# COMPARISON OF DIFFERENT DEFINITIONS OF THE METABOLIC SYNDROME IN RELATION TO CORONARY ARTERY DISEASE IN HIGH RISK SERBIAN POPULATION

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### **SUMMARY**

While different definitions for the diagnosis of metabolic syndrome (MetS) have been proposed, their applicability brings confusion about which criteria should be used in clinical practice. This was an observational cross-sectional study conducted during October 2008. in 3 university hospital centers in the north, midst and south of the Serbia. 1715 patients were recruited from outpatient clinical practice and primary health care offices: 37% males and 63% females, aged 34-80 years. To evaluate the impact of different criteria in discriminating high risk population for coronary artery disease (CAD) we used NCEP-ATP III, AHA/NHLBI and IDF definitions. 21,7% (373) from the patients included in the study sustained CAD. The prevalence of MetS in the CAD group was 84,7%, 86,1% and 82,0%, respectively, compared with 58,3%, 60,6% and 61,2% in the control group (p<0.0001). ROC curves ploted by the probabilities for CAD calculated in the logistic models for each definition (adjusted for age, sex, smoking and educational status) indicated that NCEP-ATP III and NHLBI-AHA definitions had a better predictive accuracy compared with IDF (p=0,006 and p=0,016, respectively). When the waist girth is introduced in NCEP-ATP III and NHLBI-AHA definitions as obligatory, this distinction was lost. The NCEP-ATP III and AHA/NHLBI definition is more suitable for discrimination of MetS diagnosis, than the later proposed IDF definition in the subjects of the given population. Inclusion of waist circumference as obligatory criteria failed to show increase in predictive accuracy for CAD.

of measured values.

Keywords: metabolic syndrome, central adiposity, coronary artery disease

#### INTRODUCTION

After a brief loss of interest in metabolic syndrome (MetS), apon the criticism made on account of it's diagnosis, the metabolic syndrome comes back into the spotlight, mainly because of its link with the global epidemics of cardiovascular diseases (CVD) and type 2 diabetes. This relationship was well established, but using different definitions proposed by several groups, brings confusion in clinical practice about which criteria should be used for the population of the given interest.

The most widely used is the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition [1]. In contrast to the definition of the World Health Organization (WHO) [2], it does not require the determination of insulin levels, thereby facilitating the assessment of MetS prevalence. The NCEP ATP III definition has been modified by the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) [3,4]. The major adjustment was to in-

clude persons reporting a history of current antihypertensive drug or lipid lowering medication use regardless

Later proposed, the International Diabetes Federation (IDF) definition introduced [5] a central adiposity as a prerequisite to the diagnosis of the MetS. This definition, which was made with the intent to be globally applicable, also reduced the cutoff value for discriminating the central adiposity [6].

Consequently, we have multiple definitions for metabolic syndrome using in clinical practice now, some of which require central obesity as mandatory criterion for the diagnosis, and not others, while situation is even more complicated by the existence of different limits for discrimination of abdominal obesity.

There are only few studies related to the problem of different definitions showing their effect on the actual prevalence of the MetS in the given population [7-12], and even less emphasizing the unique role of central obesity in it [13-15].

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#### STUDY OBJECTIVE

The aim of this study was [1] to assess the impact of the NCEP ATP III, AHA/NHLBI and IDF definitions on the overall prevalence rate of the MetS in high risk patients for coronary artery disease (CAD) recruited in a primary health care setting and outpatient clinical practice, [2] to determine the predictive power of these three different definitions of MetS for CAD, and [3] to establish the impact of abdominal obesity when it's introduced by different levels as a mandatory inclusion criteria for defining metabolic syndrome.

#### MATHERIAL AND METHODS

Study design and recruitment modalities: This was an observational cross-sectional study conducted during October 2008. in 3 university hospital centers in the north, midst and south of the Serbia. Physicians were recruited in different settings in clinical practice - office or hospital based cardiologists, endocrinologists / diabetologists and primary care physicians/internists - on the one third bases. Number of physicians recruited was proportional to the population size gravitating to the city outpatient clinics and primary health care offices. The every patient of a consultation day was invited to participate in the study whatever his/her condition or reason for consultation, with a target of 12 subjects to be recruited for each physician (maximum 20).

Inclusion and exclusion criteria: Patients were eligible if they were a male or female outpatient between 35 and 80 years of age and had signed an informed consent prior to any study procedures. Exclusion criteria were: subject currently hospitalized, any major surgery performed within the past 30 days, myocardial infarction or stroke within the past 30 days, pregnant or breast-feeding woman, presence of cirrhosis with ascites, known hyperthyroidism or hypothyroidism, current treatment with oral retinoïds (acne, psoriasis), systemic corticosteroids, antiretroviral or anti-obesity drugs (e.g., sibutramine, orlistat), CB1 blocker, actual or anticipated geographic or social factors that would prevent the subject from undergoing the fasting blood sample. Information on all criteria was collected using a questionnaire.

Sample size estimation: The sample size calculation was defined at country level and based on 95% confidence interval to estimate the prevalence of MetS. With computed lower bound border of expected prevalence range (20-70%) and a chosen precision of 2% the estimated number of patients was 1535. Assuming a rate of up to 10% of subjects with missing data, a total number of 1690 patients were intended for enrollment.

Data Collected: All parameters required for diagnosis of MetS were assessed - anthropometric parameters and data on cardiovascular risk factors as well as data on therapy for hypertension, dyslipidemia and diabetes mellitus. Patient's assessment was carried out during a single visit to physician, with related fasting blood samples analysis completed up in seven days (to maximum three weeks) after the visit.

Anthropometric parameters: The body weight was assessed using a calibrated standard balance beam, height was measured by standard height bar, and the

body mass index (BMI) was calculated as weight (kg) divided by height (m2) [16]. Waist circumference (WC) was measured at the midway between the lower rib and the iliac crest [16].

Blood pressure: Blood pressure measurements were taken using appropriately sized cuffs and the auscultator method recommended by the Seventh report of the Joint National Committee on prevention, Detection, Evaluation, and Treatment of High Blood Pressure [17].

Biochemical tests: For estimating the metabolic parameters, fasting blood glucose (FBG) and lipoproteins, blood samples were obtained after an overnight fast and abstention from liquids. The levels of FBG, total cholesterol (TC), serum triglycerides (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) were estimated using the commercial kits on an automated analyzer.

Smoking: Each participant was classified as a nonsmoker, former smoker, or current smoker, but for the purpose of the present study "ever smoker" status (current or former) was used.

Educational status: Educational status was assessed by terms of credentials earned. Each participant was classified as: elementary school, high school, college and university or without any education. In the present study division on lower and higher levels (college and university) of educational status was used.

Metabolic syndrome definitions: To evaluate the impact of different criteria and cutoff values for diagnosing the MetS, the prevalence was assessed using NCEP ATP III, AHA/NHLBI and IDF definitions. Since numerous studies using the NCEP ATP III definition included a history of current antihypertensive drug or lipid lowering medication use regardless of measured values, although explicitly not mentioned in the original definition (Table 1), we considered subjects using medication as having MetS (modified NCEP ATP III definition).

Statistical analysis: Data are expressed as mean values with standard deviations or as medians with interquartile ranges (for skewed data - not Gaussian distribution). The normal distribution of each variable was tested by Kolmogorov-Smirnov's test. Categorical data are presented by absolute numbers with percentages and 95% confidence intervals, and analyzed using a chisquare test. For continuous variables, Student's t test or the Mann-Whitney U-test was used. To evaluate the impact of the 3 different definitions of MetS on CAD incidence, several logistic regression models were performed: univariate models where each model separately included only one of the 3 definitions of MetS as an independent predictor variable, and multivariate models, adjusted for age, gender, smoking and educational status. In all regressions, CAD was the dependent variable. The accuracy of the definitions in predicting CAD events was assessed by the means of the Receiver Operating Characteristic (ROC) curves, and their respective areas under the curve (AUC). A ROC curve is a graph of sensitivity versus 1-specificity for various cut-off points of a positive diagnostic test result, herein the probability of CAD development was calculated by the models. Statistical analysis was performed using SPSS, version 17.0, software (SPSS Inc., Chicago, IL, USA). For comparison between ROC curves MedCalc statistical software has been used. p-value below 0.05 was considered statistically significant.

#### **RESULTS**

1715 patients were included in the study (63,1%) females, mean age:  $58,5\pm9,8$  years), of whom 373 (21,7%) sustained coronary artery disease, while for 48 patients (2,8%) there are no data on the existence of coronary disease. The clinical, demographic and laboratory characteristics of the study population, according to the presence or not of CAD and to their classification using 3 different definitions of MetS are shown in Tables 2 and 3.

By applying the different definitions of MetS according to NCEP ATP III, NHLBI/AHA and IDF, its prevalence in the CAD group was 84,7%, 86,1% and 82,0%, respectively, compared with 58,3%, 60,6% and 61,2% in the control group (statistically significant difference for all comparisons between the two groups, p<0.0001).

Univariate logistic regression models revealed that all 3 definitions of MetS were significantly associated with the presence of CAD (p<0,0001), which are also shown with definitions where is waist circumference introduced as mandatory criteria for the diagnosis of metabolic syndrome (Table 4).

After adjusting for age, gender, smoking and educational status, all 3 definitions remain independently associated with the presence of CAD (p<0,0001).

In order to distinct which definition model has a better predictive accuracy for CAD development, ROC curves were ploted and areas under the curve (AUC) with 95% confidence intervals for AUC were estimated (Table 5).



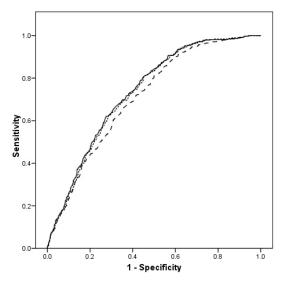


Figure 1. Plots of Receiver-Operating Characteristic (ROC) curves for the probabilities of the three multivariate models (each one containing a different definition of metabolic syndrome) used to predict coronary artery disease. (NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; NHLBI/AHA, National Heart, Lung and Blood Institute/American Heart Association; IDF, International Diabetes Federation)

Table 1. NCEP ATP III, AHA/NHLBI and IDF criteria for definition of metabolic syndrome

Criterion	NCEP ATP III	AHA/NHLBI	IDF
	Three or more of the	Three or more of the	Waist circumference plus
	following	following	any two of the following
Systolic and/or diastolic BP	≥130/85 mmHg	≥130/85 mmHg	≥130/85 mmHg
UBL de la de col	or under therapy	or under therapy	or under therapy
	<1,03/1,29 mmol/L	<1,03/1,29 mmol/L	<1,03/1,29 mmol/L
HDL cholesterol	or under therapy	or under therapy	or under therapy
Triglycerides	≥1,7 mmol/L	≥1,7 mmol/L	≥1,7 mmol/L
	or under therapy	or under therapy	or under therapy
Waist circumference M/F	>102/88 cm	>102/88 cm	>94/80 cm
Fasting plasma glucose	≥6,1 mmol/L	≥5,6 mmol/L	≥5,6 mmol/L
	or under therapy	or under therapy	or under therapy

BP - blood pressure

Table 2. Baseline clinical and laboratory characteristics in the study population, according to the presence of coronary artery disease (CAD)

Variable	Coronary artery			
vai iable	CAD - (n=1294)	CAD + (n=373)	Р	
Age (years)	57,3 ±9,9	62,6 ± 8,4	<0,0001	
Gender (male), n (%)	439 (33,9)	177 (47,5)	<0,0001	
Smoking (former/current), n (%)	609 (47,1)	186 (49,9)	0,340	
Educational status (higher level), n (%)	460 (35,7)	117 (31,4)	0,125	
BMI (kg/m²)	27,8 (6,3)	28,6 (4,7)	<0,0001	
Waist circumference in females (cm)	90,00 (17)	96,50 (16)	<0,0001	
Waist circumference in males (cm)	100,00 (15)	104,00 (13)	<0,0001	
HDL cholesterol in females(mmol/L)	1,40 (0,45)	1,33 (0,41)	<0,0001	
HDL cholesterol in males (mmol/L)	1,18 (0,36)	1,11 (0,33)	<0,0001	
Triglycerides (mmol/L)	1,59 (1,06)	1,73 (1,21)	0,002	
Systolic BP (mmHg)	136 (30)	140 (25)	0,022	
Diastolic BP (mmHg)	80 (10)	80 (10)	0,180	
Glucose (mmol/L)	5,5 (1,5)	5,8 (1,9)	<0,0001	

BP - blood pressure

Table 3. Prevalence of each item of metabolic syndrome according to the 3 different definitions of MetS

Variable	Coronary arter		
Valiable	CAD - (n=1294)	CAD + (n=373)	- Р
Systolic and/or diastolic BP increased or under therapy	1090 (84,2; 82,2-86,2)	364 (97,6; 96,0-99,0)	<0,0001
HDL cholesterol decreased or under therapy	601 (46,4; 43,7-49,2)	268 (71,8; 67,3-76,4)	<0,0001
Triglycerides increased or under therapy	687 (53,1; 50,4-55,8)	289 (77,5;73,2-81,7)	<0,0001
Waist circumference increased ATP III/NHLBI-AHA	734 (56,7; 54,0-59,4)	255 (68,4; 63,6-73,1)	<0,0001
Waist circumference increased IDF	1050 (81,1; 79,0-83,3)	328 (87,9; 84,6-91,2)	<0,0001
Glucose increased or under therapy ATP III	516 (39,9; 37,2-42,5)	199 (53,4; 48,3-58,4)	<0,0001
Glucose increased or under therapy NHLBI-AHA/IDF	636 (49,1; 46,4-51,9)	229 (61,4; 56,4-66,3)	<0,0001
MetS, NCEP-ATP III	754 (58,3; 55,6-61,0)	316 (84,7; 81,1-88,4)	<0,0001
MetS, NHLBI-AHA	784 (60,6; 57,9-63,7)	321 (86,1; 82,5-90,0)	<0,0001
MetS, IDF	792 (61,2; 58,6-63,4)	306 (82,0; 78,1-86,0)	<0,0001

Data are presented as n (%; 95%CI)

Table 4. Logistic regression analysis models for presence of coronary artery disease in relation to the MetS defined by different definitions

Presence of MetS according to	OR	95%CI for OR	OR adjusted	95%CI for OR adjusted	р
NCEP-ATP III	3,970	2,933- 5,375	4,084	2,971-5,615	<0,0001#
NHLBI-AHA	4,016	2,935- 5,494	3,956	2,854-5,482	<0,0001#
IDF	2,650	2,002- 3,507	2,652	1,967-3,576	<0,0001#
NCEP-ATP III with mandatory WC	2,403	1,892- 3,051	2,559	1,985-3,299	<0,0001#
NHLBI-AHA with mandatory WC	2,336	1,838- 2,969	2,403	1,863-3,098	<0,0001#

<sup>&</sup>lt;sup>#</sup> p value is for both unadjusted and adjusted models; adjustment were done for age, gender, smoking and educational status; WC - waist circumference

Table 5. Areas under the Receiver Operating Characteristic (ROC) curve for various models (each one containing different definition of MetS) for presence of coronary artery disease

Presence of MetS according to	AUC	95%CI for AUC	AUC adjusted	95%CI for AUC adjusted	р
NCEP-ATP III	0,638	0,614-0,661	0,736	0,714-0,757	<0,0001#
NHLBI-AHA	0,627	0,604-0,651	0,730	0,708-0,752	<0,0001#
IDF	0,597	0,573-0,621	0,709	0,686-0,731	<0,0001#
NCEP-ATP III with mandatory WC	0,607	0,575-0,639	0,717	0,695-0,739	<0,0001#
NHLBI-AHA with mandatory WC	0,603	0,571-0,635	0,714	0,691-0,735	<0,0001#

<sup>#</sup> p value is for both unadjusted and adjusted models; adjustment were done for age, gender, smoking and educational status

Probabilities of CAD development calculated by the previous (unadjusted and adjusted) logistic regression models were used to plot the ROC curves and to estimate the AUCs. The use of NCEP-ATP III and NHLBI-AHA definitions indicated better predictive accuracy compared with the definition model containing IDF: there is no statistical significance between ROC curves for NCEP-ATP III and NHLBI-AHA definitions (p=0,156), while there is significance between IDF definition and these two: p=0,006 (difference between areas 0,027; 95%CI for difference 0,008-0,046) and p=0,016 (difference between areas 0,022; 95%CI for difference 0,004-0,039), respectively. When the weight girth is introduced in NCEP-ATP III and NHLBI-AHA definitions as obligatory, this distinction between definitions is lost (p=0,163; p=0,585 and p=0,344 respectively). The AUCs of the ROC analyses for 3 official definitions (NCEP-ATP III, NHLBI-AHA and IDF) based on the multivariate models are shown in Fig. 1.

#### DISCUSSION

In this observational study we assessed the predictive power of three different definitions (ATP III,

NHLBI/AHA and IDF) of MetS in high risk patients for CAD recruited in a primary health care setting and outpatient clinical practice. Also, we assessed the impact of the introduction of waist girth as mandatory criterion in the definitions of MetS. Our findings are consistent with previous reports indicating that all 3 definitions are predictive of CAD [11,12,18,19], but also that all three definitions give a different prevalence of MetS.

Recent studies indicated that the definition proposed by IDF may have higher accuracy in identifying individuals at very high cardiovascular risk compared with NCEP-ATP III and NHLBI definitions [20-22]. The IDF definition emphasizes WC, an established index of abdominal obesity [23] which provides information not only for conventional risk factors [24], but is oriented more towards cardiometabolic risk [25]. Therefore, the assumption is that it would be more likely to have stronger discriminative power than the current definitions in identifying future CAD events.

In our study, implementation of IDF criteria did not result in an increased predictive power of MetS for CAD compared with other definitions. This can be explained primarily with too strict criteria for WC in the IDF definition, which in turn, when being a mandatory criterion for diagnosing MetS at lower cut-off in ATP III and

NHLBI/AHA definitions, hasn't reinforced their predictive power, neither.

After performing multivariate analyses, adjusted for age, gender, smoking and educational status, results of the analysis remained unchanged.

There are discrepancies among studies investigating the accuracy of various MetS definitions in CAD prediction, that could be attributed to the use of different populations (general population or population under risk) and different endpoints (CAD vs. CVD events), making the results not entirely comparable. On the other hand, major changes in definitions like the inclusion of pharmacotherapy as criteria for hypertension, diabetes or dislipydemia, i.e. [10,26-29] further hamper the interpretation of different study results. Pharmacotherapy is not mentioned in the original NCEP ATP III and AHA/NHLBI definitions and explicitly not included until the 2005 AHA/NHLBI update [4]. Besides, most of the studies included hypertensive medications, but not lipid lowering drugs. It remains an open point of discussion, if this would create a selection bias leading to an under- or overestimation of the true prevalence of MetS. In this study, subjects who were under any medical therapy were defined as meeting MetS criteria when using the NCEP ATP-III and NHLBI/AHA definitions, while IDF included this in its original definition.

In this study, the examined population was patients recruited in cardiology and endocrinology outpatient clinics and primary health care physicians' offices/internists', with the intention to compare the three most used MetS definitions as predictive tools for CAD events in the subjects who were at high risk for CAD in routine clinical practice. Also it was intended to show whether the introduction of WC as a mandatory criterion in the MetS definition increases its value for discrimination of the patients with increased risk of coronary disease. Therefore, the prevalence of MetS and increased WC was found to be high in the subjects of the given population and cannot be extrapolated to the general population.

#### **CONCLUSION**

In conclusion, the definition of MetS according to NCEP-ATP III and NHLBI/AHA criteria were found to be significantly better predictors of CAD than the IDF one, after adjustment for confounders. Although it was expected that inclusion of WC as an obligatory criterion would add more prognostic information beyond MetS official definitions, this analysis failed to show increase in predictive accuracy for CAD.

The findings of our study should be interpreted with the caution of the limitations that brings cross-sectional design, so the longitudinal study will be conducted to prove that subjects with MetS are really more prone to develop atherosclerotic cardiovascular disease, even though some recently published studies (30) concluded that MetS is not a sensible tool for predicting the risk of CAD.

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## **SRPSKI**

# KOMPARACIJA RAZLIČITIH DEFINICIJA METABOLIČKOG SINDROMA U RELACIJI SA BOLEŠĆU KORONARNIH ARTERIJA U VISOKO RIZIČNOJ POPULACIJI SRBIJE

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#### SAŽETAK

Postoje razlicite definicije metabolickog sindroma (MetS), ali su potrebni precizni kriterijumi za njihovu primenu u klinickoj praksi. Primenili smo observacionu studiju poprecnog preseka, sprovedenu tokom oktobra 2008.godine, u 3 univerzitetska bolnicka centra, u severnom, cetralnom I juznom regionu Srbije. Ispitano je 1715 pacijenata na ambulantnom lecenju I lecenih u primarnoj zdravstvenoj zastiti, od cega 37% muskaraca I 63% zena, starosne dobi od 34-80 godina. U cilju evaluacije uticaja razlicitih kriterijuma na utvrdjivanje populacije sa visokim rizikom za koronarne bolesti (KVB), koristili smo NCEP-ATP III, AHA/NHLBI I IDF definicije. Kod 27.7% (373) pacijenata ukljucenih u studiju je perzistirala koronarna bolest. Prevalenca metabolickog sindroma u grupi sa koronarnom bolescu je bila 84.7%, 86.1% I 82.0% sledstveno, u poredjenju sa 58.3%, 60.6% I 61.2% u kontrolnoj grupi (p<0.0001). ROC kriva vrovatnoće izračunata na osnovu logističke regresije za svaku od definicija za kardiovaskularne bolesti koje smo racunali smo logickim modelom za svaku definiciju (uzimajuci u obzir starost, pol, pusenje i stepen obrazovanja) je pokazala da su NCEP-ATP III I NHLBI-AHA definicije imale vecu prediktivnu preciznost u poredjenju sa IDF (p=0,006 and p=0,016, sledstveno). Uvodjenjem obima struka u NCEP-ATR III i NHLBI AHA definiciju kao obaveznu, ova razlika se gubi. NCEP-ATP III i AHA/NHLBI definicija je primenljivija za diskriminacionu analizu dijagnoze metabolickog sindroma, od kasnije predlozene IDF definicije kod ispitanika odredjene populacione grupe. Ukljucivanje obima struka, kao obaveznog kriterijuma nije pokazalo povecanje prediktivne preciznosti za koronarnu bolest.

Ključne reči: metabolički sindrom, centralna gojaznost, bolest koronarnih arterija

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