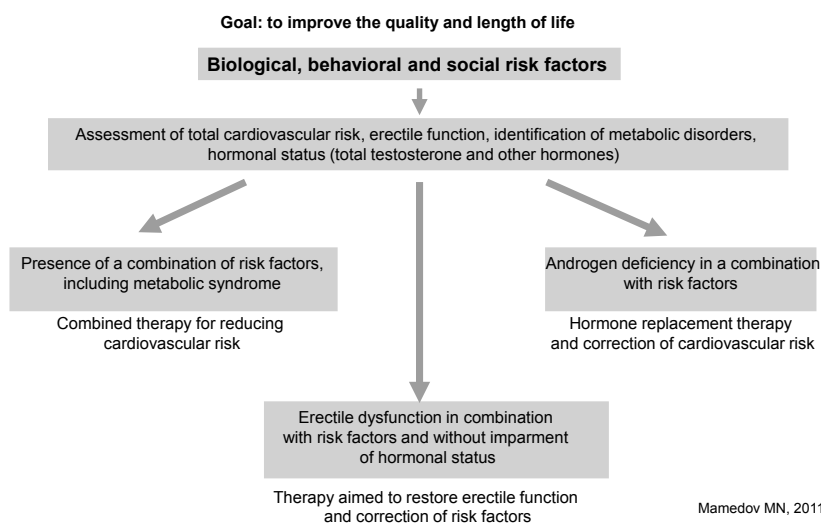


However, we cannot assume that all men who suffer from ED and / or androgen deficiency have MetS. We also cannot say the opposite. MetS is not always associated with ED and / or androgen deficiency, because these disorders have a polyetiological nature. In this regard, the development of a common diagnostic strategy is required, including differential diagnosis and correction of comorbidity.

To develop interdisciplinary algorithms we have used the main regulations of international guidelines developed by three respected societies: the European Society of Cardiology, the European Association for the Study of Diabetes and the International Society for Sexual Medicine (Figure 5.2).

Men with the presence of the following disorders: obesity, hypertension, diabetes, fatty liver disease, gout, IHD, chronic kidney disease, infertility, osteoporosis, ED, belong to the group of risk of detecting comorbidity. During the conversation with patients, along with clarifying their lifestyle, bad habits, and family history, it is necessary to use the IIEF and AMS questionnaires. Clinical examination and instrumental assessments include not only the general physical examination, but also the examination of the genitourinary system,

Figure 5.2. Consensus on early diagnosis and correction of non-infectious diseases among men



the measurement of BP, heart rate, waist circumference, and ECG at rest. Laboratory investigations include conduction of a fasting lipid profile blood test (total cholesterol, LDL cholesterol, TG, HDL cholesterol), an oral glucose tolerance test, and determination of the total and free testosterone levels (in some cases SHBG, LH and FSH levels are determined). Determination of total cardiovascular risk by the SCORE scale allows estimating not only a predictable risk of fatal cases from cardiovascular complications in the next 10 years, but also the tactics on selecting the medical correction. To determine the total cardiovascular risk it is necessary to define the following parameters: age, smoking status, BP level and total cholesterol levels. Once the total cardiovascular risk has been calculated, patients are allocated to one of three groups: low and moderate risk < 5%, high risk 5–10%, very high risk > 10% [9].

Depending on the presence of certain disorders, as well as their combinations, patients are divided into three groups:

The first group is a group of patients with MetS or a combination of several risk factors, without ED and hormonal imbalance. These patients are usually seen by a cardiologist or physician. The aim of the treatment is to prevent cardiovascular events. Usually, to achieve the target levels in the main risk factors, non-pharmacological and pharmacological methods of treatment are applied, including anti-hypertensive, lipid-lowering, and antihyperglycemic therapies. In some cases, antiplatelet agents are prescribed (for example, aspirin) to patients with high and very high cardiovascular risk. According to the STENO study data, the treatment of hyperglycemia, hypertension, and dyslipidemia in combination with aspirin therapy in patients with high risk of metabolic disorders, contributed to achieving target levels of BP in 50-80%, LDL cholesterol in 78%, TG in 62%, and glycosylated hemoglobin in 6.5% of patients, which ultimately contributed to the reduction of more than 50% of cardiovascular events [10].

Dose titration of the prescribed drugs is conducted in stages by monitoring the efficacy parameters (BP, heart rate, lipids, fasting plasma glucose and two-hour plasma glucose) and safety (liver enzymes when lipid-lowering drugs are assigned, and also creatinine when antihyperglycemic therapy is assigned). To evaluate treatment strategy the level of total cardiovascular risk is also estimated in the dynamics.

The second group is a group of men with MetS and ED without hypogonadism. Taking into consideration that the majority of metabolic disorders are long-term asymptomatic, ED can be one of their markers. In addition, it is serious motivation for men of reproductive age to go to a doctor. The presence of ED is an indication for further examination of a patient in order to identify other important disorders and diseases.

In the long term, these patients are assigned to combination therapy for correction of main risk factors. As cardiovascular risk factors make a big contribution to the development of ED, it is possible that in the majority of men the combination therapy may reduce the severity of sexual dysfunction. According to the guidelines of the European Association of Urology for treating ED (Guidelines on Male Sexual Dysfunction, 2006, update 2009), lifestyle changes and correction of risk factors have to precede the treatment of ED or be a part of combination therapy (level of evidence 1b, grade A recommendation) [11].

There are certain restrictions on the use of antihypertensive medications [12]. These medications include diuretics, beta-blockers, agonists of central alpha receptors and sympatholytic drugs (Table 5.1). In the large clinical TOMHS trial it has been studied the efficacy and safety of five groups of antihypertensive drugs (acebutolol – a beta-blocker, amlodipine – a calcium channel antagonist, chlortalidone – a diuretic, doxazosin – an alpha-adrenoblockers, and enalapril – an ACE inhibitor). After 24 months in men, who received chlortalidone, the prevalence of ED was two times more than in the placebo group (17.1% vs. 8.1%, $p = 0.025$). However, after 48 months the ED incidence were similar in both groups. At the end of the treatment the evidence of ED decreased in all groups, however, in the doxazosin group the reduction of the incidence was from 6% to 1.3% [10]. In the TAIM study it has been shown that chlortalidone and atenolol cause sexual dysfunction in men and, to a lesser extent, in women. By the way, that study was the most notable in the evaluation of the positive effects of non-pharmacological methods of treatment on patients' sexual function. In the study, conducted by Muller and co-authors, the link between taking diuretics, beta blockers and ED has been proved. On the other hand, in patients treated with antihypertensives drugs, which mechanism of action directed to block

Table 5.1. Effect of different classes of antihypertensive drugs on sexual function

	Erectile Function	Libido	Ejaculation	Gynecomastia	Priapism
Thiazide Diuretics	↓	↓	↓		
Spironolactone	↓	↓		↓	
Beta-Blockers	↓	↓		↓	
Adrenergic Blockers Central Effect	↓	↓	↓		
Adrenergic Blockers Peripheral Effect	↓		↓	↓	↓
Vasodilators	↓				↓
Calcium Antagonists			↓	↓	
ACE Inhibitors	↑	↑			
Sartans	↑	↑			

Ferrario CM, Levy P.. J Clin Hypertens (Greenwich) 2002;4(6):424-32.

the renin-angiotensin system, the risk of ED is considerably lower. According to our data, 6 month therapy with the use of combination therapy of angiotensin-converting enzyme inhibitors and diuretics (lisinopril / hydrochlorothiazide and perindopril / indapamide), like monotherapy of angiotensin-converting enzyme inhibitor (ramipril), does not worsen erectile function in men with hypertension and high cardiovascular risk (Table 5.2). Perhaps this is due to the fact that ACE inhibitors negate the adverse effects of diuretics. On the other hand, small doses of thiazide and thiazide-like diuretics do not have significant adverse metabolic effects, including on ED.

Experts have summarized the possible mechanisms for the development of sexual dysfunction in hypertension, and by using antihypertensive drugs:

- Effects of untreated hypertension
- Co-factors, such as smoking, diabetes, etc.
- Hemodynamic factors
- Neurological factors

Table 5.2. Average values of erectile function according to IIEF questionnaire in men with hypertension and metabolic disorders due to antihypertensive therapy

Group	Erectile function according to IIEF, Points	
	Before treatment	After treatment
Ramipril 5-10 mg	20.5±1.2	20.5±1.3
Perindopril 4 mg/ Indapamide 1.25 mg	19.9±0.8	19.6±0.9
Lisinopril 20 mg/ Hydrochlorothiazide 12.5 mg	19.8±1.3	19.7±1.4

Mamedov MN, Stroeva MV, 2010

- Hormonal factors
- Indirect effects (fatigue, etc.)

However, none of the mechanisms is the only one in the development of ED, as in one patient there are several mechanisms involved. In general, the reviews dedicated to hypertension, the greatest attention must be paid to adequate control of BP. At the same time we can not ignore the danger to patients' health associated with the development of uncontrolled hypertension. Therefore, there should not be any reduction in the treatment or discontinuation of antihypertensive therapy in patients with the development of ED [13]. In most cases, ED does not disappear after discontinuation of therapy. The most rational approach of solving problems associated with ED in patients, who received antihypertensive therapy, is a confidence that used drugs have the least potential impact on erectile function of patients, and an active introduction to the practice of non-drug therapy for correction of hypertension. In summary, the review of available literature suggests to make the following conclusions:

- The prevalence of sexual dysfunction is not fully evaluated by conducting a number of clinical investigations.
- ED, regardless of antihypertensive therapy, has been observed significantly more often in all men with hypertension than in men of the same age without hypertension.
- Women with hypertension have the same level of risk of sexual dysfunction as men.

- Non-pharmacological methods of therapy, such as exercise and diet, can improve sexual function impaired by taking antihypertensive medications.
- Sexual dysfunction, especially, ED, is a common complication and a reason for not providing antihypertensive therapy.
- Risk of sexual dysfunction is notably higher when taking certain classes of antihypertensive agents.
- Mechanisms by which antihypertensive drugs affect sexual function in patients are not fully established.

In recent years there have been publications that selective beta-blockers at medium doses and thiazide diuretics at low doses (e.g., hydrochlorothiazide 12.5 mg) have a significantly less impact on erectile function in men [14].

There are ambiguous data on an impact of lipid-lowering medications on erectile function. According to Saltzman and co-authors, in 8 out of 9 patients treated for 3.7 months with atorvastatin erectile function was improved in men with hypercholesterolemia. That was combined with a reduction in total cholesterol and LDL cholesterol ($p < 0.001$). Other authors, like Solomon and co-authors, showed that in men with high cardiovascular risk the initial IIEF score was 18.7 (57% of them had ED), after statin therapy the average IIEF was 10.4 points. In other words, the negative dynamics were obtained [15,16]. On the one hand, the positive impact of statins on erectile function may be due to their pleiotropic effects. In particular, there is local improvement in endothelial function and restoration of endothelium-dependent vasodilation, and also suppression of secretory activity and macrophage and smooth muscle cell proliferation. On the other hand, inhibition of cholesterol synthesis contributes to the reduction of the steroid hormone synthesis, including sex hormones. Of course, this direction is for further study. We are currently conducting clinical research on the effect of different doses of atorvastatin on erectile function in men with high cardiovascular risk. The prior results suggest that after 6 month therapy with 40 mg of atorvastatin there has been a slight reduction of erectile function in men with an initial ED. The final results of the study will be published in 2014.

In most cases, to recover erectile function and to improve the quality of life of men, PDE5 inhibitors are added to the basic etiologic

and pathogenetic therapy. It is known that PDE5 inhibitors have the vasodilating action. In a number of studies the cardiovascular effects in patients with comorbidity, including hypertension, have been specially studied. In general, the hemodynamic effects of PDE5 inhibitors do not differ from the placebo effect. It has been also shown that they are safe to use in patients receiving antihypertensive therapy. In a series of clinical studies the safety of combining PDE5 inhibitors with the main groups of antihypertensive drugs, such as amlodipine at a dose of 5 mg a day, metoprolol at a dose of 25–100 mg a day, enalapril at a dose of 10–20 mg a day, indapamide at a dose of 2.5 mg a day and losartan at a dose of 25–50 mg a day, has been demonstrated [17,18].

The third group of patients has all three disorders, including MetS, hypogonadism and ED. The presence of low testosterone levels with decreased libido and MetS is an indication for hormone replacement therapy. Studies show that combination therapy with testosterone and PDE5 inhibitors can potentiate in erectile function recovery. According to Shabsigh R and co-authors when PDE5 inhibitors are ineffective in men with ED and hypogonadism the use of androgen replacement therapy significantly increases the effectiveness of PDE5 inhibitors. Thus, according to a fixed list of IIEF, the combination therapy improves erectile function, sex life satisfaction, orgasmic function, sexual desire, and overall satisfaction [19]. According to Aversa A in patients with arteriogenic ED and hypogonadism, testosterone addition to PDE5 inhibitors improves penile arterial blood flow [20].

On the other hand, it is known that androgen replacement therapy positively affects CVD risk factors and, especially, metabolic risk factors. If during testosterone replacement therapy the total cardiovascular risk (or CVD risk factors are not reduced to the target levels) remains at a high level, then a decision about prescribing medications to reduce it is made [21].

When several drugs such as testosterone, lipid-lowering, anti-hypertensive and antihyperglycemic medications simultaneously administrated it is important to monitor the levels of safety markers (liver enzymes, creatinine, hemoglobin, and PSA).

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CONCLUSION

At the turn of the Century risk factors, including metabolic disorder risk factors, play an important role in the development of cardiovascular disease and their complications among working age men, which leads to deterioration in the quality of life and a decrease in its duration. Clinical studies show that among MetS, ED and androgen deficiency, there is a close pathogenetic link that must be considered in diagnosis and selection of preventive measures. Obviously, if a patient has multiple disorders then an integrated approach to the diagnosis and selection of medication must be applied.

Does this mean that in «real world» clinical practice a urologist has to diagnose MetS and prescribe cardiac medications? Or, vice versa, a cardiologist has to prescribe urological procedures and treatment regimens? Certainly, specialists should carry out their respective specialist responsibilities. However, knowing that in the pathogenesis of ED and / or androgen deficiency the role of metabolic risk factors is high, a urologist should promptly refer a patient to a cardiologist or endocrinologist to correct these disorders. As, in most cases, without correction of these risk factors there is little chance of successful treatment for sexual disorders. The presence of sexual disorders and / or androgen deficiency increases the severity of metabolic disorders and clinical course of cardiovascular disease. Therefore, these «cardiac» patients should have consultations with urologists and / or endocrinologists to develop integrated measures of correction.

If a patient has been diagnosed with ED and / or hypogonadism then the following should be measured:

- waist circumference
- BP level

- lipids
- fasting blood glucose

In cardiology practice, if there is MetS in men, according to preliminary questionnaire results (IIEF and AMS), then it is necessary to decide on a patient's referral to a urologist for diagnosis and treatment of ED and / or androgen deficiency.

Thus, men's health is an interdisciplinary problem, and disorders in the reproductive system are often the markers of more serious pathology which requires a comprehensive approach and the efforts of doctors from various specialties in diagnosis and treatment.

APPENDIX 1

10-YEAR PROGNOSIS FOR DEVELOPING FATAL CARDIOVASCULAR EVENTS

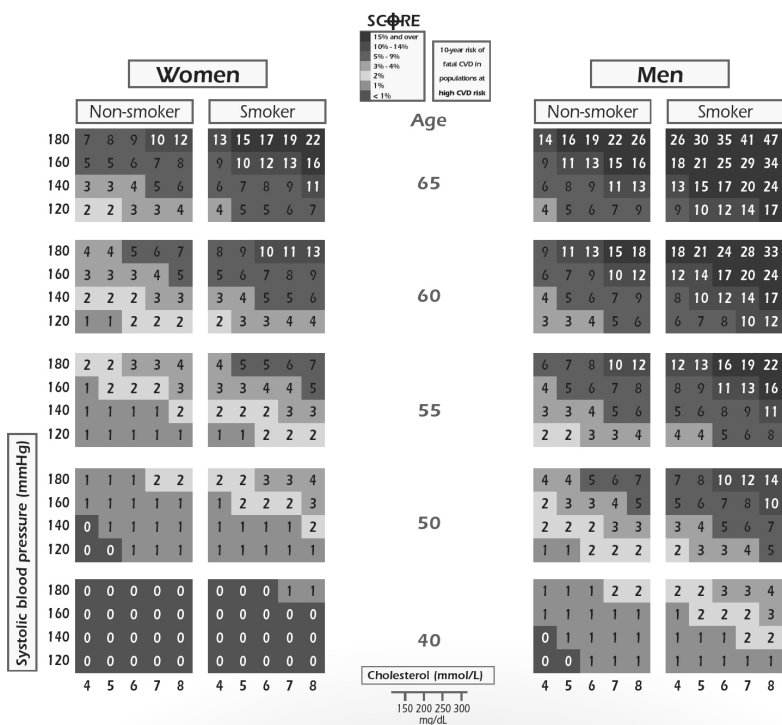
European SCORE (Systematic COronary Risk Evaluation) Scale

Instructions for using the scale

- To assess an individual's total cardiovascular risk for a 10-year period it is necessary to choose the part of the table that corresponds to the patient's sex, age and smoking status.
- Inside the selected part of the table, find the cell containing the closest measurements of the patient's individual systolic BP and total cholesterol level. The number in the cell at the intersection of these two parameters will determine the patient's individual absolute risk.
- If there are some additional risk factors (mentioned above) then it is necessary to move to the next cell of the scale, indicating an increased risk.
- Assessment of the individual relative risk is measured by comparing the absolute risk of the patient with the risk of non-smoker of the same sex and age, with systolic BP < 140/90 mm Hg and total cholesterol level < 5 mmol/L.
- On the scale it is possible to track the effectiveness reducing risk factors (and demonstrate this to a patient!). For example, the total cardiovascular risk is significantly reduced after smoking cessation, reduction of total cholesterol level or BP correction.

SCORE - European High Risk Chart

10 year risk of fatal CVD in high risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status.



Appendix 2

SCALE FOR DETERMINING ERECTILE FUNCTION (INTERNATIONAL INDEX OF ERECTILE FUNCTION)

This questionnaire is designed to assess your sexual health. Answer the following questions. Each question has five choices of answer. Circle the number of the answer that best fits your condition. You can only choose one answer.

1. How often can you achieve an erection during sexual intercourse?

- Almost never or never – 1
- A few times (much less than half the time) – 2
- Sometimes (about half the time) – 3
- Most times (much more than half the time) – 4
- Almost always or always – 5

2. When you have an erection during sexual stimulation, how often is it sufficient for penetrating of the vagina by the penis?

- Almost never or never – 1
- A few times (much less than half the time) – 2
- Sometimes (about half the time) – 3
- Most times (much more than half the time) – 4
- Almost always or always – 5

3. How often are you able during sexual intercourse to maintain your erection after penetrating of the vagina by the penis?

- Almost never or never – 1
- A few times (much less than half the time) – 2
- Sometimes (about half the time) – 3

- Most times (much more than half the time) – 4
- Almost always or always – 5

4. How difficult is it during intercourse to maintain your erection to completion of intercourse?

- Extremely difficult – 1
- Very difficult – 2
- Difficult – 3
- Slightly difficult – 4
- Not difficult – 5

5. How often do you feel satisfaction from sexual intercourse?

- Almost never or never – 1
- A few times (much less than half the time) – 2
- Sometimes (about half the time) – 3
- Most times (much more than half the time) – 4
- Almost always or always – 5

Add up the points and estimate a degree of erectile dysfunction:

- 22–25 – Normal
- 17–21 – Mild
- 12–16 – Moderately mild
- 8–11 – Moderate
- 5–7 – Severe

APPENDIX 3

**QUESTIONNAIRE FOR THE ASSESSMENT
OF ANDROGEN STATUS IN MEN
(AMS QUESTIONNAIRE)**

What kind of symptoms do you have at the moment?

Please tick the appropriate box for each symptom. If there are no symptoms please tick in the «no» box.

1. Deterioration of health and general condition

(general health, subjective feelings).....

2. Joint and muscle pain

(low back pain, joint pain, middle back pain, pain across the back)...

3. Increased sweating

(unexpected / sudden periods of increased sweating, hot flushes, independent of strain).....

4. Sleep problems

(difficulties in falling asleep, during sleep, with early wakening, feeling tired, poor sleep, insomnia).....

5. Increased need for sleep, often feeling tired

6. Irritability

(feeling aggressive, irritability over trifles, low spirits).....

7. Nervousness

(inner tension, restlessness, anxiety).....

8. Anxiety

(panic attacks).....

9. Physical exhaustion / lack of vitality

(general decrease in capacity to work, reduced activity, lack of interest in leisure activities, reduced self-rating, dissatisfaction

of what have been done, achieved, the need to force yourself to be active).....

10. Decrease in muscle strength

(feeling weak).....

11. Depression

(feeling down, sad, tearfulness, lack of incentives, fluctuation of mood, feeling worthless).....

12. Feeling that life's peak has passed.....

13. Emptiness, feeling of hitting rock bottom.....

14. Decrease in beard growth.....

15. Reduced capacity and frequency of sexual relations.....

16. Decrease in the number of morning erections.....

17. Decrease in sexual desire / libido

(lack of pleasure in sex, lack in desire for sexual intercourse).....

Symptoms:

Points:

No	1
Mild	2
Moderate	3
Severe	4
Very severe	5

Points

Severity of symptoms

17-26.....	Not pronounced
27-36.....	Slightly pronounced
37-49.....	Medium pronounced
> 50.....	Very pronounced