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Reliable Determination of Metabolic Syndrome Using Only One Biochemical Marker

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Abstract: Objectives of this study were to evaluate opportunities of using of mean arterial pressure (MAP) as a component of the metabolic syndrome (MS) instead systolic and diastolic blood pressures (SBP and DBP) and to create a model, using logistic regression. Multiple logistic regressions were used to determine odds ratio (OR) of MS. The first model included the following components of MS - waist (WS), HDL cholesterol, blood glucose (GLU) and serum triglycerides (TG). The second model included WS and TG. MAP was used as the last variable in the both models. All dependent variables, except MAP, were dichotomous. Each dichotomous variable received value 1 if the criterion for corresponding component in definition was met. The p-values for overall models fit statistic was less than 0.00001. The values of regression coefficients and corresponding p-values were calculated. Thresholds for OR above which the decision about presence of MS should be made, were found. The results indicated strong relation between value of MAP and MS. The proposed model showed a reliable determination of MS, using only one biochemical marker. Reducing the number of used biochemical marker could improve the cost efficiency in the diagnostication of MS. MAP showed itself as a promising indicator, which after some broader studies could replace SBP and DBP in the MS definition.

Keywords: Metabolic syndrome, Biochemical marker,

Introduction

According to the definition of NCEP ATP III (National Cholesterol Education Program Third Adult Treatment Panel), the metabolic syndrome (MetS) is a manifestation of at least three of the following five clinical and laboratory risk factors: abdominal obesity (waist line >102 cm in males and >88 cm in females), hypertension (arterial pressure ≥ 130/85 mm Hg), hyperglycemia (fasting sugar ≥6 mmol/l), hypertriglyceridemia (serum glycerides ≥1.7 mmol/l) and lower levels of HDL-cholesterol (HDL < 1.03 mmol/l in males and < 1.3 mmol/l in females). WHO defines MetS as hyperinsulinemia or hyperglycemia in addition to two of the above risk factors – waist line ≥ 94cm, dyslipidemia (triglycerides ≥1.7 mmol/l or HDL<mmol/l), or AP ≥ 140/90 mm Hg (Schunemann et al., 2008).

At present, the International Diabetes Association defines MetS as “presence of central obesity (defined as waist line ≥ 94 cm in European males and ≥ 80 cm in European females, with ethnic specificity for both groups plus two of the following characteristics:

1. increased triglycerides (≥ 17 mmol/l) or specific treatment received for these lipid disorders;
2. reduced HDL-cholesterol level (< 1.03 mmol/l in males, < 1.29 in females) or specific treatment received for these lipid disorders;
3. increased AP (for systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg), or treatment for previously diagnosed hypertension;
4. increased fasting blood sugar levels ≥ 5.6 mmol/l.

Because of these criteria, MetS varies between 10 and 25%. It increases with age and is more expressed in patients with DM. Individuals with MetS are at a risk twice as high for cardiovascular disease (CVD), as compared to those without MetS (Gocheva, 2009). In addition, the metabolic syndrome increases the risk for developing diabetes mellitus type II at least five times (Mirzaei et al., 2009).

Contemporary data show that in most countries it can be assumed that 20 to 30% of the adult population are with MetS (Chapman & Ginsberg 2011). The metabolic syndrome has reached the size of an epidemic in the USA. According to data obtained in the NHANES III (National Health and Nutrition Examination Survey), 48 million (23%) of adult Americans have MetS (European Heart Network. European Cardiovascular Disease Statistics. 2008). The incidence of MetS is comparable to that of hypertension, the latter being 24% (Tzekova, 2002, 2012). With ageing of the US population, the incidence of MetS increases among males and females of nearly all age groups. The spread of MetS among the older population groups may reach 50%. At age 70 and after, the spread of the syndrome reaches a plateau in women and decreases in men.

New biomarkers have a limited benefit, when added to the evaluation of the cardiovascular risk when using the SCORE algorithm. Highly sensitive CRP (hsCRP) and homocysteine can be used in patients at moderate cardiovascular risk (Gocheva, 2009). New biomarkers can be tested as alternative or can be considered as leading ones together with classical risk factors, using their capability to predict a 10-year cardiovascular morbidity or mortality. In view of this, the circulating biomarkers only are discussed here, i.e. those evaluated by standardized and validated methods, and are considered risk factors in clinical practice (Tzekova, 2012). Two groups of biomarkers are differentiated for evaluation of cardiovascular risk:

- Inflammatory: hsCRP, fibrinogen
- Thrombopoietic: homocysteine, lipoprotein-associated phospholipase (LpPLA2).

The highly sensitive CPR is a risk factor, integrating a multitude of metabolic and low-grade inflammatory factors, which are crucial for the development unstable atherosclerotic plaques (Berger & Jordan, 2010). Few drawbacks of this biomarker are seen when assessing the risk:

- Dependence on basic classical risk factors
- Lack of precision: a narrow diagnostic range for the level of hsCRP and the risk for CVD.
- Lack of specificity: a risk level similar to that for non-cardiovascular causes for morbidity and mortality.
- Lack of cause-effect relationship between changes in hs-CPR level and the risk for CVD.
- Lack of specific therapeutic strategies or agents referring to circulating CPR and demonstrating decrease in the incidence of CVD.
- High cost of the tests as compared to that of traditional biological factors (e.g. blood sugar and lipids)

Homocysteine has a modest influence on cardiovascular risk (Clarke et al., 2010). Intervention studies on using B-group vitamins to decrease the level of plasma homocysteine have proved their inefficiency for reduction of risk for CVD (Kaptoge et al., 2007). Having in mind the cost of the test, homocysteine remains a marker of second choice in cardiovascular risk assessment.

Not long ago, LpPLA2 emerged as a marker of high sensitivity and an independent risk factor for plaque rupture and atherothrombotic events. However, LpPLA2 has a small effect on risk in the general population and remains a second-line marker in cardiovascular risk assessment because of the cost of the test (Garza & Montori, 2007). The new emerging validated biomarkers can be added to make evaluation of the risk for CVD in specific subgroups of patients with moderate, uncommon or undefined levels of risk, e.g. asymptomatic patients without multiple major risk factors but with metabolic, inflammatory, endocrine or social indicators, associated with atherosclerosis or manifest signs of atherosclerotic progression.

Method

A total of 104 persons without any apparent disease were selected. Among these people MS was found in 35, according to NCEP-ATP III definition. One way ANOVA test, multiple comparison tests of means and multiple logistic regression analyses were used. The MAP was obtained by the formula MAP=SBP/3+2*DBP/3.

Results and Discussion

The mean values andstandard deviations of the clinical characteristics of the investigated individuals were obtained (Table 1). There were clear differences between mean values of SBP, DBP and MAP for people with and without metabolic syndrome. The average value of mean arterial pressure for all personswas 95.17 [mm Hg] and the standard deviation was 10.65 [mm Hg].

Table 1. Clinical characteristics of the participants

Characteristics	**Group with MetS**		**Group without MetS**	
	Mean value	**SD**	**Mean value**	**SD**
Waist circumference [cm]	98.36	±8.38	82.81	±13.76
SBP [mm Hg]	136.57	±16.28	119.43	±11.82
DBP [mm Hg]	87.85	±8.19	77.39	±9.11
MAP [mm Hg]	103.90	±9.38	90.73	±8.29
APO B [mg/dl]	92.39	±29.63	103.88	±24.2
APO A1 [mg/dl]	172.19	±33.73	169.22	±34.04
LDL - cholesterol [mmol/l]	3.41	±1.27	3.73	±1.02
HDL - cholesterol [mmol/l]	1.37	±0.41	1.17	±0.3
Blood sugar [mmol/l]	4.83	±1.3	5.45	±1.69
Total cholesterol [mmol/l]	5.34	±1.5	5.79	±1.21
hs-CRP [mg/l]	2.52	±2.99	4.24	±3.95
Triglyceride levels [mmol/l]	1.85	±1.93	2.89	±2.86
HbA1C [%]	5.32	±0.3	5.51	±0.23
BMI [kg/m2]	27.06	±5.38	31.48	±4.37

The mean values of SBP, DBP and MAP in three age groups for men and women were shown on Figures from 1 to 6. The analysis of results indicated that the variation of values of the mean values were relatively small with the age for men. The mean values increased with the age for women, but the changing wasn't so great. The results showed that the age wasn't a major factor influencing on mean values of blood pressures.

The four groups used in ANOVA were men and women with and without MS. The ANOVA F-statistic is 17.71 with p-value less than 0.00001 (Table 2). The box plot of ANOVA was shown on Figure 1. The multiple comparison tests showed statistically significant differences between groups of people with and without MS and negligible differences between men and women (Table 3). Regarding MAP, the differences between the groups of men and women with MS, as well as between the groups of men and women without MS are small. There was a statistically significant difference between the persons with MS and the health ones, irrespective of the gender. For the women, the difference between the mean values of MAP for those with MS and those without MS was greater than the differences registered between the respective groups of men. These results confirmed that the mean arterial pressure is a major risk factor, and it is better expressed in females as compared to males.

Table 2. Data from ANOVA analysis of MAP.

Deviations	**Sum of squares**	**Degrees of freedom**	**Mean value**	**F-test statistic**	**p-value**
Between groups	4055.26	3	1351.75	17.71	<0.00001
Within groups	7633.407	101	76.33407		
Total	11688.67	104			

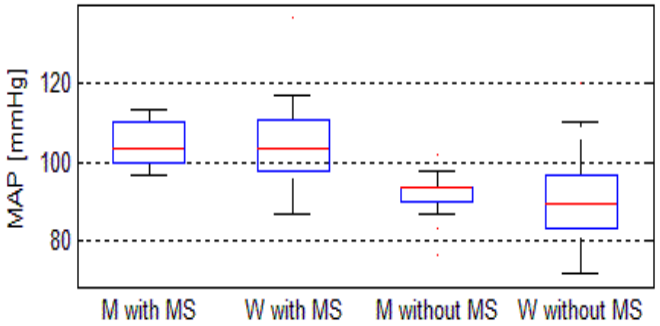

Figure 1. Men and women with and without MS

Table 3. Data from multiple component analysis of map by gender

Group One	**Group Two**	**Lowest value of CI [mm Hg]**	**Difference between means [mm Hg]**	**Highest value of CI [mm Hg]**
Menwith MS	Womenwith MS	-7.83656	0.039683	7.915929
Menwith MS	MenwithoutMS	4.892007	12.41005	19.9281
Womenwith MS	WomenwithoutMS	7.557816	13.65873	19.75964
MenwithoutMS	WomenwithoutMS	-4.34253	1.28836	6.919248

Multiple logistic regressions were used to determine odds ratio (OR) of MS. The first model includedthe following components of MS - waist (WS), HDL cholesterol, blood glucose (GLU) and serum triglycerides (TG).The second model included WS and TG. MAP was used as the last variable in the both models:

$$\text{Logit}(P) = \ln\left(\frac{P}{1-P}\right) = b_0 + b_1 * WS + b_2 * GLU + b_3 * TG + b_4 * HDL + b_5 * MAP\ ; \quad (1)$$

$$\text{Logit}(P) = \ln\left(\frac{P}{1-P}\right) = b_0 + b_1 * WS + b_2 * TG + b_3 * MAP\ . \quad (2)$$

All dependent variables, except MAP, were dichotomous. Each dichotomous variable received value 1 if the criterion for corresponding component in definition was met. The p-values for overall models fit statistic was less than 0.00001. The values of regression coefficients and corresponding p-values were calculated (Table 4). Thresholds for OR above which the decision about presence of MS should be made, were found (Table 4).There were two types of wrong decisions. The first was when a healthy person was determined as a one with metabolic syndrome. The second was when a person with metabolic syndrome was determined ashealthy one. When the first model was used with threshold for OR equal to 1 there were 1 wrong decision of first type and 2 wrong decisions of second type. The relative mistakes were respectively 1.45% and 5.71%. The model showedvery good results regarding the NCEP-ATP III definition of metabolic syndrome. When the second model was used with threshold for OR equal to 0.82 there were 3 wrong decision of first type and 2 wrong decisions of second type. The relative mistakes were respectively4.35% and 5.71%. This model also showed very good results regarding the NCEP-ATP III definition of metabolic syndrome. The basic advantage of the second model was the using only of one biochemical marker.

Table 4. Coefficientsof the two logistic regression models

Model 1							**Model 2**			
Coefficients	b0	b_1	b_2	b_3	b_4	b_5	b0	b_1	b_2	b_3
	-97.86	10.55	8.41	11.35	8.28	0.83	-49.16	6.42	8.24	0.42
p	0.015	0.025	0.035	0.021	0.047	0.016	0.0008	0.005	0.002	0.001
Thresholds	1						0.82			
Wrong	with MS	1 (1.45%)					3 (4.35%)			
decisions	without MS	2 (5.71%)					2 (5.71%)			

The analysis of the first model indicated that increasing of MAP with 1% (0.9517 mm Hg) of its mean value resulted in 2.2 times increase of OR. When the second model was used increasing of MAP with 1% of its mean value resulted in 1.5 times increase of OR. This indicated the significance of MAP as a component of metabolic syndrome. In previous work of author other logistic regression models were studied. One model used SBP, TG and HDL as components, until another one used DBP, TG and HDL. The results showed that increasing of SBP with 10% (13 mm Hg)of its mean value led to 1.78 times growth of OR for men and 2.16 times for women. The increasingof OR for the model with DBP (increasing with 8.2 mm Hg) were respectively1.13 times and 2.19 times. In these models the increasing of blood pressures with value around 10 times greater than increasing of MAP in proposed here models led to almost one and the same growth of OR. This comparison was another proof that MAP is much stronger marker of metabolic syndrome than SBP and DBP.

Conclusion

The results indicated strong relation between value of MAP and MS. The proposed model showed a reliable determination of MS, using only one biochemical marker. Reducing the number of used biochemical marker

could improve the cost efficiencyin the diagnostication of MS.MAP showed itself as a promising indicator, which after some broader studies could replace SBP and DBP in the MS definition.

Scientific Ethics Declaration

* The author declares that the scientific ethical and legal responsibility of this article published in EPSTEM Journal belongs to the author.

Conflict of Interest

* The authors declare that they have no conflicts of interest

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