

Influence of inflammation and adipocyte biochemical markers on the components of metabolic syndrome

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Abstract. Metabolic syndrome is associated with increased risk of cardiovascular disease. This study investigated the correlation between adipocyte and inflammation biomarkers, and metabolic syndrome and its components. The study included 80 patients with normal body-mass index and 80 obese patients. The groups were assessed for serum values of adiponectin, leptin and highly sensitive C reactive protein (hsCRP), the homeostatic model assessment of insulin resistance (HOMA-IR), as well as the influence of these biochemical markers on the prevalence of metabolic syndrome and its components. Leptin, HOMA-IR and hsCRP had statistically significant ($P<0.01$) higher values in the group of obese subjects, while adiponectin had statistically significant ($P<0.01$) lower values. The prevalence of metabolic syndrome was 35% in the obese group and 5% in the normal weight group. Adiponectin and HOMA-IR were the variables significantly associated with metabolic syndrome ($P<0.01$), adiponectin/HOMA-IR ratio and leptin/adiponectin ratio were also associated with metabolic syndrome ($P<0.01$). No relationship was found between metabolic syndrome and hsCRP. Adiponectin and adiponectin/HOMA-IR were associated with all the components of metabolic syndrome and they can be useful to identify patients with high risk of diabetes mellitus and cardiovascular disease.

Introduction

Metabolic syndrome is an association of several risk factors for cardiovascular disease and other diseases (1,2). Many criteria have been proposed for the diagnosis of metabolic syndrome, all of them included the presence of high blood pressure, high fasting glycaemia, dyslipidaemia and obesity; however, the cut-off values for these variables differed depending on the organisations. A meeting of several major organisations including International Diabetes Federation and American Heart Association attempted to give unifying criteria for the definition of metabolic syndrome. For the diagnosis of metabolic syndrome 3 of the 5 following criteria must be present: increased waist circumference, in the case of Caucasian patients ≥ 94 cm for men and ≥ 80 cm for women; elevated triglycerides ≥ 150 mg/dl; elevated blood pressure, systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg; reduced high-density lipoprotein (HDL) cholesterol < 40 mg/dl for men and ≤ 50 mg/dl for women (3).

The prevalence of metabolic syndrome began to increase worldwide because of obesity epidemics. The observation is supported by the findings of National health and nutrition examination survey (NHANES) where the prevalence of metabolic syndrome was 5% among individuals with normal body mass index (BMI) and 60% among individuals with obesity (4). The importance of metabolic syndrome consists in the high burden of complications it generates, epidemiological studies proving that subjects affected by metabolic syndrome have a 3-4 times greater risk of myocardial infarction and a 2-4 times greater risk of stroke, as well as therapeutic implications (5,6).

Lifestyle changes have triggered the obesity epidemic; obesity is the main cause for metabolic syndrome because obesity generates insulin resistance and insulin resistance is associated with all the components of metabolic syndrome (7). Adipocytes are metabolically active cells generating different metabolites called adipokines that act at different levels, some of them increasing the risk of diabetes and cardiovascular

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disease such as C-reactive protein (CRP), tumour necrosis factor α (TNF α) and interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), some of them decreasing, at least theoretically, the risk of diabetes and atherosclerosis such as adiponectin (8).

CRP is an inflammatory and endothelial dysfunction biomarker generally considered accurate in predicting cardiovascular disease. Correlations were established between highly sensitive C-reactive protein (hsCRP) levels, coronary events and different metabolic risk factors especially BMI and insulin resistance (9). It appears that CRP interferes with the insulin signalling pathway and therefore generates insulin resistance (10). Despite a variety of studies, the role of hsCRP in the pathogenesis of metabolic syndrome and cardiovascular disease remains controversial. Risk factors, such as smoking, age, BMI, blood pressure, triglycerides have been associated with elevated hsCRP levels (11).

In addition, because of the role of hsCRP levels in identifying prognosis and recurrent events in patients with stroke and peripheral arterial disease, it may be useful in assessing cardiovascular risks and in identifying high-risk populations as target for prevention (12). Racial and ethnic differences have been demonstrated in the hsCRP levels and sex difference (women having higher hsCRP levels than men). One of the possible explanations is relatively higher degree of adiposity in women so the body fat quantity and distribution appear to influence hsCRP levels to a greater extent in women than men (13).

Adiponectin or adipocyte complement-related protein is the most abundant peptide secreted by adipocytes that negatively correlates with obesity and type 2 diabetes because it acts by increasing insulin sensitivity; it is probably the only adipokine with higher levels correspond to lower BMI and decreased cardiovascular risk because of its anti-inflammatory, and antiatherogenic effects (14). These are reasons to be proposed as novel therapeutic target for diabetes and metabolic syndrome.

Human adiponectin is encoded by the *Adipo Q* gene, which spans 17 kb on chromosome locus 3q27. This chromosome has been identified as carrying a gene susceptible for type 2 diabetes and metabolic syndrome (15). Adiponectin is also involved in energy homeostasis by action in hypothalamus, therefore the name 'starvation gene' has been proposed.

AdipoR1 and AdipoR2, two structurally related seven transmembrane receptors, have been identified to function as adiponectin receptors, structurally and functionally distinct from classical G-protein coupled receptors. AdipoR1 is expressed ubiquitously, but most abundantly, in skeletal muscle while AdipoR2 is predominantly expressed in the liver (16). It was demonstrated that adiponectin improves the utilization of glucose at the level of the skeletal muscle, protects against atherosclerosis plaque formation, decreases liver glucose production and decreases visceral adiposity (17). Insulin and adiponectin interact with their receptors, fact that generates a cascade of metabolic actions such as increased protein synthesis, lipogenesis, reduces plasma glucose levels (increase glucose uptake and utilization), glycogen synthesis, lipolysis and gluconeogenesis (18).

Leptin is a polypeptide hormone produced by adipocytes in proportion to their triglyceride content. It is involved in

the central control of energy balance. Its action consists in binding to and activating the long form of its receptor in the brain and the result is decreasing food intake while increasing energy expenditure. Plasma leptin concentration increases in proportion to body fat content, regulate food intake and energy expenditure to maintain body fat stores. Circulating leptin is secreted into the blood and after crossing the brain-blood and cerebrospinal fluid barrier, it acts in the hypothalamus, where leptin inhibits neuropeptide Y (NPY) neurons and causes anorexia. The arcuate nucleus has been proposed as an important site of leptin action. The central administration of leptin increases glucose turn-over and glucose uptake in peripheral tissues (heart, skeletal muscle, adipose tissue), stimulates hepatic gluconeogenesis and hepatic insulin sensitivity via the hepatic branch of the vagus nerve.

This study evaluated the correlation between the adipocyte biomarkers: adiponectin, leptin, HOMA-IR and inflammation biomarker, hs-CRP, and metabolic syndrome and its components.

Patients and methods

Patients. The study included 160 individuals, 80 with normal body weight defined as BMI ≥ 18.5 kg/m² and < 25 kg/m² and 80 with obesity defined as BMI ≥ 30 kg/m²; all of them were selected from the list of patients of a primary care physician from Oradea, Romania. The inclusion criteria were as follows: subjects aged between 18 and 65 years, subjects that gave their written consent for the participation in the study. For the reference group, the additional criteria were BMI ≥ 18.5 kg/m² and < 25 kg/m²; for the control group the additional criteria was BMI ≥ 30 kg/m². Since the study addresses to the general population, to the clinically healthy individuals (with the exception of obesity), the idea was to include individuals without significant chronic comorbidities therefore the exclusion criteria were: patients with diabetes mellitus, patients with stage II or III hypertension, patients with proved coronary artery disease or cerebrovascular disease (history of myocardial infarction or stroke), patients with other chronic diseases (cirrhosis, chronic obstructive pulmonary disease, chronic kidney disease, cancer, endocrine, haematological, psychiatric and neurological diseases), patients that were taking medications that can influence blood pressure or glycaemia. The exclusion criteria were similar for the reference and the control group. The research was performed according the WMA Declaration of Ethics, Helsinki - Medical Research Involving Human Principles for Subjects; the study was also approved by the Ethics Commission of the Council of Clinical County Emergency Hospital of Oradea (Romania). All subjects gave their written consent for the participation in the study and the medical practitioner gave written consent for the selection of the subjects from the patient lists.

Method. The method for selection of subjects was the following: in an interval of three months (1st June 2019-1st September 2019), the individuals that addressed the primary care physician for administrative reasons (requirement of medical certificate that attests the general health condition) were considered for inclusion in the study. When presented to the primary care physician, the subject was evaluated regarding the

Table I. Characteristics of the normal weight and obese subjects.

Variable	Normal weight (n=80)	Standard deviation	Obese (n=80)	Standard deviation	P-value
Sex (women/men) %	60/40	-	57.5/42.5	-	0.74
Age (years)	43.05	10.93	46.74	10.37	0.01
Weight (kg)	62.35	8.21	97.68	14.71	<0.01
Height (m)	1.67	0.08	1.68	0.09	0.29
BMI (kg/m ²)	22.32	1.81	34.68	3.82	<0.01
Waist circumference (cm)	78.19	7.36	108.42	14.61	<0.01
Hip circumference (cm)	94.29	6.43	117.08	10.98	<0.01
Waist/hip circumference	0.83	0.08	0.93	0.08	<0.01
SBP (mmHg)	116.8	11.41	127.51	14.27	<0.01
DBP (mmHg)	72.24	7.49	80.28	9.61	<0.01
Glycaemia (mg/dl)	88.11	8.6	92.9	9.76	<0.01
HbA1c (%)	5.2	0.26	5.46	0.39	<0.01
Triglycerides (mg/dl)	80.94	(60, 91.5)	114.08	(73.25, 135.5)	<0.01
Cholesterol (mg/dl)	181.69	36.72	186.06	37.59	0.46
LDL-cholesterol (mg/dl)	106.65	31.8	114.94	34.3	0.11
HDL-cholesterol (mg/dl)	58.95	13.94	49.01	13.22	<0.01

Table II. Inflammation and adipocyte biomarkers in the two groups (P<0.01).

Parameter	Normal weight (n=80)	Standard deviation	Obese (n=80)	Standard deviation
Insulin (μ U/ml)	6.17	(3.8, 7.82)	13.31	(7.77, 15.75)
HOMA-IR	1.36	(0.79, 1.69)	3.06	(1.78, 3.55)
hsCRP (mg/dl)	0.22	(0.08, 0.21)	0.58	(0.17, 0.73)
Leptin (ng/ml)	7.21	(2.02, 10.75)	25.7	(12, 33.79)
Adiponectin (ng/ml)	16.84	(14.34, 17.69)	7.52	(6.16, 8.55)
Adiponectin/HOMA-IR	17.11	(9.62, 19.53)	3.41	(1.73, 4.51)
Leptin/adiponectin	0.42	(0.13, 0.61)	3.47	(1.77, 4.50)

fulfilment of inclusion criteria and absence of exclusion criteria. A total of 80 obese subjects (reference group) and 80 normal weight subjects (control group) met the criteria and were further selected for clinical and biochemical evaluation. When selected, the subject was instructed to return the following day for physical examination that included measurement of height, weight, BMI calculation, waist circumference measurement and hip circumference measurement, determination of blood pressure, and collection of venous blood samples. Special determinations included serum insulin, adiponectin, leptin and hsCRP protein. hsCRP was determined using the immunoturbidimetric method, adiponectin and leptin were determined using ELISA method, insulin was determined by the chemiluminescence immunoassay. Quality control was conducted before testing samples. Normal values were: for adiponectin 12-25 ng/ml, for leptin (14.1-37.0) ng/ml in women and (3.3-14.3) ng/ml in men, for hsCRP <0.3 mg/dl and for insulin 2.5-25 μ U/ml. Determinations were performed in the Laboratory Department of Clinical County Hospital of Oradea (Oradea, Romania).

Statistical analysis. Statistical analysis was performed using Biostat software. P<0.05 was considered statistically

significant. The comparison of variables between the two groups was performed using t-test for variables with normal distribution and Mann-Whitney U test for variables with skewed distribution.

Results

Increased BMI is associated with statistically significant higher age, waist circumference, hip circumference, systolic blood pressure, diastolic blood pressure, fasting glycaemia, hemoglobin A1c (HbA1c), triglycerides and lower HDL-cholesterol as shown in Table I. The adipocyte biomarkers of the two groups are presented in Table II.

The prevalence of metabolic syndrome was statistically significantly higher (35%) in obese subjects than in normal weight subjects (5%) (P<0.01). The prevalence of metabolic syndrome components was statistically significantly higher (P<0.01) in obese subjects than in normal weight subjects (Fig. 1).

Subjects with metabolic syndrome had statistically significantly higher weight, BMI, waist circumference, hip circumference, systolic blood pressure, diastolic blood

Table III. Characteristics of the subjects with and without metabolic syndrome.

Parameter	Without metabolic syndrome (n=128)	Standard deviation	With metabolic syndrome (n=32)	Standard deviation	P-value
Sex (women/men) %	64/36	-	43.75/56.25	-	0.05
Age (years)	44.07	11.19	48.15	8.39	0.05
Weight (kg)	75.95	19.93	96.27	18.82	<0.01
Height (m)	1.67	0.08	1.7	0.08	0.03
BMI (kg/m ²)	27.32	6.79	33.2	4.86	<0.01
Waist circumference (cm)	89.67	17.18	107.83	14.72	<0.01
Hip circumference (cm)	103.16	13.48	115.78	14.11	<0.01
Waist/hip circumference	0.86	0.1	0.93	0.06	<0.01
SBP (mmHg)	119.57	13.08	132.5	12.67	<0.01
DBP (mmHg)	74.59	8.9	82.94	8.9	<0.01
Glycaemia (mg/dl)	88.6	8.51	98.28	9.29	<0.01
HbA1c (%)	5.29	0.33	5.49	0.41	<0.01
Triglycerides (mg/dl)	85.31	(60, 104)	95.25	(84.25, 189.5)	<0.01
Cholesterol (mg/dl)	182.34	37.11	190	37.05	0.3
LDL-cholesterol (mg/dl)	108.87	32.36	118.5	35.96	0.14
HDL-cholesterol (mg/dl)	56.84	14.16	42.56	9.01	<0.01

Table IV. Inflammation and adipocyte biomarkers in the subjects with/without metabolic syndrome.

Parameter	Without metabolic syndrome (=128)	Standard deviation	With metabolic syndrome (n=32)	Standard deviation	P-value
Insulin (μ U/ml)	8.95	(5.32, 11.7)	12.89	(6.62, 14.97)	<0.01
HOMA-IR	1.97	(1.15, 2.69)	3.16	(1.61, 3.82)	<0.01
hsCRP (mg/dl)	0.4	(0.09, 0.46)	0.41	(0.13, 0.46)	0.28
Leptin (ng/ml)	15.22	(4.76, 21.98)	21.4	(5.30, 28.36)	0.14
Adiponectin (ng/ml)	13.27	(8.49, 16.74)	7.79	(6.03, 8.01)	<0.01
Adiponectin/HOMA-IR	11.77	(3.81, 15.61)	4.23	(1.50, 5.13)	<0.01
Leptin/adiponectin	1.64	(0.27, 2.57)	3.18	(0.57, 3.87)	<0.01

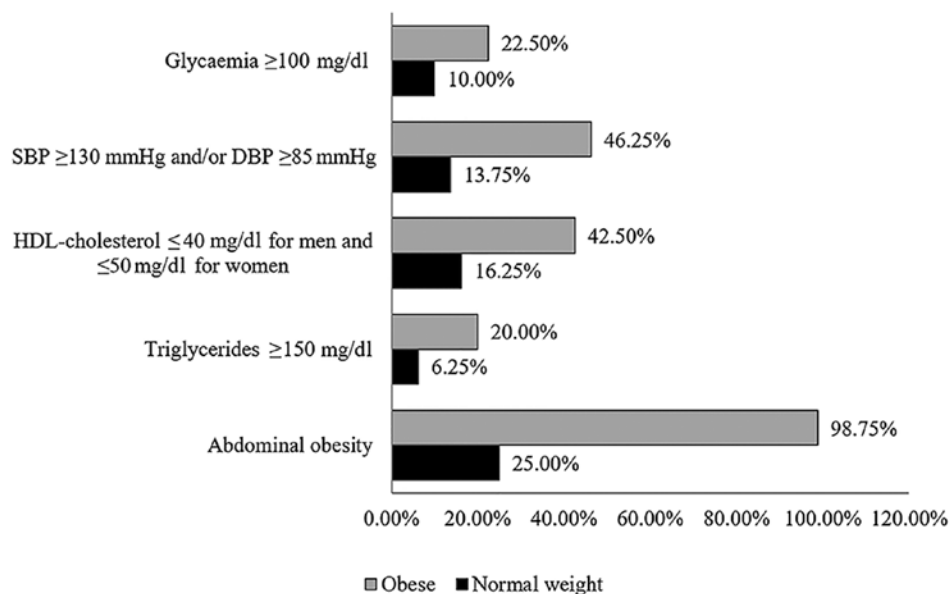


Figure 1. Prevalence of metabolic syndrome components among normal weight and obese subjects.

Table V. Correlation between inflammation and adipocyte biomarkers and metabolic syndrome and its components.

Parameter	Univariate regression					
	Metabolic syndrome	Abdominal obesity	Raised triglycerides	Low HDL	Increased blood pressure	Increased glycaemia
HOMA-IR	0.0002	0.0001	0.09	0.001	0.004	0.0001
Leptin (ng/ml)	0.05	0.0001	0.91	0.17	0.039	0.01
Adiponectin (ng/ml)	0.0001	0.0001	0.005	0.0001	0.0001	0.01
hsCRP (mg/dl)	0.87	0.0002	0.79	0.05	0.26	0.72
Adiponectin/HOMA-IR	0.0005	0.0001	0.03	0.0005	0.03	0.006
Leptin/adiponectin	0.0007	0.0001	0.41	0.01	0.0001	0.03

Multivariate regression adjusted by age and sex						
Sex	0.5187	0.0238	0.0975	0.9951	0.3345	0.0645
Age	0.1250	0.0039	0.2134	0.2032	0.0074	0.6219
hsCRP (mg/dl)	0.1756	0.7135	0.9193	0.2979	0.7130	0.5728
HOMA-IR	0.1229	0.6734	0.4094	0.0133	0.5291	0.0102
Leptin (ng/ml)	0.8549	0.0815	0.6002	0.1475	0.2036	0.8684
Adiponectin (ng/ml)	0.0003	0.0000	0.1290	0.0037	0.0343	0.1203

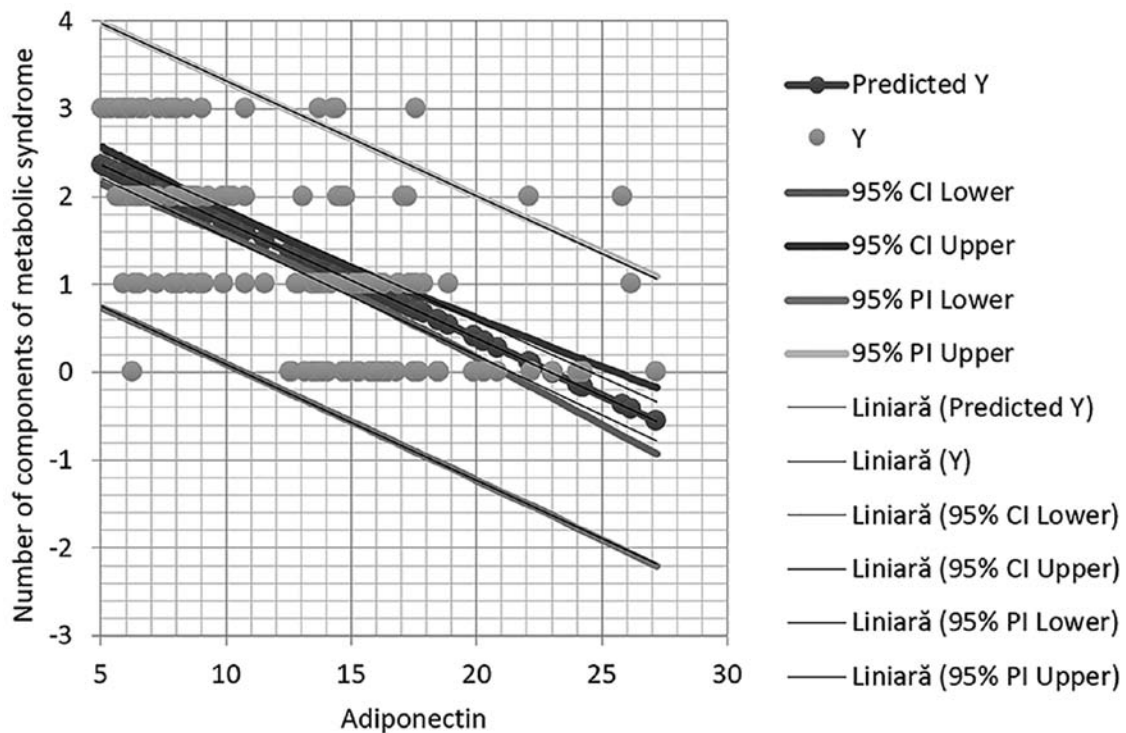


Figure 2. Correlation between adiponectin levels and the number of components of metabolic syndrome.

pressure, glycaemia, HbA1c, triglycerides and lower HDL-cholesterol compared with subjects without metabolic syndrome (Table III).

The presence of the metabolic syndrome was associated with statistically significant higher values of serum insulin, HOMA-IR, leptin and leptin/adiponectin ratio and statistically significant lower values of adiponectin and adiponectin/HOMA-IR ratio (Table IV).

The parameters that correlated statistically significantly with metabolic syndrome were HOMA-IR, adiponectin, adiponectin/HOMA-IR ratio and leptin/adiponectin ratio. Adiponectin and adiponectin/HOMA-IR ratio correlated with all the components of the metabolic syndrome. In multivariate regression analysis of adiponectin was the only biochemical marker that correlated with metabolic syndrome. Also, adiponectin correlated with abdominal obesity, low HDL-cholesterol

and raised blood pressure. HOMA-IR correlated with low HDL-cholesterol and raised glycaemia (Table V).

It should be indicated that in multivariate regression analysis adiponectin remained statistically significantly associated with high blood pressure (Fig. 2).

Discussion

Increased prevalence worldwide predisposes to insulin resistance, which is the central key of metabolic syndrome. The aetiology of the metabolic syndrome is complex, being involved in genetic mechanisms and environmental factors that predispose to it (19-21). Therapeutic intervention may be a preventive measure, at first disease should be recorded to register and monitor the chronic patients in order to assess their needs and improve their care (22-24).

The present study confirmed that lower adiponectin levels are negatively associated with the presence of obesity and metabolic syndrome, a finding reported by previous studies (25). Adiponectin was associated with the presence of all the components of metabolic syndrome: abdominal obesity, hypertriglyceridemia, low HDL-cholesterol, high blood pressure and high glycaemia. Studies report that adiponectin levels are lower with increasing number of metabolic syndrome components (25). A study performed on a large population including 2,471 men and 3,463 women of Korean origin confirmed that adiponectin levels are associated with metabolic syndrome phenotype and all its components (26); similarly to the present study, all these individuals were persons not suffering of diabetes mellitus. Also, increased levels of serum adiponectin were associated with higher number of metabolic syndrome components.

The usefulness of these findings consists in the metabolic action of adiponectin, it is important to mention that low levels of adiponectin are not only a consequence of increased adiposity, but also adiponectin has substantial beneficial roles in many metabolic pathways and therefore obese individuals do not benefit of the favourable effects of adiponectin. Firstly, adiponectin activated APPL1 signalling pathway. APPL1 has many roles, among them is activating the insulin receptor substrate proteins, therefore adiponectin stimulates the activity of insulin pathway and reduces insulin resistance (27). On the other hand, adiponectin activates AMPK signalling pathway increasing fat oxidation and energy expenditure (28,29). An increase of adiponectin can be obtained with the help of pharmacotherapy, by administration of thiazolidinediones, or by aerobic exercise (17). There is also a negative relationship between adiponectin levels and hypertension. Experimentally, in mice with reduced levels of adiponectin, the existence of endothelial dysfunction was found with alteration of vasodilatation and increased transformation of macrophages into foam cells, therefore adiponectin is associated with decreased atherosclerosis (16). In the present study adiponectin was negatively associated with increased blood pressure, systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg.

Adiponectin/HOMA-IR ratio and leptin/adiponectin ratio were statistically significantly associated with metabolic syndrome in the present study. Similar findings have been reported by Ding *et al* (30), who demonstrated that adiponectin/HOMA-IR is a better predictor of metabolic

syndrome than adiponectin or HOMA-IR alone. In the present study the degree of correlation in univariate regression between adiponectin, HOMA-IR, adiponectin/HOMA-IR and leptin/adiponectin ratio and the presence of metabolic syndrome was comparable.

No relationship between hs-CRP and metabolic syndrome was found in this study. Also, except for obesity, hs-CRP did not correlate with any components of metabolic syndrome. Results from literature are contradictory regarding the association between hs-CRP and metabolic syndrome and its components. There are studies that reported that patients with metabolic syndrome had values of hs-CRP 4 times higher than patients without metabolic syndrome and that hs-CRP was associated with metabolic syndrome and all its components (31). However, other scientists reported that hs-CRP has limited capacity to predict metabolic syndrome (32).

Leptin/adiponectin ratio was a strong predictor of metabolic syndrome revealed in the present study. Leptin has higher levels in patients with obesity mainly because of leptin resistance. Also, it was demonstrated that high levels of leptin are associated with increased insulin secretion which further exacerbates obesity and increases leptin levels (33). Leptin increases insulin resistance and has proinflammatory effects, adiponectin increases insulin sensitivity and decreases inflammatory response, therefore because of their antagonistic actions the leptin/adiponectin ratio is a good predictor of diabetes risk and of metabolic syndrome (34).

Although individuals included in the study were not suffering of diabetes mellitus type 2, the metabolic syndrome group are at high risk for progression towards this disease, showing statistically significant higher levels of HOMA-IR index, leptin and lower adiponectin. Adiponectin is genetically linked with diabetes mellitus type 2, it was proven that one of the loci of diabetes mellitus susceptibility is 3q27, in this region the gene responsible for adiponectin synthesis is also located (35).

Given these findings, adiponectin emerges as a target molecule for reducing the risk of metabolic syndrome, type 2 diabetes mellitus and atherosclerotic disease. Research is currently conducted to determine the measures, pharmacological or non-pharmacological, that may increase the circulating levels of adiponectin (19,36-38). Physical effort appears to be associated with an increase in serum adiponectin levels; one week of aerobic exercise was reported to lead to a significant increase in adiponectin in obese men (39). Complex experiments involving administration of adiponectin using adenoviruses as vectors in obese mice, with low blood adiponectin levels, demonstrated that adiponectin reduces obesity related hypertension (40).

Increased leptin/adiponectin ratio is strongly influenced by radical measures such as bariatric surgery. Severely obese type 2 diabetes mellitus patients that underwent Roux-en-Y gastric bypass had significantly lower leptin levels and significantly higher adiponectin levels compared to baseline values (41), these modifications of adipokines could contribute to the remission of glycaemic misbalance frequently observed in this category of patients.

In conclusion, adiponectin appears to be the hallmark molecule negatively associated with metabolic syndrome and its components. The derived variables such as leptin/adiponectin ratio or adiponectin/HOMA-IR gain statistical significance

mainly because of the markedly decreased levels of adiponectin in metabolic syndrome. HsCRP is associated only with obesity, not with the metabolic syndrome. Therefore, assessment of adiponectin in population could help identify patients with high risk of diabetes mellitus and cardiovascular disease.

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Availability of data and materials

At the private medical offices where the data were collected.

Authors' contributions

DCZ, CV, DU, OF and CP selected the patients, analyzed and interpreted the patient data regarding BMI and biochemical markers. OB, DMT, CCD and SB made substantial contributions to the conception of the work and interpretation of data; also, they drafted the manuscript and were major contributors in writing the manuscript. All authors read and approved the final manuscript to be published. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The research was performed according the WMA Declaration of Ethics, Helsinki - Medical Research Involving Human Principles for Subjects; the study was also approved by the Ethics Commission of the Council of Clinical County Emergency Hospital of Oradea (Romania). All subjects gave their written consent for the participation in the study and the medical practitioner gave written consent for the selection of the subjects from the patient lists.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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