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Original Article

Relationship between the insulin resistance and circulating predictive biochemical markers in metabolic syndrome among young adults in western Algeria

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ABSTRACT

Aim: The metabolic syndrome (MetS) becomes increasingly obvious from an early age. The current study aimed at exploring the relationship between insulin resistance and the main biomarkers of MetS in young adult algerian patients.
Methods: Glucose, HbA1C, total cholesterol (TC), hjgh bensity lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), insulinemia and C-peptide, adipokins (leptin, adiponectin), inflammatory cytokines (IL-6 and TNF-a), us-CRP and GLP-1 were measured by suitable methods. Homeostasis model assessment (HOMA) was used to detect the degree of insulin resistance.
Results: The MetS patients displayed higher glucose, insulin, HbA1c values and impaired lipid profile as judged by increasing TC, TG, LDL-C levels and lower HDL-C. Furthermore, adipokines, HDL-C and CRP contents were significantly higher whilst TG and LDL-C were much lower in MetS female group as compared to male patients suggesting most pronounced metabolic perturbation in the latter group. The probability of a significant correlation between HOMA and studied variables was often higher in female than male subjects. Such was the case for total cholesterol, HDL-cholesterol, triglycerides, adiponectin, interleukin-6, TNF-α and hs-CRP.
Conclusion: The high rate of metabolic syndrome among young obese adults is alarming, this requiring extensive investigations in prone subjects.
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1. Introduction

Cardiovascular diseases represent the first cause of mortality at the world level [1,2]. Risk factors commonly recognized to favour the occurrence of these pathologies include tabagism, arterial hypertension, dyslipidemia, diabetes, obesity, sedentarity, alcohol consumption, stress and socio-economic status [3,4].

The association of certain of these factors was often proposed as a determinant of the metabolic syndrome, also referred to as the plurimetabolic or insulinoresistance syndrome [5].

Algeria has experienced since a few years, an important demographic and epidemiological transition characterized by drastic changes in lifestyle, rapid urbanization and environmental deterioration [6], resulting in the regression of infection diseases and the increased incidence of cardiovascular diseases, which now represent a true plague of public health, underlining the imperative need of a rigorous control of child obesity in order to improve metabolic and vascular prognostic [7].

Population aging and genetic ground only account to a limited extent for the increased incidence of the above mentioned pathologies, since young subjects are more and more affected. We know already the importance of environmental factors impact in drastic emergence of metabolic disorders (metabolic syndrome, diabetes, obesity) [8–12]. The arteriosclerotic process begins at a young age. Moreover, the biological and behavioral risk factors associated to MCV become obvious in infants and predict the presence of the same risk factors at the adult age [13]. The need of suitable cardiovascular prevention programs specifically oriented

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to children and young adolescents is now recognized, even more so that an alarming increase of overweight, sedentarity and poor dietary habits indeed now prevails.

The main purpose of this work was to explore the anthropometric parameters and metabolic makers of glycemic, lipidic inflammatory and pro-inflammatory status, adipose tissue and satietogen intestinal incretin glucagon like peptide-1 (GLP-1) function in order to define the biological characteristics of metabolic syndrome young adult patients from western Algeria, to accurately characterize it physiopathology by establishing different correlations between the studied markers.

2. Subjects, materials and methods

2.1. Study population

The population under study consisted of a cohort of 100 patients (60 men and 40 women) aged between 30 and 40 years among the 2365 cases of diagnosed metabolic syndrome patients that have been admitted for consultation in diabetology at the Department of Internal Medicine of both the Military Regional Universitary Hospital of Oran (HMRUO) and University Hospital Establishment (EHU) of Oran. The study was conducted from November 2015 to December 2017. The study was approved by an ethical committee, the concerned subjects having given a signed consent after having been duly informed. On occasion, the consent was orally given after explaining the aim of the biological assays. For each subject, a file was prepared to include all relevant information (age, sex, residence, ethnicity, profession, instruction, matrimonial status, family antecedents of diabetes, obesity, hypertension and vascular accident, tobacco use, physical and paraclinical data).

2.2. Data collection

The criteria for the diagnostic of metabolic syndrome were those defined by the NCEP-ATPIII (National Cholesterol Education Program-Adult Treatment Panel III). A subject was considered to present a metabolic syndrome if 3 of the 5 following criteria were found: abdominal obesity with an abdominal perimeter $\geq$102 cm for men and $\geq$88 cm for women, triglycérides $\geq$1.5 g/L, HDL-cholesterol < 0.4 g/L for men and <0.5 g/L for women, fasting glycemia $\leq$1.1 g/L (threshold decreased to 1.0 g/L in 2005 following the recommendation of the American Diabetes Association) and arterial blood pressure $\geq$ 130/85 mm Hg. The criterion to define obesity was based on the Quetelet or body mass index (BMI) defined as the ratio between body weight (Kg)/height (m), five types being defined, i.e. normal weight (between 18.5 and 24.9), overweight (between 25.0 and 29.9), Obesity (between 30.0 nd 34.9, class I), massive obesity (between 35.0 and 39.9, class II) and morbid obesity (above 40.0, class III). Non-consenting young adults patients or not meeting at least 3 of the 5 outreach NCEP-ATPIII criteria or those having kidney or hepatic diseases or any endocrine problem especially Cushing's disease and thyroid dysfunctions and type 1 diabetic patients and pregnant women under estro-progestins drugs were excluded. The same applies to patients under weight control, corticoids, antidepressants, and non-steroidal anti-inflammatory drugs were excluded.

A control group consisted of 10 male and 10 female healthy subjects aged between 27 and [36] years and with a body weight/height ratio between 18.5 and 24.9 kg/m. These subjects presented no pathology, did not smoke and did not consume alcohol.

3. Materials and methods

3.1. Blood sampling

Venous blood samples were collected from the antecubital fossa between 8:00 and 9:00 a.m. after 12 h of fasting. Whole blood specimens were collected in different tubes to obtain serum and plasma. The samples were separated in aliquots and frozen immediately at −80 °C until being analyzed.

3.2. Biochemical analyses

Glucose, glycated hemoglobin, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and tiglycerides were measured by multiparametric automated procedure using Cobas 6000 analyzer with Roche Diagnostic's reactives. Insulinemia and C peptide were determined by electrochemiluminescence (ECLA) assay in a random access analyzer (Cobas E411, Roche Diagnostics).

Homeostasis model assessment (HOMA) was used to detect the degree of insulin resistance. The resistance can be assessed from the fasting glucose and insulin concentrations by the formula: resistance (HOMA) = [insulin (mU/l) x glucose (mmol/l)].

Antigenic immunoassay procedure based on enzyme linked immunosorbent assays from RD Systems (Wiesbaden- Nordenstadt, Germany) was used for the quantification of leptin (Human leptin Quantikine), adiponectin (human adiponectin, Acrp30 Quantikine), IL-6 (human IL-6 Quantikine) and TNF-α (Human TNF-α Quantikine) carried out in a microtiter plate analyzer (Human-Reader, Wiesbaden, Germany).

Plasma GLP-1 and us-CRP were measured using Abcam kit (Cat N°184857) and Cell Biolabs kit (Cat N° STA-392), respectively.

3.3. Statistical analyses

Statistical assessment was conducted With GraphPAD Prism V.7 (GraphPAD Software, San Diego, CA, USA). Abnormal values (outliers) were excluded. Results were expressed as mean ± SEM, with a 95% confidence interval (95% CI). The mean values of the groups were compared using Student's unpaired *t*-test.

Correlation between insulin resistance and other measured variables was evaluated using Pearson's correlation coefficient followed by regression analysis. Statistical significance was set at $p < 0.05$.

4. Results

The mean age averaged 31.65 ± 2.64 years in the 20 control subjects (10 males and 10 females) and 34.28 ± 2.57 years in the 100 MetS subjects (60 males and 40 females). These two mean values did not differ significantly from one another ($p > 0.05$).

Table 1 provides information (mean values ± SEM) for 15 variables. The information concerning age, abdominal perimeter, arterial blood pressure and corporal mass index was also duly collected.

The only individual data collected in the 20 control subjects and displaying an abnormal value for a parameter selected to define the MetS were 3 glycemia (5.56, 5.62 and 5.73 mM) recorded in 2 males and one female subjects.

In the 60 male MetS subjects, only 16 of them were non-diabetic as judged by a glycemia below 7.0 mM averaging 6.16 ± 0.16 mM. Forty-four of the male MetS subjects were considered as diabetic (glycemia>7.0 mM), with individual values between 7.0 and

Table 1
Biochemical parameters in two genders of metabolic syndrome (MetS) patients and control group.

	Control	MetS patients	Male	Female
Glycemia (mM)	4.78 ± 0.11 (n = 20)	7.50 ± 0.11 (n = 100)[a]	7.56 ± 0.15 (n = 60)	7.42 ± 0.17 (n = 40) [NS]
Insulinemia (μU/ml)	11.05 ± 0.88 (n = 20)	31.84 ± 0.38 (n = 100)[a]	30.97 ± 0.49 (n = 60)	33.14 ± 0.54 (n = 40)[b]
C-peptide (ng/ml)	1.44 ± 0.06 (n = 20)	2.79 ± 0.06 (n = 100)[a]	2.88 ± 0.08 (n = 60)	2.66 ± 0.10 (n = 40) [NS]
HOMA (mM μU/ml)	53.5 ± 4.95 (n = 20)	241 ± 5.77 (n = 100)[a]	236.4 ± 7.72 (n = 60)	248 ± 8.61 (n = 40) [NS]
HbA1C (%)	5.29 ± 0.0 (n = 20)	6.58 ± 0.06 (n = 100)[a]	6.60 ± 0.08 (n = 60)	6.55 ± 0.1 (n = 40) [NS]
Total cholesterol (g/l)	1.60 ± 0.04 (n = 20)	2.04 ± 0.01 (n = 100)[a]	2.05 ± 0.01 (n = 60)	2.03 ± 0.02 (n = 40) [NS]
HDL-C (g/l)	0.57 ± 0.01 (n = 20)	0.43 ± 0.01 (n = 100)[a]	0.39 ± 0.01 (n = 60)	0.48 ± 0.01 (n = 40)[a]
LDL-C (g/l)	1.00 ± 0.04 (n = 20)	1.22 ± 0.01 (n = 100)[a]	1.24 ± 0.04 (n = 60)	1.18 ± 0.02 (n = 40)[b]
Triglycerides (g/l)	1.06 ± 0.05 (n = 20)	1.99 ± 0.03 (n = 100)[a]	2.06 ± 0.04 (n = 60)	1.89 ± 0.035 (n = 40)[b]
Leptin (ng/ml)	7.11 ± 1.17 (n = 12)	17.96 ± 0.76 (n = 66)[a]	16.36 ± 0.97 (n = 39)	20.31 ± 1.10 (n = 27)[b]
Adiponectin (μg/ml)	7.43 ± 0.69 (n = 12)	3.89 ± 0.15 (n = 62)[a]	3.43 ± 0.18 (n = 37)	4.57 ± 0.20 (n = 25)[a]
Interleukin-6 (pg/ml)	7.70 ± 0.73 (n = 14)	12.91 ± 0.53 (n = 63)[a]	13.11 ± 0.66 (n = 36)	12.65 ± 0.87 (n = 27) [NS]
TNF-α (pg/ml)	14.90 ± 2.27 (n = 14)	20.80 ± 1.09 (n = 66)[b]	22.22 ± 1.26 (n = 39)	18.79 ± 1.90 (n = 27) [NS]
CRP (mg/l)	1.52 ± 0.10 (n = 20)	5.14 ± 0.30 (n = 50)[a]	4.07 ± 0.24 (n = 30)	6.74 ± 0.47 (n = 20)[a]
GLP-1 (pmol/l)	24.52 ± 0.55 (n = 20)	12.74 ± 0.45 (n = 62)[a]	12.76 ± 0.60 (n = 36)	12.73 ± 0.69 (n = 26) [NS]

[NS] not significant; [a] $P < 0.001$; [b] $P < 0.01$.

8.0 mM in 26 subjects (averaging 7.52 ± 0.06 mM), between 8.0 and 9.0 mM (8.41 ± 0.09 mM) in 12 subjects and above 9.0 mM (9.80 ± 0.36 mM) in 6 subjects. Likewise, in the 40 female MetS subjects, about a quarter of them were non-diabetic (5.77 ± 0.21 mM, n = 9), 21 of them moderately diabetic (7.56 ± 0.06 mM, individual value not exceeding 8.0 mM) and again a quarter of them severely hyperglycemic (>8.0 mM) with a mean value of 8.58 0.10 mM (n = 10).

The glycemia was below 5.56 mM in only 10 MetS subjects (4 males and 6 females). Even so, it averaged in these 10 subjects 5.38 ± 0.04 mM, as distinct ($p < 0.01$) from 4.78 ± 0.12 mM in the 20 control subjects.

The HDL-cholesterol exceeded the reference value of 0.4 g/L in 14 male MetS subjects and 0.5 g/L in 12 female MetS subjects. Even so however, the mean values recorded in these 14 male and 12 female subjects did not exceed 86 ± 1.95% (n = 14) and 89.2 ± 1.06% (n = 12) ($P < 0.01$ in both cases) as compared to of the mean corresponding values found in male 100 ± 2.14% (n = 10) and female 100 ± 1.92% (n = 10) control subjects, respectively.

Last, to complete the information concerning the criteria used to identify the MetS subjects, the triglyceride values exceeded 1.50 g/L in all subjects of the MetS group, and the abdominal perimeter also exceeded the reference value (102 cm in males and 88 cm in females) in all subjects of the MetS group.

All other 14 variables listed in Table 1 displayed highly significant differences ($p < 0.001$) between control and MetS subjects. In the latter group, seven of these variables were not significantly different in male and female MetS subjects. Moreover, in the case of the other seven variables, the difference between males and females suggested a more severe perturbation either in males (two cases) or females (four cases). Nevertheless, in those cases in which the difference between male and female MetS subjects was highly significant ($p < 0.001$), i.e. the HDL-C, adiponectin and CRP data, the metabolic perturbation was most pronounced in female subjects.

Fig. 1 illustrates four correlations between the HOMA index and another metabolic variable, with either unsignificant or obvious relationship between the two sets of data. Table 2 provides the results of the correlation analysis between the HOMA index and 12 other variables in either male or female MetS subjects. In order of decreasing statistical significance, these correlation with the HOMA index were most obvious for the LDL-cholesterol in both male ($P = 0.82$) and female ($P = 0.70$) subjects. No other variable yielded a probability of more than 0.05 in both male and female subjects. The probability of a significant correlation was often higher in female than male subjects. Such was the case for total cholesterol, HDL-cholesterol, triglycerides, adiponectin, interleukin-6, TNF-α and hs-CRP.

5. Discussion

More and more frequent in young adults, the metabolic syndrome increases with growing urbanization and unfavourable modifications of lifestyle affecting the developing countries [14]. The aim of our study is to define the physiopathological characteristics of insulin resistance in young adults of Western Algeria presenting a metabolic syndrome.

In our study, the BMI mean was estimated at 32.7 ± 2.7 (kg/m^2) and abdominal perimeter at 101 ± 7 cm for all patients. The ISOR study conducted in an Oran population of West Algeria has reported comparable results [15].

We observed a significant positive correlation between the Body Mass Index and HOMA whether in male or female patients (Table 2). These results are in perfect agreement with the studies of Romero-Corral et al. [16] and Makni et al. [17]. Among the male patients, only 27% were considered as non-diabetic with a mean glycemia of 6.16 ± 0.16 mM. Among the diabetic patients (n = 44), 59% had a mean glycemia of 7.52 ± 0.06 mM, 27% a mean glycemia of 8.41 ± 0.09 mM and 13.6% a mean glycemia of 9.80 ± 0.36 mM. In the female patients, only 22.5% were non-diabetic, 52.5% modestly diabetic and 25% severely diabetic. Moreover, the glycemia and insulinemia were increased by 57% and 188%, respectively, in the MetS group as a result of the increased hepatic glucose output and peripheric insulin resistance, when compared to the control group. This finding is further supported by the positive and highly significant ($P < 0.01$) correlation between HOMA and glycosylated hemoglobin observed both in male patients (r = + 0.79) and female patients (r = + 0.88).

The total cholesterol and triglycerides concentrations were significantly higher in the MetS than control group. This correlated with the accumulation of lipids in adipose tissue and increase in hepatic synthesis and secretion of lipoproteins [18]. These anomalies may be responsible for hepatic steatosis leading to the perturbation of glucose metabolism and insulinemia [19], as further supported by the highly significant correlation between HOMA and triglycerides in males (+0.48; $P < 0.01$) and females (+0.43; $P < 0.01$). These findings agree with those reported by Sameer et al. [20], Chang et al. [21], Abramas et al. [22] and Simental-Mendia et al. [23].

HDL-C data correlated negatively with HOMA in male MetS patients (r = - 0.32; $P = 0.01$), at variance with observations made by Waldman et al. [24]. The mechanisms responsible for the alterations of lipid metabolism associated to the MetS involve a high

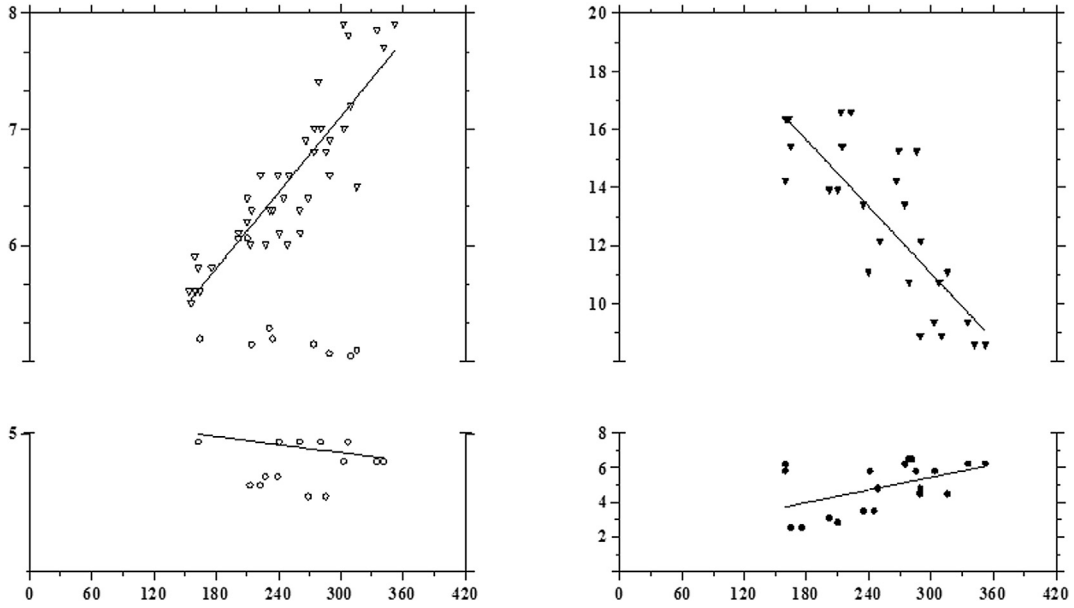


Fig. 1. Relationship between insulin resistance HOMA index (y-axis in both panels), HbA1C (upper left panel), adiponectin (lower left panel), CRP (lower right panel) and GLP-1(upper right panel) in MetS female patients. The oblique lines correspond to the regression lines.

lipolytic activity in visceral adipose tissue resulting in a supply to the liver of large amounts of free fatty acids associated to increased glucose and insulin concentrations, eventually resulting in the increased circulatory concentration of triglycerides and cholesterol and their accumulation in muscle and other tissues. This phenomenon of lipotoxicity provokes both the inflammation of pancreatic β cells and a decrease of their mass [25].

It is well established that cardiovascular diseases and the metabolic syndrome are associated to high acute-phase proteins, indicating the presence of a chronic subclinical inflammation. High leptin levels and hypoadiponectinemia may contribute to insulinoresistance [26], as well as acceleration of the atherogenic process associated to obesity [27,28]. Our results document the hypoadiponectinemia in MetS patients, compared to control subjects, with mean values of 4.58 ± 0.21 mg/ml in female patients and 3.43 ± 0.18 mg/ml in male patients. Correlation analysis revealed a negative relationship between insulin resistance HOMA and circulating adiponectin levels in male MetS subjects and a positive linear relationship with plasma leptin in female subjects ($r = +0.64$, $P < 0.05$; Table 2). These findings are in good agreement with the work of Lihn et al. [29] and Raji et al. [30]. It was indeed demonstrated that the alteration of adiponectin levels affects directly glucidic and lipidic metabolism and inflammatory cytokines [31].

TNF-α, C-reactive protein and interleukin-6 represent prototypic and predictive inflammatory markers of cardiovascular diseases [32–35]. In the present study, the MetS components are tightly linked to high levels of CRP, TNF-α and IL-6, when compared to the control group. CRP and IL-6 are positively correlated to HOMA only in male patients. The increase of TNF-α is negatively correlated to adiponectin ($r = 0.31$; $P < 0.01$). This result agrees with the work of Ouchi et al. [26] who demonstrated that a decrease in adiponectin levels leads to activation of the NFκb nuclear factor via the increased TNF-α levels and, hence, the activation of monocytes adhesion at the endothelial cell level. Such a hypoadiponectinemia increases the catching capacity of oxidized adipokines by macrophages via activation and expression of class A-1 genes expressed by scavenger receptors. Thus, inflammation acting in concert with pro-inflammatory cytokines of the adipose tissue (IL-6) and adipokines may play a preponderant role in the etiopathogeny of MetS. Hyperinsulinemia associated to obesity accounts, in major part, for the increased production of cytokines [37,38].

The glucagon-like peptide-1 (GLP-1) represents a major incretin hormone secreted by the intestinal L-cells into the blood stream. This stimulates insulin secretion and inhibits glucagon secretion. Apart from these effects on glucose and energy homeostasis, GLP-1 rules gastric emptying, body weight and appetite [39] and displays anti-inflammatory properties by decreasing the secretion of macrophage inflammatory cytokines in insulin resistant obese subjects [40,41]. Hence, GLP-1 impairment represents a physiopathologic link between obesity, postprandial reactive hypoglycemia and type 2 diabetes [42–44]. Our study draws attention to an appreciable decrease of GLP-1 levels in MetS patients, compared to control subjects. Our results agree with those concerning decreased GLP-1 levels and glucose-stimulated secretion in obese subjects [45]. This decrease in GLP-1 dependent on the extent of insulin resistance could lead to a decrease of the insulinotropic potential, intestinal secretion or enzymatic degradation by dipeptidyl peptidase-4 of this incretin. Nevertheless, the impact of GLP-1 on obesity development could be mostly linked to its physiological effects on appetite and food intake [43,46].

The correlation analysis documented a significant negative association between HOMA and incretin only in female patients. This could be explained by the fact that insulin resistance would represent an independent predictive factor of the GLP-1 response in male subjects. It was indeed suggested that obese subjects display GLP-1 hyposecretion in response to food intake, when compared to lean subjects, and that GLP-1 levels even fail to increase after body weight loss in obese subjects [47,48]. Other authors have either documented that the GLP-1 responses are comparable in obese and lean subjects [46] or failed to find any difference in GLP-1 levels between obese or overweighed and lean subjects, suggesting that the decrease of GLP-1 secretion in obesity represents a phenomenon independent of adiposity and that this incretin does not represent a significant isolated marker for determination of obese status [49,50].

Table 2
Correlation analyses between HOMA index and selected variables in male and female patients.

Body mass index (BMI)		Glycated hemoglobin (HbA1C)		Total cholesterol	
Male	Female	Male	Female	Male	Female
+0.7077 (P < 0.01)	+0.7045 (P < 0.01)	+0.7974 (P < 0.01)	+0.8818 (P < 0.01)	+0.1867 (P = 0.1531)	−0.0205 (P = 0.900)
HDL-cholesterol		LDL-cholesterol		Triglycerides	
Male	Female	Male	Female	Male	Female
−0.3262 (P = 0.01)	−0.2448 (P = 0.128)	−0.0298 (P = 0.82)	−0.0620 (P = 0.70)	+0.4850 (P < 0.01)	+0.4342 (P < 0.01)
Leptin		Adiponectin		Interleukin-6	
Male	Female	Male	Female	Male	Female
−0.2234 (P = 0.171)[a]	+0.6395 (P < 0.05)[b]	−0.5088 (P < 0.01)[c]	−0.2552 (P = 0.2182)[d]	+0.5431 (P < 0.01)[e]	+0.2199 (P = 0.27)[b]
TNF-α		hs-CRP		GLP-1	
Male	Female	Male	Female	Male	Female
+0.2810 (P = 0.087)[f]	−0.2601 (P = 0.19)[b]	+0.5782 (P < 0.01)[g]	+0.3989 (P = 0.08)[h]	−0.1443 (P = 0.4013)[e]	−0.7568 (P < 0.01)[i]

n = 60 male and 40 female in all other cases. TNF-α: tumor necrosis factor -α; hs-CRP: high sensitive C reactive protein; GLP-1: glucose like peptide-1.
[a] n = 39.
[b] n = 27.
[c] n = 37.
[d] n = 25.
[e] n = 36.
[f] n = 38.
[g] n = 30.
[h] n = 20.
[i] n = 24.

6. Conclusion

The High rate of metabolic syndrome among obese young adults is alarming. Early detection and screening of glucose homeostasis, lipid, adipokines, inflammatory and incretin parameters by systematic biochemical check-up should be recommended for all obese young adult and adolescents for predicting development of insulin resistance and adding important prognostic information in terms of future cardiovascular risk management.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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