CORRELATION BETWEEN THE WAIST CIRCUMFERENCE, DIASTOLIC BLOOD PRESSURE AND INSULIN RESISTANCE IN NON-OBESE YOUNG ADULTS

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Abstract

Context. The metabolic syndrome is a profound, systemic impairment of the metabolism of lipids, carbohydrates and branched amino-acids, affecting specially obese people. Recently, many studies outlined the presence of the metabolic syndrome, also in non obese persons.

Objective and design. To assess the relationship between insulin resistance and the cardiovascular component of the metabolic syndrome in a group of young, non obese subjects using a cross sectional study.

Subjects and methods. We enrolled 103 subjects with body mass index < 30 Kg/m², without metabolic syndrome to whom fasting glucose, triglycerides, high density lipoprotein cholesterol, insulinemia, waist circumference and arterial pressure were recorded in a cross-sectional approach. Insulin resistance was evaluated using the homeostasis model assessment for insulin (HOMA-IR) index. Statistic data processing included Pearson relation and multiple regression (backward method), using the SPSS version 21 software.

Results. A significant relationship between waist circumference, diastolic blood pressure and HOMA-IR is found. High value of HOMA-IR (>2.6) was more frequently in men (p=0.011). The incidence of the 2 metabolic components mentioned above was higher in the high value HOMA-IR group: 33% vs. 7% in women and 50% vs. 4% in men. Multiple regression showed a strong correlation between HOMA-IR and waist circumference (p<0.001) and diastolic blood pressure (p=0.008) that was maintained inside the women group (p=0.016 and p=0.032, respectively). In men, HOMA-IR correlated with waist circumference (p=0.031).

Conclusion. We found a significant interdependence between waist circumference, diastolic blood pressure and HOMA-IR. Based on our results, we consider that lifestyle intervention should start as soon as abnormal waist circumference is recorded.

Key words: metabolically non-obese young population, HOMA-IR, waist circumference, diastolic blood pressure.

INTRODUCTION

The metabolic syndrome (1) is a profound, systemic impairment of the metabolism of lipids, carbohydrates and branched amino-acids (2), affecting obese people. Recently, several studies outlined the presence of the metabolic syndrome in non obese persons (3- 5).

Insulin resistance (IR) may be measured directly (using a relatively arduous technique) or using the homeostasis model assessment for insulin (HOMA-IR) based on blood levels of fasting glucose and insulin.

Waist circumference (WC) is currently a widely accepted surrogate for visceral adiposity (VA) (6). VA differs from subcutaneous adipose tissue by the profile of adipokines secreted and adipogenesis – lipolysis balance, contributing to a larger extent to generation of subclinical inflammation of patients with metabolic syndrome favoring the onset of insulin resistance (7, 8). Intensity of the link between insulin resistance estimated by HOMA-IR and WC measured in general population is statistically significant (9).

Metabolically obese (or metabolically abnormal) non-obese individuals are defined as individuals having body mass index (BMI) < 30 Kg/m² and 2 cardio-vascular risk factors (4).

In general population, the healthy metabolically obese phenotype occurs in 15-45% of obese population, and the normal-weight metabolically obese phenotype occurs in 5-30% of non-obese individuals (3).

Despite this significant incidence, the characteristics of the cardio-vascular risk factors and IR were rarely studied. Progression from normal metabolic state to unhealthy metabolic state in non-obese population seems to be more intensely influenced by environmental factors (e.g. alcohol abuse or physical activities) compared to obese population (5) and therefore active intervention should be more efficient.

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Incidence of metabolic syndrome increases with age, but the pathophysiological process is presumed to start in the teen years (10, 11). A recent extensive systematic review and network meta-analysis of the metabolic syndrome risk found only one study that compared unhealthy to healthy according to BMI categories; all other studies the risk was estimated comparing individuals with metabolic risk with the lean ones (12). Since there are only few surveys on metabolic syndrome targeting non-obese young adults, and none of them conducted in Romanian young population, we aimed to assess the relationship between insulin resistance and the risk factors of metabolic syndrome defined by Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity (1) in this specific population group where metabolically obese non-obese phenotype might show an increased incidence (4). Our study assessed the relationship between insulin resistance and the cardiovascular component of the metabolic syndrome in a group of young, non obese subjects.

PATIENTS AND METHODS

We conducted a cross sectional study from January to March 2014. We included in the study non obese Romanian students of the Faculty of Medicine – Bucharest, with ages between 19-31 years. We excluded all students with a prior diagnosis of metabolic syndrome, diabetes mellitus, chronic hepatitis taking blood pressure lowering drugs, lipid lowering drugs, or anti-diabetes medication. We have also excluded pregnant women. In the remaining group of students, clinical examination and medical history was unremarkable for any chronic medical condition. None of the selected subjects were on any chronic medication. Written informed consent was obtained from all individuals before study commencement. The study was conducted in accordance with Helsinki declaration and was approved by the Ethics Committee of the “Matei Bals” National Institute for Infectious Diseases.

Variables collected: height, weight and waist circumference (WC) were measured according to standardized procedures (13). Systolic blood pressure (AP_systolic) and diastolic blood pressure (AP_diastolic) were determined. Arterial blood pressure

values were calculated as arithmetic mean of 3 measurements: first measurement after at least 10 minutes rest, the second and third at every 1 minute interval. Triglycerides, fasting glycaemia, high density cholesterol (HDL) and insulinemia were determined in the laboratory of the “Matei Bals” National Institute based on standardized biochemical methods. Test samples were collected in the morning, after minimum 10 h fasting. HOMA index was calculated based on fasting glycaemia and insulinemia values, using the formula: $\text{insulin resistance (IR)} = \frac{\text{glycaemia (mg/dL)} \times \text{insulinemia (\mu U/mL)}}{405}$, as described by Matthews *et al.* (14). A 2.6 threshold of HOMA-IR was considered for the analysis. Metabolic syndrome was defined according to Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity (1).

Analysis: Statistic processing of data was made using the Pearson relation, multiple regression (backward method), using the SPSS version 21 software. Assessment of relation between each risk factor and HOMA-IR was made using linear regression method. Risk factors were considered in a multiple regression model (15). Multiple regression analysis between HOMA-IR and AP_systolic, AP_diastolic, WC and HDL was made and tested by F ratio, using the backward method. Following testing of regression models, variables with insignificant influence were eliminated, and regression models were retained that include variables with significant effect. Mann Whitney U test was used to test statistical differences for non parametric distribution of values between 2 samples.

RESULTS

Descriptive data (average, standard deviation) are shown in Table 1. The group was homogeneous in terms of age, BMI, WC and had an asymmetric distribution, for triglycerides. HOMA-IR value of 2.6 was selected as a threshold value for IR, based on previous publications (16).

Patient characteristics: a total of 103 students agreed to take part in this survey and were enrolled. Sixty eight were females (66.01%) and 35 were males, this rate reflecting the male/ female rate among medical students of this university. After applying all the exclusion criteria we included 93 students in the analysis: sixty four females (68.81%) and 29 males

(31.19%). Median age was 24 years. Within the whole group, 7.4 % of individuals were overweight. The overweight status was more frequent in men (13.8%) compared to women (4.7%). The distribution of abnormal values for the components of the metabolic syndrome measured in this study are presented in Table 2.

Correlation between metabolic syndrome components: a high linear correlation coefficient was seen between BMI and WC, especially in men ($r^2=0.82$ in men and $r^2=0.69$ in women). Despite the small proportion of overweight women, 41% of women showed WC > 80 cm. All 3 overweight women had WC above 80 cm and out of the 61 normal-weight women, 23 showed WC above the threshold value. A single normal-weight man showed WC above the normal threshold value.

HOMA-IR distribution was also asymmetrical, the median value being 1.12; values below 1 have been recorded in 44% individuals. From the total number of persons investigated, only 9 (9.4%), 3 women and 6 men, had values above the 2.6 threshold, accounting for 4.7% and, respectively, 18.8% of the subjects. Significant differences were observed by gender, the average HOMA-IR for men being higher compared to women (Man Whitney U-test, $p=0.011$). Frequency of occurrence of metabolic components

in relation to HOMA-IR is shown in Table 3. Since subjects with metabolic syndrome were excluded from the study, grouping was made only based on one or two Joint Interim Statements of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity (18). In percentage values, frequency was higher for individuals with $IR > 2.6$.

The relation between variables was assessed by regression analysis. At whole group level, simple regression between HOMA-IR and each component (AP_systolic, AP_diastolic, WC and HDLC) was significant ($p<0.05$). Multiple regression analysis between HOMA-IR and AP_systolic, AP_diastolic, WC and HDLC showed a significant correlation between waist circumference and diastolic AP values and HOMA-IR ($p<0.05$, $r=0.475$). Regression models are presented in Tables 4, 5 and 6. There was no multicollinearity between independent components considered in the model (between WC and AP).

Subgroup analysis by gender: The second step was to assess, separately, on genders, the same influences. Results on the male subgroup showed a significant Pearson correlation between HOMA-IR and WC ($p=0.016$). Relations between HOMA-IR and AP_systolic and, respectively, AP_diastolic, are found at the border of significance threshold ($p=0.059$ and 0.057). In multiple regression analysis, the backward method showed a significant relation only in the two-variable model: WC and AP_diastolic ($p=0.049$). As for results achieved for the women subgroup, the Pearson correlation ($r=0.410$) was significant for the association between HOMA-IR and WC ($p=0.016$) and between HOMA-IR and AP_diastolic ($p=0.036$) (Table 2). In multiple regression analysis, the backward method also showed a significant relation only in the two-variable model: WC and AP_diastolic ($p=0.010$).

Table 1. Main characteristics of the study group

	Average	Median
Age (years)	24 $\pm$ 1.54	24
Weight (kg)	61.81 $\pm$ 10.91	60
Height(cm)	171.04 $\pm$ 0.62	169
BMI (kg/m ²)	21.03 $\pm$ 0.41	20.62
WC (cm)	81.04 $\pm$ 6.7	81
Systolic blood pressure (mmHg)	112 $\pm$ 9.16	110
Diastolic blood pressure (mmHg)	70 $\pm$ 7.86	70
Glycaemia (mg/dL)	77.22 $\pm$ 7.39	78
Triglycerides (mg/dL)	74.49 $\pm$ 26.54	67
HDLC (mg/dL)	61.81 $\pm$ 14.26	61
Insulin (mUI/mL)	6.39 $\pm$ 5.83	5.93
HOMA-IR	1.22 $\pm$ 1.16	1.11

Table 2. Abnormal values distribution of the metabolic syndrome components

	Men	Women	All group
BMI between 25-30 kg/cm ²	4 (13.8%)	3 (4.7%)	7 (7.4%)
WC > 94 cm in men and 80 cm in women	2 (6.8%)	26 (40.6%)	28 (30.1%)
Systolic blood pressure >130 mmHg	3 (10.3%)	4 (6.3%)	7 (7.5%)
Diastolic blood pressure > 85 mmHg	2 (6.8%)	2 (3.1%)	4 (4.3%)
Glycaemia (mg/dL) >100 mg/dL	0 (0%)	0 (0%)	0 (0%)
Triglycerides (mg/dL) >150 mg/dL	0 (0%)	1 (0.02%)	1 (1.1%)
HDLC < 40 mg/dL in men and < 50 mg/dL in women	7 (24.1%)	8 (12.5%)	7 (7.5%)
HOMA-IR > 2.6	6 (20.7%)	3 (4.7%)	3 (3.2%)

Table 3. Frequency of metabolic syndrome components according to HOMA IR value

	Women		Men		All group	
	HOMA IR	HOMA IR	HOMA IR	HOMA IR	HOMA IR	HOMA IR
	> 2.6	< 2.6	> 2.6	< 2.6	> 2.6	< 2.6
0 metabolic syndrome component	0	29	1	17	1	46
1 metabolic syndrome component	2	28	2	5	4	33
2 metabolic syndrome components	1	4	3	1	4	5

Table 4. Regression models of metabolic components correlation in the whole group

	Model	Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-6.052	2.094		-2.89	0.005
	WC	0.056	0.019	0.303	2.952	0.004
	Systolic blood pressure	0.006	0.015	0.046	0.408	0.684
	Diastolic blood pressure	0.039	0.017	0.25	2.254	0.027
	Triglycerides	0	0.004	0.01	0.107	0.915
	HDLC	-0.012	0.009	-0.144	-1.426	0.158
2	(Constant)	-6.053	2.083		-2.907	0.005
	WC	0.056	0.019	0.305	3.027	0.003
	Systolic blood pressure	0.006	0.015	0.047	0.416	0.679
	Diastolic blood pressure	0.039	0.017	0.25	2.266	0.026
	HDLC	-0.012	0.009	-0.144	-1.431	0.156
3	(Constant)	-5.656	1.842		-3.07	0.003
	WC	0.057	0.018	0.311	3.125	0.002
	Diastolic blood pressure	0.043	0.015	0.274	2.917	0.004
	HDLC	-0.013	0.009	-0.151	-1.534	0.129
4	(Constant)	-7.054	1.613		-4.374	0
	WC	0.067	0.017	0.364	3.882	0
	DBP	0.04	0.015	0.255	2.718	0.008

Table 5. Regression models of metabolic components correlation in men

	Model	Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-7.108	4.462		-1.593	0.125
	WC	0.072	0.05	0.309	1.457	0.159
	Systolic blood pressure	0.007	0.034	0.044	0.192	0.849
	Diastolic blood pressure	0.035	0.034	0.207	1.016	0.32
	Triglycerides	0.002	0.011	0.041	0.213	0.833
	HDLC	-0.018	0.023	-0.151	-0.792	0.437
2	(Constant)	-6.876	4.209		-1.634	0.115
	WC	0.077	0.044	0.327	1.761	0.091
	Diastolic blood pressure	0.037	0.031	0.222	1.209	0.238
	Triglycerides	0.002	0.01	0.038	0.204	0.84
	HDLC	-0.018	0.023	-0.153	-0.817	0.422
3	(Constant)	-6.758	4.088		-1.653	0.111
	WC	0.078	0.042	0.332	1.836	0.078
	DBP	0.038	0.03	0.223	1.243	0.225
	HDLC	-0.02	0.021	-0.164	-0.931	0.361
4	(Constant)	-8.136	3.8		-2.141	0.042
	WC	0.082	0.042	0.351	1.957	0.061
	DBP	0.037	0.03	0.221	1.231	0.23
5	(Constant)	-6.433	3.573		-1.801	0.083
	WC	0.094	0.041	0.4	2.27	0.031

Table 6. Regression models of metabolic components correlation in women

	Model	Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-6.101	2.809		-2.172	0.034
	WC	0.056	0.024	0.288	2.332	0.023
	Systolic blood pressure	0.005	0.018	0.036	0.25	0.804
	Diastolic blood pressure	0.045	0.023	0.298	1.97	0.054
	Triglycerides	0	0.005	-0.012	-0.098	0.922
	HDLc	-0.013	0.011	-0.163	-1.216	0.229
2	(Constant)	-6.081	2.779		-2.189	0.033
	WC	0.056	0.023	0.286	2.37	0.021
	Systolic blood pressure	0.004	0.018	0.034	0.241	0.811
	Diastolic blood pressure	0.045	0.022	0.3	2.007	0.049
	HDLc	-0.013	0.011	-0.165	-1.264	0.211
3	(Constant)	-5.733	2.353		-2.437	0.018
	WC	0.055	0.023	0.284	2.377	0.021
	Diastolic blood pressure	0.048	0.019	0.319	2.539	0.014
	HDLc	-0.014	0.01	-0.172	-1.367	0.177
4	(Constant)	-6.352	2.325		-2.732	0.008
	WC	0.059	0.023	0.302	2.523	0.014
	Diastolic blood pressure	0.039	0.018	0.263	2.199	0.032

DISCUSSION

In this study of a non-obese young population we found a significant correlation between waist circumference and diastolic AP values and of the HOMA-IR. The positive correlation persisted in both genders. These results could identify risk clusters for metabolic syndrome independent of classical obesity definition based on the BMI ranges. In normal-weight or overweight individuals (classified based on BMI criteria), the percentage of excess adipose tissue favors insulin resistance (17) and it is a predictor of success to diet-based intervention (18). WC and total mass of adipose tissue act synergically in forecast the metabolic syndrome risk (11).

In the Romanian population, obesity in teenagers (19) or children (20) and their associated metabolic profile has been subject of previous analysis. However, over or under nutrition in this particular age range might have a different impact compared to young adulthood, when final growth is already achieved. To the best of our knowledge, this is the first study focused only on non obese young adults in the Romanian population.

The direct relation between WC and HOMA-IR was also confirmed by other studies performed in non-obese population (11). As for the relation between HOMA-IR and AP_{diastolic}, it was also reported by other authors (21, 22); the pathological

justification relies on the endothelial inflammation associated to insulin resistance. The relation between WC and HOMA-IR in non-obese population is a solid argument for the necessity of clinical monitoring of this anthropometric parameter.

We have also found an increased incidence of metabolic syndrome criteria in subjects with HOMA-IR > 2.6. Selection of HOMA-IR as test for assessment the insulin resistance was based on its higher sensitiveness and specificity in healthy population compared to other alternative tests like the quantitative insulin-sensitivity check index (QUICKI) (23, 24). The second important reason is that it may be used on a larger scale compared to the current golden standard (euglycemic clamping) for definition of non-obese, metabolically obese population. The HOMA-IR distribution was asymmetric, only 9.4% of individuals surveyed showing values > 2.6. In a synthesis (25) of results achieved from various surveys measuring the insulin resistance concomitantly by euglycemic clamping method (26) and by HOMA-IR method, IR in subjects with BMI < 27.1, with triglycerides count <250 mg/dL, amounted to 6.73%. The higher incidence that we have found could be explained by the higher BMI threshold used by us (30 *versus* 27.1), and to the different sensitiveness of HOMA-IR compared to the clamping method. If we had used the 27.1 threshold for BMI, insulin resistance incidence would have amounted to 5.5%. We noticed a significant variation

of HOMA-IR based on gender, with higher average values in men compared to women ($p < 0.001$). This finding is consistent with the results published by other authors (25, 27) for general, non-diabetic population, and it is supported by experimental data on animals where administration of estrogens lowered hepatic synthesis of glucose and the cellular uptake, production of reactive oxygen species at mitochondrial level and lowered visceral deposits of fat (27, 28).

Although individual incidence of risk factors for cardio-vascular disease and diabetes was lower in our sample compared to the general population (for the same age group) (4, 28-32), results show that if HOMA-IR is of > 2.6 , 44% of subjects cumulate 2 metabolic components. In this respect, our results are consistent with other published surveys on young adults (29). As tendency of increase in prevalence of metabolic syndrome components in young population has been well documented (33), it is expected that high HOMA-IR prevalence will increase, accordingly.

Our study has several strengths: it assesses characteristics of a young adult, non-obese population, a sample that has been only rarely surveyed for the metabolic syndrome (30). The work methodology selected is valid and reproducible to prove that significant influences between HOMA-IR, adipose tissue distribution (estimated by WC) and AP_diastolic value are also maintained in non-obese population. Our study supports the correlation between HOMA-IR and WC and AP_diastolic. The 2 latest components of the metabolic syndrome are easily measured in clinical practice and, based on their correlation with HOMA-IR, whenever abnormal values are found, a lifestyle intervention should be started, even in young non obese individuals. As previously reported by us, in this population, the western type diet is frequent with 97% of persons not fully complying to the WHO recommendations (34) and no correlation between physical activity and WC was found in men; a weak, but significant one has been found in women (35).

The number of subjects was medium which might be considered a limitation, but our findings (HOMA-IR distribution, gender-based variation of HOMA-IR, frequency of association of component of metabolic syndrome) were similar to those reached by general population surveys (26, 27, 31, 33). Smoking habits were not collected in this study and in the analysis. We are aware of the fact that WC was higher in smokers than in non smokers in cross sectional studies (36) in a dose dependent relationship (higher in high number of pack-years) (37, 38). This relationship

had higher statistical significance for a smoking history of more than 10 pack-years (36). In our study, the average age was 24 years, therefore a history of more than 10 pack-years is highly improbable. However, for a conclusive remark on the impact of smoking on the relationship found in this study, this variable should be assessed as well.

We are aware that, since this was not a longitudinal survey, we cannot formulate causality conclusions on the relation between WC, AP_diastolic and HOMA-IR and the cardiovascular risk in non-obese population. Reiteration of our results on a representative sample of non-obese population, in a cohort survey assessing predictability of HOMA-IR on occurrence of metabolic syndrome would supplement the results of our cross sectional study.

The significant interdependence between WC, diastolic blood pressure and HOMA-IR supports the hypothesis that these relations are not an exclusive characteristic of the obese population. WC maintains relevance in forecasting insulin resistance for non-obese subjects as for the obese population. Based on our results, lifestyle intervention should start as soon as abnormal waist circumference or high diastolic blood pressure is recorded in young adults. However, larger prospective studies are needed to confirm our data and the efficacy in terms of metabolic syndrome incidence reduction.

Identification of HOMA-IR increase, in serial determinations, could become the synthetic criteria for initiation of the nutritional or medical intervention, even in non obese young subjects.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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