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Original article

# Association between serum levels of vascular endothelial growth factor, macrophage inhibitory cytokine and markers of oxidative stress, with the metabolic syndrome and its components in obese individuals

## *Association entre les valeurs sériques du facteur de croissance vasculaire endothélial, la cytokine inhibitrice des macrophages et les marqueurs du stress oxydatif, avec le syndrome métabolique et ses composants chez les personnes obèses*

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**Abstract**

*Aim.* – Metabolic syndrome (MetS) is a clinical disorder with widespread prevalence. In the current study, we aimed to investigate the serum values of macrophage inhibitory cytokine (MIC)-1, vascular endothelial growth factor (VEGF) and markers of oxidative stress among patients with metabolic syndrome.

*Material and methods.* – Twenty obese patients with MetS and 20 obese apparently healthy controls were participated in the current case-control study. The participants' body mass index (BMI), waist circumference (WC), systolic and diastolic blood pressure (SBP and DBP) were measured. Serum levels of total cholesterol (TC), triglyceride (TG), low and high density lipoprotein cholesterol (LDL-c and HDL-c), vascular endothelial growth factor (VEGF), MIC-1 (macrophage inhibitory cytokine 1), superoxide dismutase (SOD) and glutathione peroxidase (GPX) were also determined by commercial ELIZA kits.

*Results.* – Participants in MetS group had higher levels of WC, DBP and higher serum concentrations of TG and TC compared with control group ($P < 0.05$). Serum VEGF and MIC-1 levels were significantly higher in patients with MetS compared with control subjects ($P < 0.05$). There was a significant and positive association between serum levels of VEGF and LDL ($P = 0.027$; $\beta = 0.453$) in all of the study participants. Moreover, an inverse association between serum GPX with DBP and between SOD with WC were also seen ($P < 0.05$).

*Conclusion.* – The higher serum values of MIC-1 and VEGF in patients with MetS and the negative association of VEGF with serum LDL concentrations opened a new window about the possible pathologic role of these factors in the etiology or pathophysiology of MetS. Further studies are warranted for solidification of achieved results.


*Keywords:* Metabolic Syndrome; VEGF; MIC-1; Oxidative stress

**Résumé**

*Objectif.* – Le syndrome métabolique (SMet) est un trouble clinique très fréquent. Nous avons étudié les valeurs sériques du facteur de croissance endothélial vasculaire (FCEV), de la cytokine inhibitrice des macrophages CIM-1, et des marqueurs de stress oxydatif chez les patients atteints de SMet.

*Matériel et méthodes.* – Vingt patients obèses avec SMet et 20 témoins obèses apparemment sains ont participé à l'étude. L'indice de masse corporelle (IMC) des participants, leur tour de taille (TT), leur pression artérielle systolique et diastolique (PAS et PAD) étaient mesurés, ainsi que leur cholestérolémie total (CT), leur triglycéridémie (TG), leur cholestérolémie LDL et HDL, leur taux sériques de FCEV, CIM-1, superoxyde dismutase (SOD) et glutathion peroxydase (GPX).

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*Résultats.* – Les participants du groupe SMet avaient un TT et une PAD plus élevés, des concentrations plus élevées en CT et TG par rapport au groupe témoin ($p < 0,05$). Leurs taux sériques de FCEV et CIM-1 étaient plus élevés par rapport au sujets contrôles ($p < 0,05$). Une association positive était notée entre les taux sériques de FCEV et ceux de LDL (P : 0,027, B : 0,453) chez tous les participants, ainsi qu'une association inverse entre GPX et PAD et entre SOD et TT ($p < 0,05$).
*Conclusion.* – Les valeurs sériques plus élevées de FCEV et CIM-1 chez les patients atteints de SMet et l'association négative de FCEV avec les concentrations sériques de LDL ont ouvert une nouvelle fenêtre sur un rôle possible de ces facteurs dans la physiopathologie du SMet. Ces résultats doivent être confirmés par d'autres études.


*Mots clés :* Syndrome métabolique ; FCEV ; CIM-1 ; Stress oxydatif

## 1. Introduction

Metabolic syndrome (MetS) is a cluster of pathologic abnormalities such as hypertension, hyperglycemia, abdominal obesity and dyslipidemia with increased risk of cardiovascular disease, stroke, diabetes, and mortality. MetS prevalence ranges from 8% to 80% around the world depending on the race, ethnicity, age, and gender of the population; International Diabetes Federation (IDF) estimates that one-fourth of the world's populations are living with MetS [1–3]. In fact, in persons with MetS but without diabetes the increased risk of CVD and CHD mortality remain [4]. Several previous studies reported that metabolic syndrome is associated with 3 to 4.3 fold increase in mortality from CVD [5] and subjects with metabolic syndrome are 3.5 to 5 times more likely to develop type 2 diabetes mellitus [6]. Imbalance in the coordination of energy intake and expenditure contributes to increment of waist circumference (WC), abdominal obesity and insulin resistance, which are the most important manifestations of MetS [7]. Recent evidences indicated that some factors such as vascular endothelial growth factor (VEGF) [8], macrophage inhibitory cytokine 1 (MIC-1) [9], superoxide dismutase (SOD) and glutathione peroxidase (GPX) [10] have pivotal role in progression of MetS complications.

VEGF is an important angiogenesis regulator. Serum VEGF levels are increased under conditions of angiogenesis enhancement. So, VEGF has attracted considerable attention for its function in progression of metabolic diseases complications such as cardiovascular disease. According to previous reports, VEGF is a potent pathologic indicator of vascular damage in patients with MetS [11,12]. VEGF is a potent multifunctional cytokine reported to induce migration and proliferation of endothelial cells, enhance vascular permeability and modulates thrombogenicity [13]. Therefore, VEGF is implicated in normal and pathologic vascular development; the pathogenic neovascularization plays a major role in development of various abnormalities including atherosclerosis, tumor growth, rheumatoid arthritis [13]. Enhanced serum concentrations of VEGF has been reported as significantly associated with the components of metabolic syndrome, such as body mass index (BMI), WC, blood pressure and inflammation [14,15]. Alongside, macrophage inhibitory cytokine 1-growth differentiation factor 15 (MIC-1/GDF15) as a member of a large family cytokine, transforming growth factor β [TGF-β]), is secreted by the number of cells including adipose tissue macrophages, adipocytes, heart and vascular cells [16]. MIC-1/GDF15 has important roles in energy metabolism by reducing energy intake and increasing energy expenditure. However, increased serum concentration of MIC-1/GDF15 in obese individuals is a possible evidence of MIC-1/GDF15 resistance in obesity [16,17]. Recent studies revealed serum concentration of MIC-1 increased in obese subjects [18,19]. However, its role in development of metabolic syndrome has not been studied in the current study. Although the exact physiological role and the regulation of MIC-1 in humans are poorly understood, however the current knowledge about its effects in humans suggests that it might play an important role in the development and progression of inflammatory and atherosclerotic processes and cancer [20] and oxidative stress is a possible potent stimulator of its secretion [21]. Moreover, oxidative stress plays a key role in progression of Mets and its complications. Oxidative stress occurs when the production of free radicals exceed the antioxidant. Increment of oxidative stress directly enhances the risk of cardiovascular complications [22,23]. Considering, the above mentioned introduction about the possible association between MIC-1, VEGF and markers of oxidative stress with metabolic syndrome, in the current case-control study the researchers aimed to investigate the association of serum VEGF, MIC-1, SOD and GPX with components of MetS and to compare their concentrations in patients with MetS and healthy individuals.

## 2. Materials and methods

### 2.1. Study design and participants

The current case-control study was performed between August to October, 2016. Metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) [24]. MetS were recognized when the subjects had at least 3 of 5 following criteria: WC more than 88 and 102 cm for women and men respectively, serum TG $\geq$ 150 mg/dL, serum HDL-c $\leq$ 50 mg/dL for women and $\leq$ 40 mg/dL for men, BP $\geq$ 130/85 mmHg, FBG $\geq$ 100 mg/dL. Accordingly, twenty obese patients with MetS and 20 obese apparently healthy age and BMI-matched controls were participated in the current case-control study. Inclusion criteria included: BMI $\geq 30\,kg/m^2$ aged between 20–50 years. Exclusion criteria included: any history of kidney diseases, atherosclerosis, cancer, acute infections, recent surgery, use of

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