Original Article:

High prevalence of metabolic syndrome in populations at high and low cardiovascular risk in Bulgaria

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Abstract:

Objective: Metabolic syndrome (MetS) is associated with cardiovascular risk. We examined the prevalence of MetS in well-defined groups with manifested cardiovascular disease (CVD) or at high CVD risk, and in a low-risk population. We also analysed the CVD burden of the MetS in these populations. **Methods:** A total of 2123 subjects were examined: 1.with history of acute myocardial infarction (AMI) (n=372); 2.with hypertension (n=620); 3.with type 2 diabetes mellitus (n=556) and 4.healthy controls (n=575). All participants underwent standardised examination of cardiovascular risk. **Results:** The prevalence of the MetS was: 80% in men and 89% in women according to the Adult Treatment Panel III (ATPIII) definition, 85% in men and 93% in women according to the International Diabetes Federation (IDF) definition in the AMI group; 43% in men and 53% in women (ATPIII criteria), 47% in men and 61% in women (IDF criteria) in the hypertensive group; 70% in men and 79% in women (ATPIII), 77% in men and 86% in women (IDF) in the diabetic patients; and 23% in men and women (ATPIII), 30% in men and 36% in women (IDF criteria) in the controls. In logistic regression analysis the presence of MetS was found an independent determinant of previous AMI in the examined population. **Conclusion:** Excessively high prevalence of MetS was found in populations with or at high CVD risk, and a high prevalence even in a low-risk group in Bulgaria. The presence of MetS increased CVD risk.

Keywords: metabolic syndrome, cardiovascular risk, type 2 diabetes mellitus, hyper/dyslipidemia

Introduction:

Metabolic syndrome (MetS) is characterized by the clustering of central obesity, dyslipidemia (hypertriglyceridemia and low high-density-lipoprotein (HDL) cholesterol), hyperglycemia (or type 2 diabetes mellitus) and hypertension, is currently showing a dramatic explosion worldwide in association with the modern lifestyle of physical inactivity and unhealthy nutrition [1-3]. The differences in the definition of the MetS according to the World Health Organization (WHO) from 1999 [4], the European Group for the study of Insulin Resistance (EGIR) from 1999 [5], the National Cholesterol Education Program (NCEP) in the USA from 2001 [6] and the International Diabetes Federation (IDF) from 2005 [1,7] have resulted in some confusion among physicians in identifying the affected individuals. Many authors have reported different prevalence of the MetS in the same populations when applying different definitions [8, 9].

Despite current disagreements on how exactly to diagnose the MetS, it has been convincingly shown that it is associated with increased cardiovascular risk [10-13]. Thus, type 2 diabetic patients with MetS were shown to have a worse cardiovascular prognosis than diabetic subjects without the syndrome [14]. In the Botnia study [11] the presence of the MetS was strongly correlated with adverse cardiovascular outcomes, irrespective of the glycemic status at

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study baseline. Similarly, the Kuopio Ischemic Heart Disease Risk Factor study revealed that the MetS was associated with a 34-fold increased risk for death from coronary heart disease [12].

Bulgaria is among the countries with the highest death rate in Europe from macrovascular disease [15]. Thus, cardiovascular disease (CVD) mortality in Bulgarian men alone exceeds the EU average mortality from all causes [15]. Epidemiological studies show that in contrast to the decrease in age-standardized death rates of coronary heart disease in the European Union by 32 % in men and 30 % in women, in Japan by 29% in men and 36 % in women, in Canada by 60 % in men and 59 % in women, in USA by 63 % in men and 60% in women, in Australia by 64 % in men and 61 % in women in the period from 1965 to 1998 in Bulgaria it increased by 41 % in men and decreased by only 3 % in women [16]. According to a WHO report from 2006 Bulgaria was found to have the second highest CVD mortality, both in men and women, in the world, following Russia [17]. The high CVD mortality in Bulgaria could be partially explained by the high prevalence of smoking, by differences in diet and in the age class above 75 years by consequences of poverty [15-18]. It seems reasonable to assume that the MetS, a worldwide major cause of atherosclerosis, could be responsible for the high rate of cardiovascular events in the country.

In the present work we examined the prevalence of the MetS according to its most commonly used definitions – the ATP III and the IDF definition - in well-defined large groups with manifest CVD or at high risk for CVD in a country with excessively high CVD mortality as Bulgaria. For this purpose, we evaluated the prevalence of MetS in patients with history of acute myocardial infarction, patients with hypertension and patients with type 2 diabetes mellitus, as well as in a low-risk population without these cardiometabolic diseases. In addition we analysed the CVD burden of the MetS in these populations and compared the relevance of the two definitions of the MetS in this respect.

Methods:

In the time period from 2005 to 2008 in the "Robert Koch" Medical center in Sofia and the International Scientific Institute, National Sports Academy in Sofia 2123 subjects, aged 19 to 98 years, were examined with respect to their CVD risk. As recruitment sources we used advertisement by newspaper articles, TV broadcasts, invitation of our own patients and referral of eligible subjects by a network of cardiologists, general practitioners and endocrinologists. All candidates were admitted if they met either of the following criteria:

1. AMI group (n = 372): history of acute myocardial infarction with onset of cardiovascular disease (CVD) at the age below 50 years for men and below 55 years for women and a history of CVD in first degree relatives.

2. Hypertension group (n = 620): hypertension (blood pressure > 140/90 mmHg or intake of antihypertensive drugs) with onset at the age below 60 years and at least two first degree relatives with arterial hypertension.

3. Diabetes group (n = 556): type 2 diabetes mellitus with clinical onset at the age below 60 years, treated by diet only or by oral antidiabetic drugs and/or insulin and a history of diabetes in first degree relatives.

4. Healthy controls (n = 575): subjects without history of CVD, hypertension or diabetes mellitus, without first degree relatives with these diseases and with a normal ECG, fasting glucose level below 7 mmol/l and blood pressure below 140/90 mmHg on the day of examination.

The controls had to be at least as old or older than the other three groups. The gender ratio had to be the same in all examined groups. Our study complies with the Declaration of Helsinki and the ethics committee of the Bulgarian Physicians Union has approved the research protocol. Written informed consent was obtained from each subject.

The study participants underwent a standard examination according to a special protocol including: short physical examination by a physician; resting ECG; filling a questionnaire on medical history (emphasis on hypertension, hyperlipidemia and diabetes mellitus), current medication, lifestyle and on family history of obesity, diabetes mellitus, hyperlipidemia and macrovascular disease (myocardial infarction, angina pectoris, stroke and peripheral arterial occlusion). All subjects underwent standardised measurements of anthropometric parameters such as body weight, height and waist circumference. Blood pressure was examined twice in a sitting position after a rest of at least 10 minutes and the second values were taken into consideration.

Venous blood was drawn after an overnight fast of at least 10 hours for the examination of atherosclerosis risk factors, such as glucose, lipids, etc. Plasma and serum were separated by centrifugation (4000 rpm for 8 minutes at 4°C). Serum glucose and lipids were determined using fresh material. Total cholesterol and triglycerides were determined by enzyme colorimetric assay (CHOD-PAP) on a Clima Plus analyser, using commercially available test kits (Giesse Diagnostics, Italy). High-density lipoprotein (HDL) cholesterol was measured after precipitation with dextran sulphate. Serum glucose was examined by the hexokinase method (interassay CV = 1.8 %). C-reactive protein was examined by the highly sensitive method. Commercial analysis kits for highly sensitive C reactive protein (CRP) were provided by Thermo Electron, Vantaa, Finland.

The MetS was diagnosed using the definitions of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in the USA from 2001 [6] and the International Diabetes Federation (IDF) from 2005 [1,7].

Statistical analysis was conducted using the SPSS/PC + programme. The level of significance was determined by $p < 0.05$. Cardiovascular risk factors such as lipids, serum glucose, blood pressure etc. were evaluated in the patients groups using ANOVA. Data are presented as mean and standard deviation. Sex distribution was tested by χ^2-test. The relation between the two categorical variables - history of acute myocardial infarction and presence of the MetS - was assessed using the Fischer´s exact test. The probability in the occurrence of AMI in relation to the MetS was estimated as odds ratio (OR) (95% CI). To assess the relevance of the MetS as an independent determinant of AMI in the examined population we performed logistic stepwise regression analysis.

Results:

Basic characteristics of the examined subjects are given in table 1. The healthy controls were older than the patients of the other three groups, which corresponded to the inclusion criteria.

Table 1. Characteristics of the examined patients with history of acute myocardial infarction (AMI), hypertension, type 2 diabetes mellitus and healthy controls.

Parameters	AMI patients (n = 372)	Hypertensive patients (n = 620)	Diabetic patients (n = 556)	Healthy controls (n = 575)
Age (years)	50.2 (7.7)*	54.2 (8.6)*	54.0 (8.1)*	60.5 (9.1)
Gender (male/female)	182/190	303/317	272/284	280/295
Body mass index (kg/m^2)	27.1 (4.8)*	28.4 (4.3)*	27.1 (4.4)*	25.4 (3.8)
Waist circumference (cm)	94.0 (10.0)*	95.1 (11.0)*	101.4 (10.2)*	87.4 (8.1)
Blood pressure systolic (mmHg)	132.0 (11.1)*	143.1 (12.6)*	131.0 (12.3)*	123.0 (11.0)
Blood pressure diastolic (mmHg)	86.5 (9.1)*	89.7 (7.3)*	85.3 (8.5)*	78.1 (7.1)
Fasting glucose (mmol/l)	6.2 (1.6)*	5.7 (1.1)*	8.1 (2.3)*	5.4 (0.7)
Total cholesterol (mmol/l)	6.0 (1.4)*	5.4 (1.1)*	5.8 (0.8)*	4.9 (0.7)
Triglycerides (mmol/l)	2.3 (0.9)*	1.5 (0.8)*	2.18 (1.02)*	1.1 (0.5)
HDL-cholesterol (mmol/l)	0.9 (0.2)*	1.2 (0.3)*	0.96 (0.28)*	1.4 (0.3)
Hypertension (%)	60.0	100	68.5	0
Type 2 diabetes mellitus (%)	32.3	12.0	100	0
History of AMI (%)	100	1.6	13.9	0
Antihypertensive treatment (%)	83.0	80.2	63.2	0
Medical therapy of diabetes (%)	26.6	4.9	82.2	0
Lipid lowering therapy (%)	71.7	4.5	10.7	0
Aspirin intake (%)	47.3	8.1	11.2	6.5

Table 2. Prevalence (in %) of the metabolic syndrome (MetS) in patients with history of acute myocardial infarction (AMI), hypertension, type 2 diabetes mellitus and healthy controls.

Population	Prevalence of the MetS defined by the ATPIII criteria			Prevalence of the MetS defined by the IDF criteria		
	Overall	Men	Women	Overall	Men	Women
AMI patients (n = 372)	84	80	89	89	85	93
Hypertensive patients (n = 620)	48	43	53	54	47	61
Diabetic patients (n = 556)	74	70	79	81	77	86
Healthy controls (n = 575)	23	23	23	33	30	36

The sex distribution was similar in all examined groups. The mean body mass index of the controls was slightly above the upper limit of the normal range, and was significantly increased in all three patients groups in comparison to the controls. Similarly, waist circumference was significantly higher in the patients with history of AMI, hypertension and type 2 diabetes than in the healthy subjects. Blood pressure level, both systolic and diastolic, was significantly higher in all patient groups in comparison to the healthy controls. The levels of serum glucose, total cholesterol and triglycerides were significantly higher in all patient groups in comparison to the healthy subjects. HDL cholesterol level was significantly lower in all examined patient groups than in the controls. Among the AMI patients 32 % had type 2 diabetes mellitus and 60 % had known hypertension. In the hypertensive group 12 % had known type 2 diabetes mellitus, and in the diabetic group 69 % had known hypertension. Medical treatment of the patients with antihypertensives, antidiabetic, lipid lowering drugs and aspirin intake are given in table 1.

The AMI patients were under regular treatment by cardiologists, while the hypertensive patients were treated mostly only by their general practitioners, and a small part of them visited cardiologists in addition, and the diabetic patients were under a regular treatment by endocrinologists.

As shown in table 2 the prevalence of the MetS in patients with history of AMI was 80 % in men and 89 % in women according to the ATPIII definition, and 85 % in men and 93 % in women according to the IDF definition. Among the hypertensive patients 43 % of the men and 53 % of the women had MetS, defined by the ATPIII criteria, and 47 % of the men and 61 % of the women, defined by the IDF criteria. Among the diabetic patients the MetS was found in 70 % of the men and 79 % of the women, as defined by the ATPIII criteria, and in 77 % of the men and 86 % of the women, defined by the IDF criteria (table 2). The prevalence of the MetS in the group of the "healthy" controls was found to be 23 % in men and women, according to the ATP III definition, and 30 % in men and 36 % in women, as defined by the IDF criteria (table 2).

Table 3. Proportion (in %) of subjects with history of acute myocardial infarction (AMI) among subjects with and without MetS, defined by the IDF and ATPIII criteria

	without MetS	with MetS	p*
IDF criteria	20.4	41.2	< 0.001
ATPIII criteria	11.3	47.2	< 0.001

*** Fischer´s exact test**

In figure 1 the prevalence is given of subjects affected by type 2 diabetes and the MetS, alone or in combination. As shown, diabetes is much more common in combination with the MetS. In figure 2, the prevalence is presented of the subjects suffering from hypertension and the MetS, alone or in combination. Hypertension was found to be more common in a combination with the MetS in the AMI and diabetic patients, whereas in the hypertensive group the proportion of subjects with or without MetS was similar.

Figure 1. Prevalence (in %) of type 2 diabetes mellitus (DM) and metabolic syndrome (MS), alone or in combination, in the patients with history of acute myocardial infarction (AMI), hypertension (HT) and type 2 diabetes (DM).

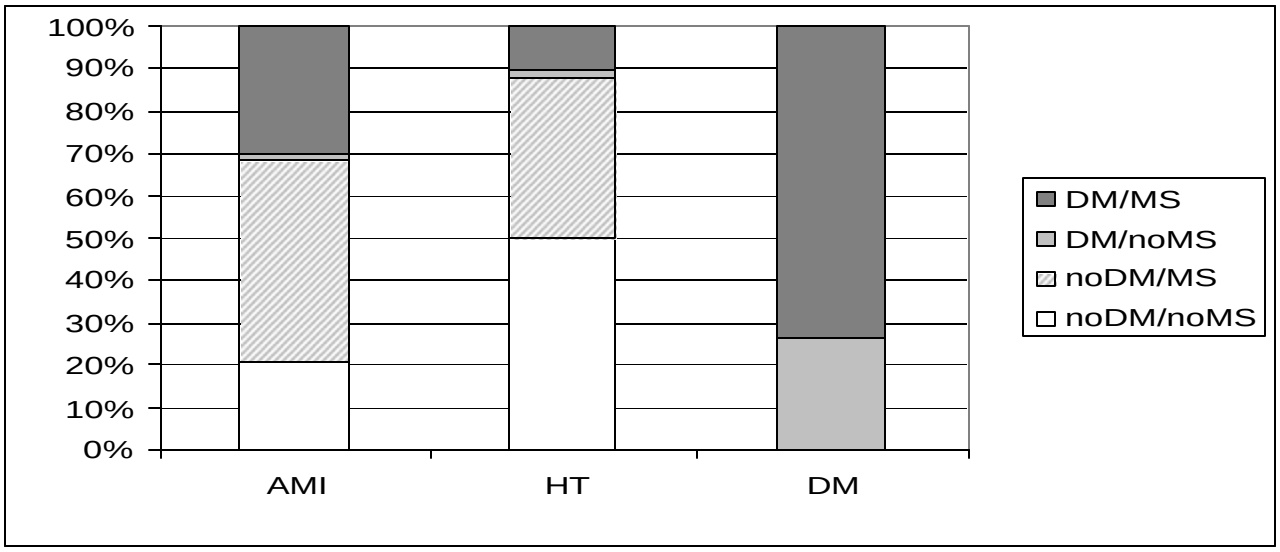
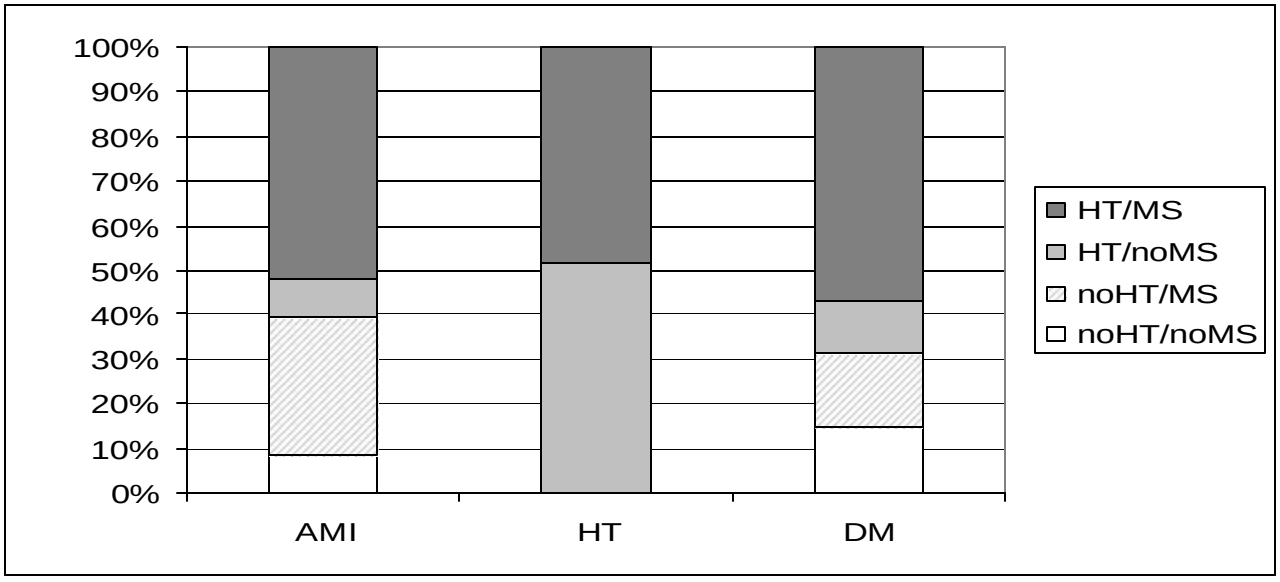


Figure 2. Prevalence (in %) of hypertension (HT) and metabolic syndrome (MS), alone or in combination, in the patients with history of acute myocardial infarction (AMI), hypertension (HT) and type 2 diabetes (DM).



The probability for a positive history of AMI was found to be much higher ($p<0.001$, Fischer´s exact test) among the subjects with MetS than among subjects without MetS, which was valid

for both IDF and ATPIII definitions, and was somewhat more strongly expressed if the ATPIII definition was applied (table 3). Besides, the odds ratio (OR) for AMI risk of the MetS, diagnosed by the ATPIII definition, was higher than the OR for AMI risk of the MetS when the IDF definition was applied: OR (95% CI) 7.04 (5.17-9.59) and 2.74 (2.12-3.54) respectively.

In logistic regression analysis we found the presence of the MetS along with age, menopause in women, smoking, CRP and total cholesterol levels to be independent determinants of previous AMI in the examined population. This was valid for both definitions of the MetS – the ATPIII and the IDF one.

Discussion:

The major findings of the present analysis on the prevalence and CVD burden of the MetS in well-defined groups in a country with an excessively high CVD mortality were: 1) excessively high prevalence of the MetS among patients with history of AMI, as well as in patients with hypertension, and in type 2 diabetic patients; 2) high prevalence of the MetS even in a well-defined group of subjects at low CVD risk; 3) the prevalence of the MetS was higher in all examined groups when the IDF definition was applied, compared to the ATPIII definition; and it was higher in women than in men; 4) both diabetes and hypertension were more often found in a combination with MetS than alone; 5) the presence of MetS was significantly related with the history of AMI; the odds ratios for AMI risk of MetS were significant, no matter which definition of MetS was used; and the presence of MetS was an independent determinant of the history of AMI; 6) the CVD burden of MetS was higher when the ATPIII definition was used (compared to the IDF definition).

The finding of the excessively high prevalence of MetS in the patients with history of AMI in Bulgaria is alarming. It has been shown that the presence of MetS worsens the outcome of myocardial infarction and is a strong predictor of severe heart failure [19]. Among the 633 patients of the Infarctus de Cote-dOr survey 46 % fulfilled the ATPIII criteria for MetS [19], and this was almost twice higher in the Bulgarian AMI population.

Although a direct comparison with the prevalence of MetS in risk populations of other countries is difficult because of the different age and sex structure of the populations, the fact that approximately half of hypertensive and more than 80 % of diabetic patients in Bulgaria are affected by MetS remains a matter of concern. In a German diabetic population, with average diabetes duration 8.4 years and mean HbA1c 7%, the prevalence of MetS by WHO criteria was 26.1%, by AHA/NHLBI 79.3%, and by IDF 82.6% [9].

The finding of high prevalence of MetS in patients with history of AMI, in hypertensive patients and in diabetic patients confirms the necessity of implementation of screening for MetS in these patients groups which are in a regular treatment by cardiologists, general practitioners or endocrinologists, respectively. This could enable the successful complex treatment of these patients. Although it is beyond the scope of the present work to analyse the quality of therapy of the patients, we would briefly mention that the control of glucose, lipids and blood pressure in these patients was not satisfactory.

The high prevalence of MetS in the low-risk group indicates the necessity of screening for the MetS also in the general population. The Sofia Metabolic Syndrome (SMS) study reported preliminary data on high prevalence of the components of MetS among the citizens of Sofia, and a very high percentage of unknown type 2 diabetes, hypertension and hyperlipidemia [20].

In this population, both in the low-risk group and in the risk populations of patients with AMI, hypertension and type 2 diabetes, women were more often affected by MetS than men. In some countries, like Greece and USA similar prevalence was also observed for both sexes [21,22]. In Turkey, India, Iran, African Americans, Mexican Americans etc. women were reported to be much more frequently affected [3,22], whereas in France and Australia the MetS was found to be more common among men [3].

Our experience of applying the ATPIII and IDF definitions of MetS confirms other observations that the prevalence of the syndrome is higher if an IDF criterion is used [23-25]. However, although the IDF definition detects a higher number of affected individuals, the CVD burden of MetS is higher if diagnosed using the ATPIII definition. This finding in the Bulgarian population is consistent with some reports in the literature indicating that ATPIII definition of MetS confers a significantly higher risk of vascular events than the IDF definition [23,24,26). Thus, in a prospective study of 750 coronary patients followed over 4 years, MetS, as defined by the ATPIII criteria,

significantly predicted vascular events, whereas MetS, as defined by the IDF criteria, did not [23]. Similarly, in a 3-year follow-up study in 882 Caucasian type 2 diabetic patients, IDF-defined MetS was shown to have a lower prognostic value than Adult Treatment Panel III (ATP-III) criteria [24]. In a population-based cohort of 5047 non-diabetic subjects from Malmö, followed for over 11 years, the ATPIII definition was superior to the IDF definition for prediction of CVD events [26]. In the Women´s Angiographic Vitamin and Estrogen trial in 372 postmenopausal women (mean age 65 years; mean body mass index 30.5 kg/m²) with angiographic coronary artery disease, however, incident cardiovascular events were similar in both MetS classifications [25].

In our study in multivariate analysis the presence of MetS along with age, menopause in women, smoking, C-reactive protein and total cholesterol levels were found to be independent determinants of previous AMI. There are many data showing that subclinical chronic inflammation is strongly related to cardiovascular disease [26-31]. Increased CRP, as well as increased leucocyte count, as markers of chronic subclinical inflammation, have also been reported to be associated with the development of type 2 diabetes and insulin resistance [30,31] and some authors have suggested that this is the mechanism by which they contribute to the increased cardiovascular risk. The data of our study, consistent with other reports, indicate that subclinical inflammation could be an independent determinant of cardiovascular events [26-30].

Conclusions: Our data demonstrate an excessively high prevalence of the MetS in populations with or at high risk for CVD, and a high prevalence even in a low-risk group in Bulgaria, a country of the second highest CVD mortality worldwide. The presence of MetS is associated with an increased CVD risk. The high prevalence of the MetS, both in high-risk and low-risk population groups in Bulgaria, could explain the excessively high cardiovascular mortality in the country, and urgently demands improvement of health care.

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