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Metabolic syndrome and arterial hypertension in the adult population of Romania: subanalysis of data from the SEPHAR IV study

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Abstract

Cardiovascular disease (CVD) continues to be the leading cause of mortality worldwide, with a significant increase in cardiovascular mortality trends in Eastern Europe. Metabolic syndrome (MS) represented the association between six cardiovascular risk factors: arterial hypertension, hyperinsulinemia, low levels of HDL-cholesterol, increased levels of triglycerides and conditions with insulin resistance as a common etiopathogenic link, arises from a combination of genetic and acquired factors that contribute to insulin resistance and chronic inflammation. We evaluated the prevalence of metabolic syndrome in a subgroup of 835 subjects who were included in SEPHAR IV (Study for Evaluation of Prevalence of Hypertension and Cardiovascular Risk in an Adult Population in Romania) from May 15 to July 20th 2021, and had complete data available for statistical analysis, using The National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP-ATP III) criteria: waist circumference ≥102 cm in men and ≥88 cm in women, hypertriglyceridemia (≥150 mg/dL) or under specific treatment, low HDL-cholesterol (less than 40 mg/dL in men and less than 50 mg/dL in women), blood pressure readings higher than 130/85 mmHg, fasting blood glucose levels greater than 110 mg/dL or under specific treatment. Metabolic syndrome was present if at least three of the five criteria were present. The prevalence of NCEP-ATP III arterial hypertension criteria was significantly higher in men (70.5%) compared to women (55.1%), $p<0.01$. Metabolic syndrome, according to the NCEP-ATP III Criteria, was significantly more prevalent in women than men in the general study population and was significantly more prevalent in the population first diagnosed with arterial hypertension or under current antihypertensive treatment.

Keywords: metabolic syndrome, arterial hypertension, SEPHAR, cardiovascular risk factors.

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Introduction

The worldwide prevalence of arterial hypertension is around 30% (31% in men and 30% in women), with 29% in the general population of the United States of America and 44% of Europeans [1, 2, 3].

Metabolic syndrome (MS) arises from a combination of genetic and acquired factors that contribute to insulin resistance and chronic inflammation. When left unaddressed, it poses a substantial risk for the development of diabetes and cardiovascular disease [4]. The worldwide prevalence of metabolic syndrome ranges from 20% to 30% of the adult population and increases in higher-developed countries [5]. In a 2008 review of nine European population-based studies, which included 7782 men and 7739 women with a median follow-up of 8.55 years, 41% of the men and 38% of the women had the International Diabetes Confederation criteria for metabolic syndrome [6]. The prevalence for MS in the United States of America was 35% in 2012, according to the Center of Disease Control and Prevention [4, 7, 8].

Moreover, 80% of patients with metabolic syndrome have high-normal blood pressure or arterial hypertension. Among hypertensive patients, 34% to 58% associate MS and have a higher prevalence of target organ damage[9, 10].

Arterial hypertension is a significant burden in Romania's general population, accounting for 62% of cardiovascular disease total deaths [11]. Since genetic factors still require further studies, the most effective approach at this moment is to address the main cardiovascular risk factors by monitoring their prevalence and implementing cardiovascular disease prevention strategies. In order to gather representative data on the prevalence of cardiovascular risk factors across Romania, the "Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk in Romania (SEPHAR)" project was initiated in 2005, SEPHAR I, confirming a prevalence of arterial hypertension of 44.9%. In 2012, SEPHAR II revealed a decreasing trend in hypertension prevalence but also indicated an increasing prevalence of other cardiovascular risk factors, such as type 2 Diabetes Mellitus, obesity and dyslipidemia. SEPHAR III, conducted in 2016, assessed the prevalence of hypertension, blood pressure control and hypertension-related organ damage [12]. Sephar IV was a cross-sectional survey conducted in 2021 and enrolled 1533 subjects from a representative adult population.

Material and Methods

We evaluated the prevalence of metabolic syndrome in a subgroup of 835 subjects who were included in SEPHAR IV [12] (Study for Evaluation of Prevalence of Hypertension and Cardiovascular Risk in an Adult Population in Romania) from May 15 to July 20 th 2021and had complete data available for statistical analysis.

The recruitment criteria in SEPHAR IV, based on the recommendations provided by the National Institute of Statistics, were designed to adhere to the population distribution across different territorial regions, type of residence (rural and urban), gender (men and women), and age groups (18-24, 25-34, 35-44, 45-54, 55-64 and 65-80 years old). The available data for our analysis consisted of information collected during 2 visits during a 4-day interval. The subjects underwent various assessments, including anthropometric (weight, height, arm, waist, neck and hip circumferences) and blood pressure measurements, 12-lead electrocardiogram, non-invasive hemodynfamic measurements and transthoracic echocardiography with standardized measurements for all subjects, and a laboratory work-up that included measurement of serum lipids, fasting plasma glucose level, glycosylated hemoglobin, serum creatinine, serum potassium All blood samples were analyzed using the same laboratory.

In order to evaluate metabolic syndrome in our study population, we used the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP-ATP III) criteria: waist circumference ≥102 cm in men and ≥88 cm in women, hypertriglyceridemia (≥150 mg/dL) or under specific treatment, low HDL-cholesterol (less than 40 mg/dL in men and

Table 1. Distribution of individual NCEP-ATP III criteria in the study population.

NCEP-ATP III criteria distribution among the 835 subjects	
Waist circumference ≥102 cm in men and ≥88 cm in women	58.9% (n=492)
Hypertriglyceridemia (≥150 mg/dL) or treatment	25.0% (n=209)
Low HDL-cholesterol (less than 40 mg/dL in men and less than 50 mg/dL in women) or treatment	34.4% (n=287)
Blood pressure readings higher than 130/85 mmHg or treatment	61.2% (n=511)
Fasting blood glucose levels greater than 110 mg/dL or treatment	35.8% (n=299)

less than 50 mg/dL in women), blood pressure readings higher than 130/85 mmHg, fasting blood glucose levels greater than 110 mg/dL or under specific treatment. Metabolic syndrome was present if at least three of the five criteria were present.

We defined hypertension as a systolic value equal to or over 130 mmHg and a diastolic value equal to or over 85 mmHg measured at both study visits, according to the NCEP-ATP III criteria, using the arithmetic mean of the second and third blood pressure measurement of each study visit, or previously diagnosed hypertension under treatment during the previous 2 weeks, regardless of the blood pressure values during the study visits.

Obesity is a body mass index equal to or greater than 30 kg/square meter.

Statistical analysis was performed using SPSS version 23 (IBM Corp., Armonk, NY, USA) software and Prism 9 (GraphPad Software, Graphpad Holdings, LLC, San Diego, CA, USA).

Results

Metabolic syndrome in the general study population

Among the 835 from this analysis, the average age was 50.79 years±16.23, the average height was 1.67 m ±0.10, the average weight was 80.36±17.44 kg, and the average BMI was 28.83 kg/square meter ±6.27.

The survey population distribution based on type of residence was as follows: 46.7% (n=388) from rural areas and 53.3% (n=443) from urban areas. 39.8% (n=332) were men, and 60.2% (n=503) were women. The prevalence of obesity was 39.4% (n=327) of the study population. 25.9% (n=216) of subjects were active smokers. The distribution of individual NCEP-ATP III criteria is found in Table 1.

Among the 835 subjects analyzed from the SEPHAR IV survey, metabolic syndrome, defined by the NCEP-ATP III criteria, was present in 37.1% (n=287) subjects. (22.4% had three present criteria, 10.5% had four present criteria, and 4.2% had all five present criteria) (Figure 1).

Regarding age distribution, the prevalence of metabolic syndrome increased with age, being 13.6% in the population between 18 and 39 years old and 39.5% in the population aged 40 to 59 years old. The highest prevalence of MS (52.1%) was found in the oldest study population of 60 to 80 years old.

NCEP-ATP III Criteria distribution among sexes

The prevalence of NCEP-ATP III arterial hypertension criteria was significantly higher in men (70.5%) compared to women (55.1%), p<0.01.

Regarding the abnormal level of HDL-cholesterol criteria, its prevalence was higher in women (48.7%) compared to men (12.7%), p<0.01.

There were no significant differences between sexes regarding the prevalence of high fasting blood glucose levels (in men - 33.1%, in women - 37.6%, p=0.2), of hypertriglyceridemia (in men 21.4%, in women 27.4%, p=0.05), nor of waist circumference (54.5% men, 61.5% women, p=0.037).

Metabolic syndrome was significantly more prevalent in women than men, according to the NCEP-ATP III Criteria (26,2% men (n=87) and 39.8% (n=200) women, p<0.01).

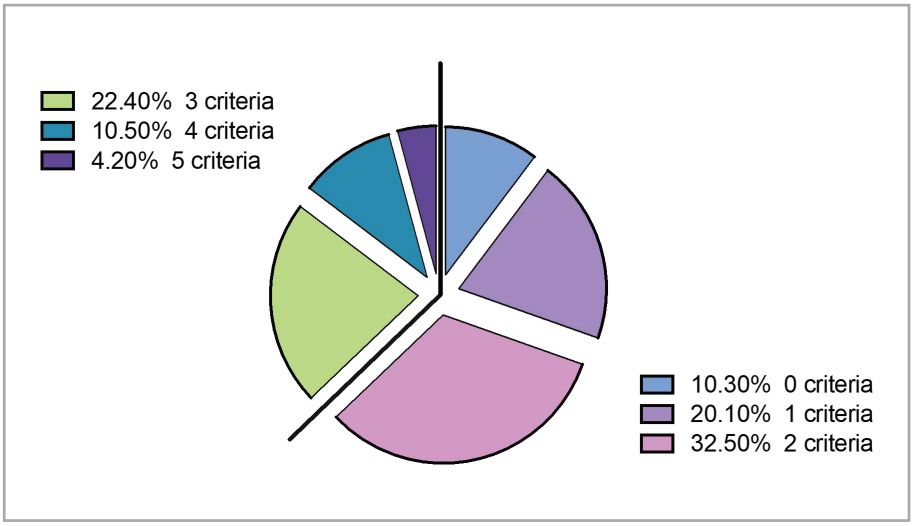

Figure 1. NCEP-ATP III Criteria Distribution in SEPHAR IV.

Metabolic syndrome in study subjects with arterial hypertension according to the NCEP-ATP III Criteria

Subjects with mean blood pressure higher than 135/80 mmHg had a significantly higher prevalence of abnormal waist circumference (79.3% versus 20.7%, p<0.01), while no difference was observed regarding serum lipid levels (low-HDL was found in 35.6% subjects, p=0.5; hypertriglyceridemia was more prevalent in hypertensive patients, 24.3%, p=0.68), nor in the prevalence of higher fasting glucose levels (35.6%, p=0.94).

Metabolic syndrome was significantly more prevalent in the population diagnosed with arterial hypertension, representing 46.9% (p<0.01).

Discussions

Metabolic syndrome (MS) was first described by Reaven in 1988 under the name "X Syndrome", which represented the association between six cardiovascular risk factors, as follows: arterial hypertension, hyperinsulinemia, low levels of HDL-cholesterol, increased levels of triglycerides and conditions with insulin resistance as a common etiopathogenic link [13, 14]. Later, in 1989, central obesity was the last criterion added to the components mentioned above of the "X Syndome" and nowadays, its name has been changed to metabolic syndrome, which associates an increased cardiovascular risk through important vascular and metabolic changes [15].

Over the past three decades, there have been slight variations between the definitions proposed by different organizations [16].

World Health Organisation (WHO) proposed in 1999 a preliminary definition of metabolic syndrome that was intended to be refined over time. According to WHO, MS encompassed glucose intolerance, impaired glucose tolerance or diabetes mellitus, and/or insulin resistance, along with two or more of the following criteria: elevated arterial pressure, defined as blood pressure equal to or greater than 140/90 mmHg, elevated plasma triglyceride levels (equal or greater than 150 mg/dL) and/or low levels of high-density lipoprotein cholesterol (HDL-C) (less than 35 mg/dL in men and less than 39 mg/dL in women), central obesity (indicated by a waist-to-hip ratio greater than 0.9 in men and 0.85 in women and/or a body mass index (BMI) greater than 30 kg/square meter), presence of microalbuminuria (defined as urinary albumin excretion rate of equal to or greater than a 20 microgram/minute or an albumin/creatinine ratio of equal to or greater than 30 microgram/milligram) [17].

The European Group for Study of Insulin Resistance (EGIR) proposed in 1999 a modification of the WHO definition by excluding patients with type 2 Diabetes Mellitus from the syndrome criteria because insulin resistance was primarily viewed as a risk factor for diabetes and proposed using the term "insulin resistance syndrome" rather than metabolic syndrome [18].

The National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP-ATP III) released in 2001 a simpler definition, considering a positive diagnosis of MS if the patient has at least three of the following criteria: waist circumference ≥102 cm in men and ≥88 cm in women, hypertriglyceridemia (≥150 mg/dL), low HDL-cholesterol (less than 40 mg/dL in men and less than 50 mg/dL in women), blood pressure readings higher than 130/85 mmHg, fasting blood glucose levels greater than 110 mg/dL. There are several aspects of the NCEP-ATP III definition that differ from the WHO definition. The primary focus became central obesity which was assessed using waist circumference and not the waist-to-hip ratio, leaving out completely the body mass index formula. Furthermore, low-HDL and triglycerides are treated as separate components, recognizing that both of them individually contribute to atherosclerosis. Additionally, the NCEP-ATP III definition includes the proinflammatory state and prothrombotic state as components of metabolic syndrome, although they are not included as necessary criteria to define it [19].

AACE, American Association of Clinical Endocrinologists in 2003, preferred using the term "insulin resistance" and did not specify a minimum number of criteria for diagnosis, but patients with type 2 Diabetes Mellitus were also ruled out of the definition. The major criteria suggested by AACE were: impaired glucose tolerance, elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure and obesity [20, 21].

The International Diabetes Confederation (IDF) introduced a global consensus definition for metabolic syndrome in 2005 that also included race and gender-specific waist circumference cutoffs. According to this new definition, MS was defined by central obesity and any two of the following four criteria: triglyceride levels ≥150 mg/dL or history of triglyceride-lowering treatment, HDL-cholesterol levels <40 mg/dL in males and <50 mg/dL in females or history of lipid-lowering treatment, systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥85 mmHg or current specific treatment for previously diagnosed hypertension, fasting plasma glucose levels greater than 100 mg/dL or a previous diagnosis of type 2 Diabetes Mellitus.

A Joint Interim Statement (JIS) in 2009 suggested using the International Diabetes Confederation definition but without having central obesity as a mandatory parameter. As an alternative approach, a novel parameter called the index of central obesity (ICO) was introduced and defined as the ratio

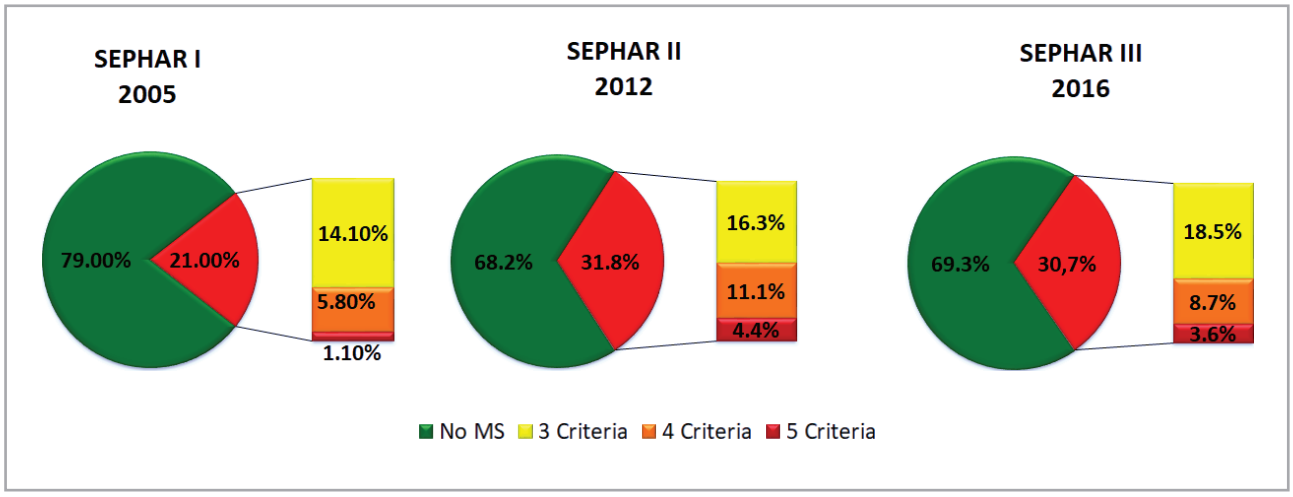

Figure 2. NCE-ATP III Criteria distribution in SEPHAR I, II, III.

of waist circumference to height. Extensive research has been conducted regarding this parameter and demonstrated a strong correlation between central adiposity and tissue glucose utilization [22]. Furthermore, it has been identified as a reliable predictor of type 2 Diabetes Mellitus and was associated with an increased cardiovascular risk [23–26].

Several studies proposed ICO cutoffs to be between 0.45 and 0.55 [16].

According to the International Society of Hypertension Practice Guidelines, patients with hypertension and metabolic syndrome have a high cardiovascular risk profile. Diagnosis of MS should be made by separate evaluation of single components and treatment should start with lifestyle changes, such as diet and exercise. Blood pressure control in people with metabolic syndrome should be performed as in the general population, along with the treatment of additional risk factors based on the level and overall cardiovascular risk (calculated using the SCORE – 10-year risk of fatal cardiovascular disease algorithm and/or atherosclerotic cardiovascular risk, ASCVD, calculator) [27, 28].

It is worth knowing that 80% of individuals with metabolic syndrome exhibit high-normal blood pressure or arterial hypertension. Among the hypertensive patients, 34-58% have metabolic syndrome, leading to a higher incidence of target-organ damage [9, 10]. Arterial hypertension poses a significant burden on the general population of Romania, accounting for 62% of total deaths related to cardiovascular diseases [11]. Comparing the current results to the past SEPHAR studies from 2005 (SEPHAR I), 2012 (SEPHAR II) and 2016 (SEPHAR III) in Figure 2, we notice an increase in the prevalence of metabolic syndrome in 2021, starting from 21% in 2005 and ending at a current percentage of 37.1% [11, 29]. Over the past decade, the prevalence of obesity, impaired glucose tolerance, hypertension and cumulative cardiovascular risk factors has experienced a notable surge among the Romanian population, even in the face of improved accessibility to healthcare and treatment options.

Conclusions

In our analysis, the prevalence of NCEP-ATP III arterial hypertension criteria was significantly higher in men (70.5%) compared to women (55.1%), $p<0.01$.

Metabolic syndrome, according to the NCEP-ATP III Criteria, was significantly more prevalent in women than men in the general study population and was significantly more prevalent in the population diagnosed with arterial hypertension. Regarding age distribution, the prevalence of metabolic syndrome increased with age, the highest was found, naturally, in the study population between 60 to 80 years old.

Romanian population suffered an increase in the prevalence of obesity, impaired glucose tolerance, hypertension and cumulative cardiovascular risk factors over the past decade, despite the increased accessibility to healthcare and treatment. This is probably due to lifestyle changes.

This research provides insights that can guide the development of targeted preventive strategies in a high-risk cardiovascular country, with the ultimate goal of reducing the overall burden of cardiovascular disease worldwide.

Conflict of interests

The authors declare no conflict of interest.

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