THE METABOLIC SYNDROME IN BULGARIA

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ABSTRACT

The prevalence of the metabolic syndrome (MetS), a cluster of central obesity, hyper/dyslipidemia, hyperglycemia, and hypertension is constantly increasing worldwide. Although, the exact mechanisms underlying the development of the MetS are not completely understood, modern lifestyle of physical inactivity and unhealthy nutrition, obesity, and their interaction with genetic factors are considered largely responsible. It has been convincingly demonstrated that the metabolic syndrome is associated with substantially increased risk for the development of type 2 diabetes mellitus, as well as, with increased cardiovascular disease (CVD) morbidity and mortality. The prevalence of obesity and type 2 diabetes in Bulgaria has dramatically increased in the last decades. For the same period CVD mortality in the country have also gradually increased and Bulgaria is nowadays among the countries with the highest macrovascular disease death rates in Europe. A number of epidemiological studies have demonstrated that the prevalence of the MetS and of its individual components has also increased during the last decades and is nowadays relatively high among the general population in Bulgarian and extremely high among high-risk individuals. Surprisingly, the prevalence of the MetS is also high among the low risk population in the country and most of its components that are independent predictors of CVD mortality are largely undiagnosed. Furthermore, the presence of the MetS is associated with history of myocardial infarction in the country. Although objective data is somewhat scarce, several studies have reported association of the low physical activity level and the unhealthy nutritional habits with the prevalence of cardiometabolic diseases among the Bulgarian population. Taking into account these observations it may be suggested that indeed the high metabolic syndrome prevalence that results as a consequence of unhealthy lifestyle is responsible for the extremely high CVD mortality rates in Bulgaria. Therefore, large-scale screening programmes should be undertaken within this population in combination with health prevention strategies promoting regular physical activity and improvement of nutritional habits.

Key words: obesity, metabolic syndrome, type 2 diabetes, cardiovascular disease, nutrition, physical activity

INTRODUCTION

Metabolic syndrome (MetS) is a clustering of interrelated abnormalities that include central obesity, hypertriglyceridemia, low high-density-lipoprotein (HDL) cholesterol levels, hyperglycemia, and hypertension.¹ Although the condition is not a novel pathological entity being reported in the medical literature as early back as in the Renaissance and Baroque times, it is at present experiencing an explosive development both in developed and developing countries.² The exact mechanisms underlying the development of the MetS are not completely understood; however, modern lifestyle of physical inactivity and unhealthy nutrition, obesity, and their interaction with genetic factors are considered largely responsible.³,⁴ It has been convincingly demonstrated that the MetS is associated with substantially increased risk of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and increased CVD-related mortality.⁵

The prevalence of obesity and T2DM in Bulgaria has dramatically increased in the last decades. From
some 4% in the 1940s obesity prevalence reached 22.6% in the 1960s, over 35% in the 1990s, and these numbers are considered to be even higher at present. A considerable rise in the prevalence of T2DM has also been observed – from some 0.2% in the 1940s it reached almost 2% in the 1990s and is currently estimated to exceed 8.5%. For the same period CVD mortality rates have also gradually increased and Bulgaria is nowadays among the countries with the highest CVD mortality in Europe. These extremely high rates could be accounted for by different factors such as smoking, diet, and consequences of poverty. One may, however, speculate that indeed the MetS, a worldwide major cause of atherosclerosis, is also responsible. The present review aims at summarizing the available literature findings on the MetS in Bulgaria and its association with lifestyle, particularly physical activity and nutrition.

CARDIOVASCULAR DISEASE IN BULGARIA

Bulgaria is among the countries with the highest death rate in Europe from macrovascular diseases. Thus, CVD mortality in Bulgarian men alone exceeds the EU average mortality for all causes. According to local observations in Bulgaria every fifth man and every fourth woman die of stroke, which is the leading cause of death in the country, followed by coronary heart disease death. Macrovascular disease in the form of stroke and myocardial infarction is responsible for 40-43% of the total mortality rate. Myocardial infarction was a rare disease in the country during the 40s and 50s of the last century. Epidemiological studies demonstrate that important and rapid changes in cardiovascular and all-cause mortality rates occur in Europe and that these changes between 1970 and 1990 had opposite directions in Western and Eastern Europe, leading to an increase in the gradient in the rates for cardiovascular and all-cause mortality. In 1990 the ratio for the highest vs. the lowest cardiovascular mortality amounted to 4.5. During the 1990s the cardiovascular and all-cause mortality rates began to decrease also in some Eastern European countries, the decline starting about 25 years later than in the Western European countries. The epidemiological analysis shows 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 and in USA by 63% in men and 60% in women, in the period from 1965 to 1998 in Bulgaria it increased by 41% in men and decreased by only 3% in women. The standardized death rate (SDR) for cardiovascular diseases in the age group 0-64 was above the average of the reference countries in the mid-1990s (reference countries: Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia). Since the mid-1980s, the Bulgarian SDR for men has increased by 20%, the highest increase among the reference countries. For women, the SDR having been stable for 25 years, increased from the mid-1990s, when a declining trend was observed in all other reference countries. According to a WHO report from 2006 Bulgaria was found to have the second highest CVD mortality, both in men and in women, in the world, following Russia.

The high mortality rates in Eastern Europe have been a matter of much speculation. They could be partially explained by the high prevalence of smoking, by the local nutritional habits, and in the age group above 75 years - by consequences of poverty. It, however, seems reasonable to assume that the MetS, a worldwide major cause for atherosclerosis, could be responsible for the high rate of cardiovascular and cerebrovascular events in general and particularly in Bulgaria.

THE METABOLIC SYNDROME IN BULGARIA

A number of epidemiological studies have demonstrated a gradual increase in the prevalence of the components of the metabolic syndrome, as well as of the metabolic syndrome itself among the Bulgarian population during the last few decades. In 1946 prevalence of 1.7-1.9% of hypertension was reported among Bulgarian workers engaged in physically demanding occupations. During the 1950s and 1960s a constant increase was observed and during the late 1970s and 1980s the prevalence reached 26% in some population groups. At present the prevalence of hypertension in Bulgaria is reported to be around 40%. Our recent findings are in accordance with these observations, since in the Sofia Metabolic Syndrome (SMS) study 41.3% of the examined subjects had a history of hypertension. Remarkably, however, from the SMS participants who considered themselves as being “normotensive”, 59% had increased blood pressure on the day of the examination (Fig. 1). Even higher prevalence (60%) was reported in an earlier study among women referred for bone mineral density testing. These data are consistent with the scarce data available on hypertension and the very high prevalence of unknown hypertension in the Eastern European countries. Hence, the
prevalence of hypertension in Bulgaria seems to be higher than what has been reported for Germany (55%), Finland (49%), Spain (47%), England (42%), Sweden (38%) and Italy (38%) and much higher in comparison with that for Canada (27%) and the USA (28%).

Similarly the frequency of dyslipidaemia in the country has been gradually increasing over time. In one of the first large-scale studies in 1965 relatively low total cholesterol levels were reported in more than 4000 individuals. Only 10 years later the prevalence of dyslipidaemia was notably higher and in 1985 prevalence of more than 15% was reported among middle-aged men and 8.1% in the general population. In the late 1980s Merdjanov et al. found even higher prevalence of hypercholesterolemia among the urban population of Sofia, Bulgaria – 12.7% and 11.5% for men and women, respectively had serum cholesterol levels higher than 6.5 mmol/l. Dyslipidaemia was more prevalent among the middle-aged individuals of this population – 40% of the examined subjects had mild cholesterol elevation, while total cholesterol was above 6.2 mmol/l in 17% and 14% of the examined men and women, respectively. Very recently in the SMS study we found 58.6% prevalence of hypercholesterolemia among the examined subjects with the majority of them having only mild cholesterol elevation and some 18% having total cholesterol above 6.5 mmol/l. Moderate and severe hypercholesterolemia were observed much more frequently in women, they were 80% of the affected individuals (Fig. 1). Our findings are in accordance with previous observations. Remarkably, 95% of the SMS participants were unaware of their having hyperlipidaemia and only 33% from the patients who knew that they had hypercholesterolemia, received lipid-lowering drugs.

Thus, hypercholesterolemia in Bulgaria seems to be somewhat more common than in other countries, but especially high is the unawareness about this metabolic disturbance. In the Minnesota Heart survey the mean prevalence of hypercholesterolemia in 2000 to 2002 was 54.9% for men and 46.5% for women. The authors of this study conclude that despite of the decrease in cholesterol level in the USA and improved awareness, treatment, and control of hypercholesterolemia, more than half of those at borderline high risk remain unaware of their condition. In the Bavarian Cholesterol Screening Project, about 20% of the examined population were found to have a hitherto unknown hypercholesterolemia and, therefore, screening projects for hypercholesterolemia were recommended for improving public health.

With respect to the prevalence of the MetS itself among the Bulgarian population, several studies have reported unfavourable results. In 2005 Boyanov et al. found that 35% and 37% of women referred for bone mineral density testing had the metabolic syndrome when assessed with the Adult Treatment Panel III (ATPIII) and WHO definition, respectively.

More recently, in the Sofia Metabolic Syndrome (SMS) study we also examined the prevalence of the disorder in Bulgaria. In the latter study a total of 1018 middle-aged subjects (334 male and 684 female) were included. Participants had a mean body mass index (BMI) of 26 kg/m², 22.6% of them exhibited one isolated component of the MetS – obesity, hypertension, hyperlipidemia or T2DM. A combination of two risk factors within the MetS was observed in 36.9% and of three risk factors in 26.8% of the subjects. Presence of MetS components was found in 5.9% of the examined population. Only 7.8% of the subjects had no risk factors (Fig. 2). The increase of the number of the MetS components was significantly associated with the history of myocardial infarction. The abovementioned findings demonstrate that the constellation of several metabolic risk factors is currently considerably higher of what have been observed only two decades ago.

Furthermore, although 10.3% of the examined individuals reported history of type 2 diabetes, on the day of examination additional 8.7% of them turned out to have hitherto unknown T2DM, classified as such if fasting glucose level exceeded 7.0 mmol/l (Fig. 1). Considering the fact that an oral glucose tolerance test was not performed, and that the prevalence of isolated postprandial diabetes is

Figure 1. Prevalence of known and hitherto undiagnosed type 2 diabetes, hypertension, and hypercholesterolemia among participants in the SMS study. (Adapted from Temelkova-Kurktschiev T, et al.16)
Prevalence of the metabolic syndrome risk factors in the population of the SMS study. (Adapted from Temelkova-Kurktschiev T, et al.16).

The data from the SMS study demonstrate that the risk factors within the MetS are very common in Bulgaria, and that they are frequently undetected. The finding about high proportion of unknown T2DM is consistent with reports in the literature on the delay in diabetes diagnosis.27,28 Thus, in the Atherosclerosis Risk in Communities (ARIC) study it was found that more than 7% of incident cases with type 2 diabetes remained undiagnosed for at least 7.5 years after the onset of the disease.28 In a population of patients undergoing an elective coronary angiography impaired glucose regulation was diagnosed in 40.4% and undetected diabetes in 22.7%, and the percentage of undiagnosed diabetes increased with the number of epicardial vessels involved.27 Early detection and treatment of diabetes is essential for the successful prevention of cardiovascular disease, since atherosclerosis develops in parallel to the development of T2DM.29 Similarly to diabetic patients in other countries, in Bulgaria stroke and myocardial infarction are the leading cause of death in diabetes. Thus, in 10 hospitals in Sofia for the period 1979–1983 various cardiovascular diseases were established in 96.52% of all deceased diabetics.30

In another Bulgarian population-based study, in 500 volunteers (300 female subjects) without clinical signs of cerebrovascular disease, aged 50-79 years, three or more modifiable vascular risk factors were detected in 52% of the subjects. Dyslipidemia, hypertension and obesity were found to be the most prevalent single risk factors.31

Recently, the prevalence of the metabolic syndrome was examined in several populations with or at risk for cardiovascular disease, as well as in a well-defined low risk population in Bulgaria.32-34 A total of 2123 subjects were examined: 1. with history of acute myocardial infarction (AMI) (n = 372); 2. hypertension (n = 620); 3. type 2 diabetes (n = 556) and 4. healthy controls (n = 575). All subjects were checked for medical history, lifestyle, anthropometric parameters and blood pressure. Venous blood was drawn after an overnight fast for the examination of atherosclerosis risk factors, such as plasma glucose, lipids, C-reactive protein, etc.32-34

The prevalence of the metabolic syndrome in patients with history of AMI was 80% in men and 89% in women according to the ATP III definition, and 85% in men and 93% in women according to the International Diabetes Federation (IDF) definition. Among the hypertensive patients 43% of the men and 53% of the women had metabolic syndrome, 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 metabolic syndrome 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. Surprisingly high was the prevalence of the metabolic syndrome in the group of the “healthy” controls amounting to 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 1).32 These findings are also in accordance with previous studies.16,18

In this population, both in the low risk group of the “healthy controls” and in the risk populations of patients with AMI, hypertension and type 2 diabetes, women were more often affected by the syndrome than men.32 In some countries, like Greece and USA, similar prevalence was also observed for both sexes.35,36 In Turkey, India, Iran, African Americans, Mexican Americans etc. women were reported to be much more frequently affected whereas in Australia the metabolic syndrome was found to be more common among men.38

A highly significant correlation was found in the Bulgarian risk population between the history of acute myocardial infarction and presence of the MetS, and this was more markedly expressed when the ATPIII definition was applied.32 This finding in the Bulgarian population is consistent with some reports in the literature indicating that the ATPIII definition of the MetS confers a significantly higher risk of vascular events than the IDF definition.39,40 Thus, in a prospective study of 750 coronary patients
followed over 4 years, the MetS, as defined by the ATPIII criteria, significantly predicted vascular events, whereas the metabolic syndrome, as defined by the IDF criteria, did not. 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 the ATP-III criteria.

Alarming is the finding of the excessively high prevalence of the MetS among patients with history of myocardial infarction in Bulgaria. It has been shown that the presence of the metabolic syndrome worsens the in-hospital outcome of myocardial infarction and is a strong predictor of severe heart failure.

Although a direct comparison with the prevalence of the MetS among patients with history of myocardial infarction in Bulgarian, it may be suggested that indeed the MetS is a major contributor to the excessive cardiovascular mortality. Therefore, development and implementation of large scale screening and treatment programmes may be necessary for the early detection and successful treatment of the metabolic syndrome and its components among the Bulgarian population.

### PHYSICAL ACTIVITY, NUTRITIONAL HABITS AND METABOLIC DISEASE IN BULGARIA

Unhealthy lifestyle characterized by physical inactivity and food over-consumption is among the leading risk factors for the development of the MetS. In general the population of Bulgaria is considered to have a very low physical activity (PA) level and poor dietary habits. Previous observations of Yanev et al. and Stanchev et al. have demonstrated a rapid decrease in the PA level from the 1960s to the 1990s with only a minor part of the population being engaged in regular PA.

With respect to the nutritional habits of the population Tashev et al. and Balabanski et al. reported that the nutritional habits of Bulgarian population have reached optimal energy levels in the 60s. Since then the consumption of carbohydrates have constantly increased to yield excessive consumption of energy-dense foods rich in fats and simple carbohydrates in the 90s.

Between August 2007 and May 2010, the Sofia Lifestyle (SLS) study was conducted among the urban population of Sofia, Bulgaria. The SLS study aimed at investigating the PA level and nutritional habits and their interaction with obesity and T2DM among the citizens of Sofia. Briefly, SLS was a survey-based investigation in which a total number of 511 participants completed a validated

### Table 1. Prevalence (in %) of the metabolic syndrome (MetS) in patients with history of acute myocardial infarction (AMI), hypertension, type 2 diabetes mellitus, and healthy controls. (Adapted from Temelkova-Kurktschiev T, et al.)

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence of the MetS defined by the ATPIII criteria</th>
<th>Prevalence of the MetS defined by the IDF criteria</th>
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<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Men</td>
</tr>
<tr>
<td>AMI Patients, (n = 372)</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>Hypertensive patients, (n = 620)</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>Diabetic patients (n = 556)</td>
<td>74</td>
<td>70</td>
</tr>
<tr>
<td>Healthy controls, (n = 575)</td>
<td>23</td>
<td>23</td>
</tr>
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questionnaire divided into three sections: general information, PA level and nutritional habits. Mean age of the respondents was $38.5 \pm 15.2$ years and mean BMI was $25.5 \pm 5.5$ kg/m$^2$. Twenty eight percent of the participants were overweight, 19.5% were obese, 4.5% had history of T2DM, 29.9% of hypertension, 12.5% of hyperlipoproteinemia (HLP), and 15.7% of CVD.\textsuperscript{46}

Results from the SLS study confirmed the previous findings on the low physical activity level and poor dietary habits\textsuperscript{47}, since 55.8% of the examined population perceived their nutritional habits as

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure3.png}
\caption{Body mass index and prevalence of type 2 diabetes in tertile groups of leisure time physical activity (A), sport physical activity (B), and uncontrolled eating behaviour (C). White, grey and black bars representing 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd} tertile group, respectively. Mean $\pm$ SD; $^*P < 0.05$ vs. 1\textsuperscript{st} tertile group; $^{\dagger}P < 0.05$ vs. second tertile group. Adapted from Stefanov T, et al.\textsuperscript{46} and modified.}
\end{figure}
unhealthy and 66.7% considered their daily PA activity insufficient.\textsuperscript{46} Data from the structured PA questionnaire utilized in the study demonstrated that the levels of PA among the participants was even greater since 81%, 78% and 68.5% of them reported physical activity below the average value of 3 for Work, Sport, and Leisure time indexes, respectively.\textsuperscript{46}

Furthermore, a significant correlation between leisure time PA and sport PA with BMI, history of T2DM, hypertension, and HLP was observed in the study.\textsuperscript{46} Of all examined aspects of eating behaviour only uncontrolled eating correlated significantly with BMI and with history of T2DM. In addition, when BMI and prevalence of T2DM were compared in tertile groups of PA and uncontrolled eating behaviour, the lowest BMI and the lowest T2DM prevalence were observed in the highest tertile of PA and in the lowest tertile of uncontrolled eating. On the other hand, PA, the highest BMI and the highest T2DM prevalence were present in the lowest tertile of PA and in the highest tertiles of uncontrolled eating behaviour (Fig. 3). Furthermore, in a multiple regression analysis leisure time PA and uncontrolled eating were independently associated with BMI.\textsuperscript{46}

The findings of the SLS study are in accordance with previous observations in other populations demonstrating independent inverse association between PA and body weight.\textsuperscript{48} Moreover, the association between physical inactivity, CVD-risk and T2DM is well established and the results observed among the citizens of Sofia are in agreement with the majority of previous findings.

Besides physical activity, unhealthy nutrition and more precisely food over-consumption is a well-established risk factor contributing to the current pandemic of obesity and T2DM.\textsuperscript{49} The results from the SLS study clearly demonstrate the existence of a link between these metabolic diseases and uncontrolled eating behaviour in the Bulgarian population.

Although objective data is somewhat scarce, the low PA level and the unhealthy nutritional habits have been considered responsible for the relatively high prevalence of metabolic disturbances in Bulgaria. Previous reports and our findings from the SLS study demonstrate association of PA level and nutritional habits with the prevalence of cardiometabolic diseases in the country.

CONCLUSIONS

Current data demonstrate a high prevalence of the MetS and of its components in Bulgaria not only among the high risk population, but also among low risk individuals. The low physical activity level and the unhealthy nutritional habits of the Bulgarian citizens may be considered responsible for this high prevalence. Furthermore, most of the MetS complications are undiagnosed and the syndrome is associated with history of myocardial infarction in the country. The extreme CVD mortality rates in Bulgaria may be attributed to the high prevalence of the metabolic syndrome that results as a consequence of unhealthy lifestyle. Therefore, large-scale screening programmes should be undertaken within this population in combination with health prevention strategies promoting regular physical activity and improvement of nutritional habits.

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РЕЗЮМЕ
Частота распространения метаболического синдрома (МетС) ( комбинация абдоминального ожирения, гипер/дислипидемии, гипертонии и артериальной гипертонии) нарастает непрерывно в мировом масштабе. Несмотря на то, что имеющиеся данные ограничены, несколько исследований сообщают о значимой ассоциации между низкими уровнями физической активности, нездоровыми навыками питания и риском развития диабета типа 2 в Болгарии. Большое число эпидемиологических исследований показывает, что частота распространения МетС, как и его отдельных компонентов, увеличивалась и в настоящее время она сравнительно высока среди общей популяции и исключительно высока среди людей с повышенным сердечно-сосудистым риском. Еще более тревожен факт, что МетС поражает и большую часть людей с низким риском развития метаболических и сердечно-сосудистых заболеваний и что его компоненты в большой степени недоанализированы. Кроме того в стране наблюдается сильная взаимосвязь между развитием инсулинорезистентности и смертностью от сердечно-сосудистых заболеваний. Чувствительно в стране увеличивалась смертность от сердечно-сосудистых заболеваний и в настоящее время Болгария одна из стран с самой высокой смертностью в Европе. Большое число эпидемиологических исследований показывает, что частота распространения МетС, как и его отдельных компонентов, увеличивалась и в настоящее время она сравнительно высока среди общей популяции и исключительно высока среди людей с повышенным сердечно-сосудистым риском. Еще более тревожен факт, что МетС поражает и большую часть людей с низким риском развития метаболических и сердечно-сосудистых заболеваний и что его компоненты в большой степени недоанализированы. Кроме того в стране наблюдается сильная взаимосвязь между распространенем МетС и развитием инсулинорезистентности. Несмотря на то, что имеющиеся данные ограничены, несколько исследований сообщают о значимой ассоциации между низкими уровнями физической активности, нездоровыми навыками питаения и риском развития диабета типа 2 в Болгарии.
питания и распространением кардиометаболитных заболеваний среди болгарского населения. На основе этих наблюдений можно предположить, что именно высокая частота MetS (результат нездорового образа жизни) является причиной высокой сердечно-сосудистой смертности в Болгарии. Вот почему необходимо своевременно начать кампанию для ранней диагностики метаболитных заболеваний в комбинации с профилактическими программами, направленными на увеличение уровня физической активности и на улучшение навыков питания населения.