# THE ASSOCIATION BETWEEN ADIPONECTIN, LEPTIN, PROINFLAMMATORY MARKERS AND METABOLIC SYNDROME IN OBESE, NONDIABETIC SUBJECTS

***R. Vasilescu*** [1], ***S. Ifrim*** [1], ***C. Ionescu-Tirgoviste*** [2], ***S. Sabau*** [3], ***A. Muresan*** [4]

[1] Department of Diabetes, Nutrition and Metabolic Diseases - Clinical Hospital Colentina, Bucharest
[2] National Institute of Diabetes, Nutrition and Metabolic Diseases "N.C.Paulescu"
[3] Hokkaido Tokai University, Sapporo, Japan
[4] CHU d'Amiens, Intensive Care Unit, France

## Abstract

***Background:*** *The aim of this study was to evaluate the association between adipokines (adiponectin and leptin), inflammatory markers, insulin resistance and metabolic syndrome in obese, non-diabetic subjects.* ***Methods****: Thirty three obese patients (19 men and 14 women) with metabolic syndrome (MetS) defined according IDF criteria, twenty three obese patients (12 men and 11 women) without MetS and eighteen controls (9 men and 9 women) lean subjects without MetS were included. In all individuals were assessed MetS components as well as serum levels of adiponectin, leptin, high sensitive C-reactive protein (hs-CRP), insulin, fibrinogen and leukocyte count (WBC).* ***Results:*** *In both sexes, obese subjects with MetS, compared to obese subjects without MetS had significantly higher systolic blood pressure (SBP), diastolic blood pressure (DBP), HOMA-IR, WBC, plasma concentrations of hs-CRP, leptin, triglyceride and fibrinogen and significantly lower concentration of HDL-cholesterol. A significantly lower concentration of adiponectin and a higher concentration of fasting insulin were observed in obese men with MetS compared to obese men without MetS. In all study subjects adiponectin was negatively correlated with BMI, body fat, triglyceride, HOMA-IR and positively correlated with HDL-cholesterol and hs-CRP was positively correlated with BMI, waist, body fat, triglyceride, HOMA-IR and negatively correlated with HDL-cholesterol. Hs-CRP was positively correlated with leptin in obese women and negatively correlated with adiponectin in obese men.* ***Conclusions****: In obese, non-diabetic subjects adiponectin, leptin, proinflammatory state and prothrombotic state are strongly correlated with MetS. Obese subjects with MetS had higher levels of hs-CRP and lower levels of adiponectin. These findings are important in clinical practice because permit an earlier identification of high risk subjects.*

***key words:*** *obesity, metabolic syndrome, adiponectin, high sensitive C-reactive protein*

The prevalence of obesity has increased dramatically in recent years [1,2]. It is associated with cardiovascular disease, type 2 diabetes, hypertension, certain cancers and sleep apnea [3]. Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors,

including visceral adiposity, hypertension, hyperglycemia and dyslipidemia [4]. The increasing prevalence of MetS worldwide is closely associated with the increasing prevalence of obesity. Subjects with MetS have a high risk for cardiovascular disease [5] and type 2 diabetes [6] .

Adipose tissue secretes several biologically active substances called adipokines [7,8]. Adiponectin is produced exclusively by white adipose tissue and in contrast to the other adipokines, its expression is reduced in obese subjects [9]. Adiponectin has anti-atherogenic action by down-regulating expression of endothelial adhesion molecules that participate in the recruitment of macrophages to inflammatory lesions, which is crucial for the development of atherosclerosis [10]. There is also evidence that adiponectin has insulin-sensitising actions [7,11] both in liver by decreasing gluconeogenesis and in skeletal muscle by increasing glucose use and fatty acid oxidation.

Prospective studies showed that a chronic low-grade inflammation is involved in the pathogenesis of atherosclerosis and hs-CRP, one of the acute phase proteins that increase during systemic inflammation, is a risk factor for cardiovascular disease [12.13]. Recent studies have demonstrated that obesity is characterized by mild chronic inflammation [8]. Obesity associated mild chronic inflammation is characterized by an increased numbers of macrophages that infiltrate adipose tissue, increased production of inflammatory cytokines, such as TNF-α and IL-6 and decreased concentration of adiponectin [14-16]. Saltevo et. al [17] showed that decreased levels of adiponectin and elevated levels of inflammatory markers IL-1 Ra (interleukin-1 receptor antagonist) and hs-CRP at adulthood are related to the change in BMI between childhood and adulthood, both in females and males.

## Material and methods

### Subjects

A total of 56 obese subjects (31 men and 25 women) mean age 52.9 years were recruited in Clinical Hospital Colentina, Department of Diabetes, Nutrition, Metabolic Diseases from February 2009 to January 2010. Subjects with diabetes, currently smoking, systolic blood pressure (SBP) / diastolic blood pressure (DBP) ≥ 170/100 mmHg, triglyceride ≥ 400mg/dl, total cholesterol ≥ 300mg/dl, history of cardiovascular diseases, use of drugs for dyslipidemia and hypertension, glucocorticoids, presence of viral hepatitis, renal disease, thyroid dysfunction, Cushing`s syndrome, hematological disorder were excluded.

### Laboratory assay

The samples of blood were taken after 12 hours of overnight fasting. Total adiponectin, leptin, high sensitive C-reactive protein (hs-CRP) and insulin were measured by ELISA (DRG Innternational, Inc.) on a Dynex analyzer. WBC, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, glucose and fibrinogen were measured using standard techniques. To estimate low-density lipoprotein (LDL) cholesterol we used Fridewald formula as follows: LDL-cholesterol = Total cholesterol – HDL-cholesterol – triglycerides/5. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as the product of

the fasting plasma insulin value (in microunits per liter) and the fasting plasma glucose value (in mg per deciliter) divided by 405. Percent body fat (%) was measured using a bioelectrical impedance analyzer (Omron BF 500).

### Diagnosis of Metabolic syndrome (MetS)

MetS was defined according to International Diabetes Federation (IDF) criteria. Abdominal obesity is a prerequisite and MetS was defined by the presence of abdominal obesity (waist circumference – men ≥ 94 cm and women ≥ 80 cm) plus any two of the following four components: 1) hypertriglyceridemia: ≥ 150mg/dl or on medication; 2) low HDL-cholesterol: men < 40mg/dl, women < 50mg/dl or on medication; 3) hypertension: SBP ≥ 130 mmHg or DBP ≥ 85 mg/dl or on medication; 4) high fasting glucose: ≥ 100mg/dl or previously diagnosed type 2 diabetes.

### Statistical analyses

Statistical analyses was performing using the program Graph Pad Instant 3. Continuous variables were tested for normality distribution with the use of the Wilk-Shapito test. Data normally distributed were expressed as mean±standard deviation (SD) and data skewed distributed were expressed as median (interquartile range). Normally distributed variables were compared by unpaired t-test and ANOVA test with Bonferroni post-test for multiple comparisons and not normally distributed variables were compared by Mann-Whitney test and Kruskal-Wallis test with Dunn post-test for multiple comparisons. Pearson`s correlation coefficients were calculated, skewed variables were log transformed before evaluation. Values of $p<0,05$ were considered statistically significant.

## Results

### Characteristics of study subjects

The clinical and biochemical characteristics of the subjects included in this study are presented in table 1. Non-diabetic obese men without MetS compared to non diabetic lean men had significantly higher levels of systolic blood pressure, diastolic blood pressure, fasting glucose, triglyceride, hs-CRP, fasting insulinemia, HOMA-IR, leptin and lower levels of HDL-cholesterol. Non-diabetic obese women without MetS compared to non-diabetic lean women had significantly higher levels of systolic blood pressure, triglyceride, fasting insulinemia and lower levels of HDL-cholesterol.

Non-diabetic obese men with MetS compared to non-diabetic lean men had significantly higher levels of systolic blood pressure, diastolic blood pressure, fasting glucose, triglyceride, hs-CRP, fibrinogen, WBC, fasting insulinemia, fasting proinsulin, HOMA-IR, leptin/adiponectin ratio and lower levels of adiponectin and HDL-cholesterol. Non-diabetic obese women with MetS compared to non diabetic lean women had significantly higher levels of systolic blood pressure, diastolic blood pressure, fasting glucose, triglyceride, fasting insulinemia, HOMA-IR, hs-CRP, fibrinogen, WBC, leptin/adiponectin ratio and lower levels of HDL-cholesterol.

**Tabel 1. Characteristics of the study subjects**

| Variable | Lean | | Obese (OB) Men | | | P MetS (-) vs. MetS (+) | Obese (OB) Women | | | P MetS (-) vs. MetS (+) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Total | MetS (-) | MetS (+) | | Total | MetS (-) | MetS (+) | |
| Number | 9 | 9 | 31 | 12 (38.71) | 19 (61.29) | - | 25 | 11 (44) | 14 (56) | - |
| Age (years) | 55.4±7.5 | 53.8±7.1 | 51.6±9.1 | 50.1±7.2 | 53.2±6.4 | 0.78 | 54.5±8.1 | 53.1±8.9[a] | 55.2±9.7 | 0.45 |
| Weight (kg) | 66.1±4.7 * | 63.9±5.9 | 103.9±11.5** | 99.8±10.1[a] | 108.3±11.9[b] | **0.002** | 88.6±10.9 | 85.1±6.7[a] | 89.3±7.2[b] | 0.07 |
| BMI (kg/m2) | 24.3±0.5 | 23.7±0.6 | 33.8±3.1 | 32.2±1.8[a] | 34.8±3.5[b] | **0.02** | 34.6±3.6 | 32.4±2.1[a] | 35.3±3.2[b] | **0.046** |
| Waist (cm) | 93.3±4.6 * | 79.8±3.1 | 118.3±8* | 112.3±9.4[a] | 121.2±10.1[b] | **0.0015** | 97±5.7 | 93.4±2.9[a] | 101.5±4.3[b] | **0.002** |
| Body fat (%) | 21.6±0.5 * | 24.8±0.4 | 32.6±1.1** | 30.2±0.9[a] | 34.1±1.2[b] | **0.0003** | 37.8±0.7 | 36.3±0.9[a] | 39.2±1.1[b] | **0.032** |
| Fasting glucose (mg/dl) | 81.1±9.8 | 79.2±9.1 | 97.5±17.5 | 94.6±14.3[a] | 98.9±16.6[b] | 0.07 | 93.2±18.6 | 89.5±13.4 | 96.4±17.5[b] | 0.13 |
| SBP (mmHg) | 125.6±10.1* | 118.7±11.5 | 145.8±13.8* | 139.6±14.77[a,*] | 147.4±16.1[b,*] | **0.003** | 138.2±13.8 | 133.6±11.4[a] | 142.5±14.9[b] | **0.003** |
| DBP (mmHg) | 78.9±7.8 * | 72.8±7.6 | 87.3±12 | 83.4±10.2[a,*] | 88.6±12.3[b,*] | **0.04** | 77.4±8.8 | 74.7±6.9 | 79.8±9.1[b] | **0.038** |

| Variable | Lean | | Obese (OB) Men | | | P MetS (-) vs. MetS (+) | Obese (OB) Women | | | P MetS (-) vs. MetS (+) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Total | MetS (-) | MetS (+) | | Total | MetS (-) | MetS (+) | |
| Total cholesterol (mg/dl) | 217.3±38.1 | 208.8±33.5 | 237.5±44.3 | 232.8±37.5 | 241.1±40.9 | 0.18 | 228.2±39.1 | 223.7±37.8 | 236.1±42.3 | 0.14 |
| HDL-cholesterol (mg/dl) | 46.2±5.7* | 56.3±6.2 | 34±6.8 | 37.2±5.6[a,*] | 31.2±7.2[b,*] | **0.004** | 47.2±7.3 | 49.2±6.2[a] | 43.1±7.7[b] | **0.003** |
| LDL-cholesterol (mg/dl) | 131.2±29.7* | 114.9±38.1 | 148.3±24.8 | 144.4±26.77 | 151.3±24.6 | 0.12 | 129.8±29.3 | 116.8±26.2 | 136.1±31.3 | 0.09 |
| Triglyceride (mg/dl) | 101.41±29.1 | 91.7±25.5 | 181.4±47.5 | 167.2±43.1[a] | 191.7±51.1[b] | **<0.0001** | 168.4±52.9 | 142.1±48.8[a] | 181.3±61.5[b] | **<0.0001** |
| Hs-CRP (mg/l) | 0.9 (0.6-1.7) | 1.45 (1.1-2.23) | 2.4 (1.4-4)* | 1.55 (1.23-2.58)[a,*] | 2.7 (2.1-4.8)[b,*] | **0.035** | 3.2 (1.8-7.35) | 2.9 (0.9-7.4) | 5.86 (2.98-7.33)[b] | **0,037** |
| Fibrinogen (mg/dl) | 289.21±41.24 | 304.16±53.47 | 331.1±61.6 | 314.5±71.2 | 386.7±58.7[b] | **0.0009** | 316.7±64.7 | 324.7±70.1 | 382.4[b] | **0,0031** |
| WBC | 5.68±1.1 | 6.04±1.4 | 7.1±1.8 | 6.1±1.6 | 7.9±2.1[b] | **0.024** | 7.8±2.5 | 6.3±1.9 | 8.7±2.8[b] | **0,0004** |

| Variable | Lean | | Obese (OB) Men | | | P MetS (-) vs. MetS (+) | Obese (OB) Women | | | P MetS (-) vs. MetS (+) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Total | MetS (-) | MetS (+) | | Total | MetS (-) | MetS (+) | |
| ($10^3$/$mm^3$) | 2 | 1 | | | | | | | | |
| Fasting insulinemia (μU/ml) | 6.6 (5.32-10.35) | 5.48 (4.3-8.05) | 18.2 (10.23-35.8)* | 14.8 (7.56-24.15)[a] | 31.3 (10.2-46.1)[b,*] | **0.038** | 14.3 (9.51-19.46) | 10.17 (7.51-15.97)[a] | 15.71 (11.63-20.61)[b] | **0.046** |
| Fasting proinsulin (pmol/l) | 5.91 (5.05-7.29) | 3.66 (2.06-5.59) | 9.64 (5.78-13.66) | 6.21 (5.44-9.36) | 11.52 (9.42-13.85)[b] | **0.018** | 4.87 (3.36-10.69) | 4.24 (3.17-8.4) | 6.13 (3.33-13.11) | 0.53 |
| HOMA-IR | 1.63 (1.43-2.5) | 2.21 (1.56-3.19) | 3.86 (2.31-8.43) | 3.26 (2.12-6.69)[a] | 5.51 (2.56-9.01)b | **0.041** | 3.19 (2.02-4.56) | 2.61 (1.79-4.18) | 4.06 (3.07-5.5)[b] | **0.048** |
| Adiponectin (μg/dl) | 4.52 (3.72-8.61) | 7.24 (5.45-8.47) | 2.01 (1.42-3.54) ** | 3.71( 3.16-4.95)* | 1.53 (0.83-3.54)[b,**] | **<0.0001** | 5.13 (3.75-6.76) | 6.59 (3.83-7.64) | 5.24 (3.59-6.57) | 0.37 |
| Leptin (ng/ml) | 10.8 (9.95-15.55) | 37.17 (25.93-52.65) | 32.1* (16.2-75.4) | 24.2 (16.35-33.27)[a,**] | 45.8 (12.7-80.3)[b,*] | **0.043** | 54 (27-73.1) | 41.7 (23.9-53) | 60 (30.75-91.9)[b] | **0.039** |

| Variable | Lean | | Obese (OB) Men | | | P MetS (-) vs. MetS (+) | Obese (OB) Women | | | P MetS (-) vs. MetS (+) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Total | MetS (-) | MetS (+) | | Total | MetS (-) | MetS (+) | |
| Leptin/Adiponectin | 2.2 (1.87-5.06) | 5.12 (3.8-8.81) | 6.28 (2.57-12.51) | 3.06 (2.19-10.29) | 7.12 (1.63-20.02)[b] | **0.03** | 5.71 (4.76-7.75) | 7.75 (5.9-11.04) | 11.57 (6.17-14.4)[b] | 0.22 |

Data are presented as mean ± standard deviation and median (interquartile range); a) p<0,05 OB (MetS -) vs. Lean; b) p<0,05 OB (MetS +) vs. Lean *) p<0,05 men vs. women (total, MetS(-), MetS(+)); **p<0,01 men vs. women (total, MetS(-), MetS(+))

Non-diabetic obese men with MetS compared to non-diabetic obese men without MetS had significantly higher levels of weight, BMI, waist, body fat, systolic blood pressure, diastolic blood pressure, triglyceride, hs-CRP, fasting insulinemia, fasting proinsulin, HOMA-IR, leptin, leptin/adiponectin ratio and lower levels of HDL-cholesterol and adiponectin. Non-diabetic obese women with MetS compared to non-diabetic obese women without MetS had significantly higher levels of BMI, waist, body fat, systolic blood pressure, diastolic blood pressure, triglyceride, hs-CRP, fibrinogen WBC, HOMA-IR, leptin and lower levels of HDL-cholesterol.

**Univariate analysis between adiponectin, hs-CRP and selected variables**

In obese men, plasma adiponectin level was negatively correlated with BMI, waist, body fat, triglyceride, HOMA-IR, hs-CRP and positively correlated with HDL-cholesterol. hs-CRP was positively correlated with age, BMI, waist, body fat, triglyceride, HOMA-IR, fasting insulinemia and negatively correlated with HDl-cholesterol and adiponectin. In obese women, plasma adiponectin level was negatively correlated with BMI, body fat, triglyceride, HOMA-IR, fasting insulinemia, leptin and positively correlated with HDL-cholesterol. HS-CRP was positively correlated with BMI, waist, body fat, triglyceride, HOMA-IR, leptin and negatively correlated with HDL-cholesterol (table 2).

**Discussion**

In this study we evaluated the metabolic profile of non-diabetic obese subjects, without cardiovascular disease, both with MetS and without MetS. We found that, in both sexes, obese subjects without MetS compared to lean subjects without MetS, had hyperinsulinemia, high systolic blood pressure, atherogenic dyslipidemia (hypertriglyceridemia and low HDL-cholesterol) and increase plasma concentration of hsCRP. Mauras et al [18] showed that clildhood obesity per se is associated with a proinflammatory and prothrombotic state before comorbidities of the MetS are present and even before the onset of puberty. Data regarding the correlation between obese individuals without the MetS, described as metabolically healthy obese (MHO)[19,20] and cardiovascular risk are contradictory. Meigs et al. [21] and St-Pierre et al. [22] showed that obese subjects without MetS were not at increased risk for cardiovascular disease. Arnlov et al. [23] found in non-diabetic middle-aged men, participants in community-based Uppsala Longitudinal Study of Adult Men (ULSAM), during median follow-up of 30 years, that overweight and obese middle-aged men without MetS had an increase risk for cardiovascular disease. Also, different studies demonstrated that normal-weight subjects with the MetS, described as metabolically obese but normal weight [24], had an increased cardiovascular risk [21-23]. In present there are data which have shown that there are similarities between obesity and atherosclerosis regarding the inflammatory processes, so this low-grade inflammation could be the link between obesity and atherosclerosis [25].

**Table 2. Pearson correlation coefficients for association between plasma adiponectin, hs-CRP and selected variables.**

| Variables | Adiponectin* | | | | Hs-CRP* | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| | r | p | r | p | R | p | r | P |
| Age (years) | 0.14 | 0.09 | 0.08 | 0.33 | **0.38** | **0.037** | 0.18 | 0.08 |
| BMI (kg/m$^2$) | **-0.74** | **<0.0001** | **-0.72** | **0.0004** | **0.39** | **0.031** | **0.53** | **0.0061** |
| Waist (cm) | **-0.56** | **0.0012** | -0.18 | 0.12 | **0.46** | **0.009** | **0.42** | **0.035** |
| Body fat (%) | **-0.72** | **<0.0001** | **-0.77** | **<0.0001** | **0.4** | **0.026** | **0.5** | **0.01** |
| SBP (mmHg) | -0.04 | 0.77 | 0.07 | 0.69 | 0.1 | 0.44 | 0.07 | 0.71 |
| DBP (mmHg) | 0.05 | 0.84 | 0.03 | 0.84 | 0.04 | 0.88 | 0.12 | 0.27 |
| Total cholesterol (mg/dl) | 0.07 | 0.67 | -0.1 | 0.23 | 0.15 | 0.081 | 0.11 | 0.35 |
| LDL-cholesterol (mg/dl) | -0.04 | 0.78 | -0.07 | 0.59 | 0.18 | 0.062 | 0.09 | 0.61 |
| Triglyceride (mg/dl) | **-0.58** | **0.0006** | **-0.66** | **0.0007** | **0.56** | **0.0011** | **0.41** | **0.04** |
| HDL-cholesterol (mg/dl) | **0.38** | **0.0344** | **0.39** | **0.035** | **-0.4** | **0.025** | **-0.51** | **0.009** |
| Fasting glucose (mg/dl) | - 0.14 | 0.33 | -0.09 | 0.48 | 0.07 | 0.68 | 0.17 | 0.24 |
| Acid uric | 0.03 | 0.8 | 0.1 | 0.66 | 0.03 | 0.91 | 0.04 | 0.087 |
| Fibrinogen | -0.16 | 0.17 | -0.13 | 0.28 | 0.21 | 0.058 | 0.17 | 0.093 |
| HOMA-IR* | **-0.51** | **0.003** | **-0.56** | **0.002** | **0.55** | **<0.0001** | **0.44** | **0.029** |
| Fasting insulinemia* | -0.21 | 0.063 | **-0.6** | **0.001** | **0.36** | **0.044** | 0.18 | 0.094 |
| Proinsulina* | -0.12 | 0.18 | -0.08 | 0.52 | 0.05 | 0.81 | 0.08 | 0.72 |
| Proinsulina/Insulina* | 0.09 | 0.62 | 0.11 | 0.54 | 0.02 | 0.84 | -0.03 | 0.79 |
| Leptin* | -0.13 | 0.16 | **-0.57** | **0.0012** | 0.16 | 0.073 | **0.41** | **0.044** |
| Hs-CRP* | **-0.44** | **0.023** | -0.21 | 0.09 | - | - | - | - |
| Adiponectin* | - | - | - | - | **-0.44** | **0.043** | -0.21 | 0.09 |

* log transformation because of the skewed distribution

In this study we showed that in non-diabetic obese subjects, proinflammatory state, prothrombotic state, hyperinsulinemia and leptin resistance are associated with MetS, in concordance with data reported by other authors [26-28]. In both sexes, subjects with MetS had higher levels of fasting insulinemia, hs-CRP, leukocyte count, fibrinogen and leptin, markers of the previous disturbances. Leptin is secreted by adipocytes in direct proportion to adipose tissue mass and is a modulator of the appetite and the energetic balance [29]. Also, recent studies demonstrated that leptin promotes atherogenesis through the following effects: induction of endothelial dysfunction, stimulation of inflammatory reaction, oxidative stress, decrease in paraoxonase activity, platelet aggregation, migration, hypertrophy and proliferation of vascular smooth muscle cells [30].

In the present study we found gender differences in adiponectin and hs-CRP levels. Median adiponectin levels were lower in men compared to women and median hs-CRP levels were higher in women compared to men, both in subjects without MetS and with MetS. These data are in concordance with results reported by other authors [31-33]. Previous studies showed that obese subjects with MetS have lower levels of adiponectin [34-37]. In the present study, adiponectin concentration was lower in obese subjects with MetS compared to obese subjects without MetS only in men. In this study we showed that adiponectin negatively correlated with BMI, body fat, HOMA-IR and triglyceride and positively correlated with HDL-

cholesterol in both sexes. Data are concordant with the results reported by other studies. Wang et al. [34] showed in 3193 subjects (44,44% male) aged 50-70 years that adiponectin is negatively associated both with MetS, independent of BMI, physical activity and life habits and MetS components, except blood pressure. Matsubara et al. [36] demonstrated in 352 non-diabetic women, with mean age 54 years and mean BMI 22,9kg/$m^2$, that plasma adiponectin concentrations were inversely correlated with triglyceride, atherogenic index, apo B and positively correlated with HDL-cholesterol and apo A-I, independently of BMI and body fat. Barrate et al. [38] showed in 242 non-diabetic subjects (35.95% male) that in both non-obese and obese subjects, low adiponectin concentrations are associated with triglycerides, HDL-cholesterol and insulin resistance independently of BMI. Hivert et al. [39] found in 2365 subjects, participants in Framingham Offspring Study, that HOMA-IR was inversely related to adiponectin and positively related to resistin and TNF-α, independently of BMI.

We also reported that, in both sexes, hs-CRP positively correlated with adiposity, insulin resistance, triglyceride and negatively correlated with HDL-cholesterol, in concordance with the results reported by other authors who demonstrated that elevated hs-CRP levels are associated with obesity [40-43], blood pressure [41], HDL-cholesterol [41], triglyceride [41], diabetes [42], insulin resistance [41,43], endothelial dysfunction [41] and coronary heart disease [44].

Another important finding of this study is that we found gender differences regarding the correlation between hs-CRP and adipokines. We showed that in non-diabetic obese men hs-CRP correlated negatively with adiponectin and in non-diabetic obese women hs-CRP correlated positively with leptin. Ouchi [44] showed that in male patients with coronary heart disease adiponectin levels were lower and hs-CRP levels were higher compared to subjects without coronary heart disease and demonstrated an inverse relationship between hs-CRP and adiponectin in both plasma and adipose tissue. Devaraj et al. [45] demonstrated that adiponectin suppress CRP synthesis and secretion in human aortic endhotelial cells, by modulating AMP-kinase (AMPK) signaling pathways and suppressing nuclear factor-kB (NF-kB) activation. Nishida et all.[46] showed in 326 apparently healthy men, aged 45.1 years, the importance of abdominal obesity in the aggravation of inflammatory status, demonstrated by the increase of hs-CRP and IL-6 and the decrease of adiponectin concentrations. Also, the authors found that inflammation is not exaggerated by clustering of MetS components in the subjects without abdominal obesity and a significant negative correlation was observed between adiponectin and hs-CRP levels only in the subjects with abdominal obesity. In this study we found a close relation between adiponectin, hs-CRP and MetS. Adiponectin levels were lower and hs-CRP levels were higher in subjects with MetS, in concordance with previous studies [26,34,47,48]. Maachi et al. [49] showed in non-diabetic obese women that systemic low-grade inflamtion is related to both circulating and adipose tissue TNFα, leptin and IL-6 levels. Sugiura et al. [50] reported that leptin (positively) and adiponectin (negatively) were independently associated with CRP. Among

obese subjects, leptin was more strongly related to CRP levels.

In conclusion this study showed that the levels of proinflammatory markers, hs-CRP, leukocyte count and fibrinogen, leptin, fasting insulinemia and HOMA-IR were higher and the levels of adiponectin were lower in obese, nondiabetic subjects with MetS, compared to obese, nondiabetic subjects without MetS. Furthermore, there is a positively correlation between hs-CRP and obese subjects without MetS. Leptin is strongly related to hs-CRP in obese women and adiponectin is strongly related to hs-CRP in obese men.

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**Correspondence Data**:
Dr. Vasilescu Razvan
19-21, Clinical Hospital Colentina, Bucharest, ROMANIA
Email: razvanv@mailbox.ro
Tel: 0040722163247