Research & Reviews

ISSN: 2319-9865

Research and Reviews: Journal of Medical and Health Sciences

Assessment of Serum Interleukin-18 Level as a Risk Predictor of Metabolic Syndrome: Case-Control Study.

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Research Article

Received: 17/04/2013
Revised: 30/05/2013
Accepted: 25/06/2013

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Keywords: Metabolic syndrome, pre-metabolic syndrome, IL-18

ABSTRACT

Metabolic syndrome is a multiplex risk factor accompanying abnormal adipose deposition and function. It is associated with a chronic, low-grade inflammation. Several pro-inflammatory cytokines have been shown to be elevated in parallel with an increasing number of components of the syndrome, whereas the anti-inflammatory and adipocyte-specific substance adiponectin is consistently lower. Increasing levels of circulating IL-18 have been reported to be closely associated with the components of metabolic syndrome and to predict type 2 diabetes, cardiovascular events, and mortality. to assess serum level of IL-18 metabolic patients compared to premetabolic patients and healthy subjects. It was conducted on 25 metabolic syndrome patients, 25 pre-Metabolic syndrome patients, and 25 normal persons. IL-18 was significantly higher in both pre-metabolic and metabolic groups in comparison to the control one and still lower in pre-metabolic than the metabolic. Concentrations of IL-18 was significantly positively correlated with waist circumference, blood pressure , fasting blood sugar and negatively with HDL level in both metabolic and premetabolic groups. A cut off value of > 210 pg/dL provided 92.0% sensitivity and 88.0% specificity for patients with pre-metabolic syndrome. While a cut off value of > 250 pg/dL provided 72.0% sensitivity and 96.0% specificity for diagnosis of patients with metabolic syndrome. IL-18 has been be elevated in subjects with the metabolic syndrome and to increase in parallel with an increasing number of components of the syndrome. Its level can be used as an additional predictive risk factor for development of pre-metabolic and metabolic syndrome.

INTRODUCTION

Obesity and the related metabolic syndrome (MetS) is major public health problems that are associated with an increased risk of the development of atherosclerotic cardiovascular disease [1]. The mechanism of which may be mediated by increased secretion of pro-inflammatory cytokines by the adipose tissue [2]. The syndrome has received increased attention after practical definitions by the Adult Treatment Panel III and International Diabetes Federation [3].

MetS consists of atherogenic dyslipidemia (elevated triglycerides and low high-density lipoproteins [HDLs]), elevated blood pressure and glucose levels, and abdominal obesity with prothrombotic and pro-inflammatory states [4]. MetS is associated with a 5-fold higher risk of the development of type 2 diabetes and a 2.6- to 3 fold higher risk of the development of cardiovascular disease[5,6]. In obese individuals there is an increased expression of IL-18 in adipose tissue [7] and a 3-fold increased secretion from adipocytes compared with lean controls[8]. Interestingly, experimental hyperglycemia has been shown to increase the expression of IL-18 in adipocytes, an effect that was even more pronounced in the presence of intermittent hyperglycemia.[9] However, other studies have reported that non-adipocytes are the main sources of IL-18 in adipose tissue [10]. In view of all these considerations, the current study was designed to investigate serum interleukin-18 level as a potential risk predictor of metabolic syndrome.

SUBJECTS AND METHODS

Treatment Panel III report (ATP III) Criteria of MetS are shown in Table 1. When 3 of 5 of the listed characteristics are present, a diagnosis of MetS can be made [11]. Based on this criteria for MetS, patients who had no less than two components of MetS but did not meet the criteria for the diagnosis of MetS were considered as having pre-MetS (incomplete MetS). The study was

ISSN: 2319-9865

conducted upon attendants of the outpatient clinics of the Suez Canal university hospitals. The study included three groups, matched with age and gender and total 75 subjects (25 in each group). The first group metabolic syndrome patients, second subjects with pre-MetS conditions, while the third groups are healthy adults (control group).

Table 1: Treatment Panel III report (ATP III) Criteria of MetS

Diagnosis of metabolic syndrome Measure (any 3 of 5)	Categorical Cut-points
Elevated waist circumference	>102 cm in men / >88 cm in women
Elevated triglycerides	>150 mg/dL (1.7 mmol/L) Or On drug treatment for elevated Triglycerides
Reduced HDL-C	<40 mg/dL in men / <50 mg/dL in women Or On drug treatment for reduced HDL-C
Elevated blood pressure	>130 mm Hg systolic blood pressure Or >85 mm Hg diastolic blood pressure Or On antihypertensive drug treatment
Elevated fasting glucose	>100 mg/dL or On drug treatment for diabetes

All were subjected to medical history taking with systemic clinical examination as weight, Height, Body mass index, Waist circumference.

Laboratory Investigations: Fasting blood samples was collected for total cholesterol, HDL cholesterol, triglycerides and glucose were determined. Human IL-18 ELISA Kit measures human IL-18 by sandwich ELISA.

Ethical consideration: Informed consent was obtained from the patients. The study was approved by the Ethics Committee of Faculty of Medicine, Suez Canal University.

Statistical analysis: The analysis was carried out by a computer program (SPSS Ver. 12). *P* value was set at <0.05 for statistically significant results and <0.001 for highly significant results.

RESULTS

Demographic and laboratory data of the three groups are presented in table 2. Metabolic patients' ages ranged from 41 to 69 years with a mean age of 55.6 ± 7.8 years. They are 11 males and 14 females. Premetabolic patients' ages ranged from 44 to 77 years with a mean age 55.7 ± 8.9years. They are 15 males and 10 females . In normal subjects, their ages ranged from 44 to 66 years with a mean age 53.8 ± 5.7 years. They are 12 males and 13 females.

Table 2: Basic characteristics of studied groups

Characteristics	MetS (*n*=25)	Pre-MetS (*n*=25)	Control (*n*=25)	*P* value
Age (years)	55.6 ± 7.8	55.7 ± 8.9	53.8 ± 5.7	N.S
Male %	44.0%	60.0%	48.0%	N.S
Female %	56.0%	40.0%	52.0%	
Diabetes %	92.0%	32.0%	0	< 0.001
Hypertension %	84.0%	44.0%	0	< 0.001
FBS mg/dl	230.2 ± 94.9	107.2 ± 30.5	88.1 ± 9.5	< 0.001
Triglycerides mg/dl	180.8 ± 68.9	142.1 ± 65.3	112.0 ± 33.8	< 0.001
Cholesterol mg/dl	232.2 ± 56.0	224.5 ± 26.2	206.4 ± 9.6	N.S
HDL mg/dl	32.1 ± 22.6	62.4 ± 3.9	63.2 ± 3.6	< 0.001
LDL(mg/dL	169.8 ± 47.8	166.1 ± 36.3	143.8 ± 38.5	N.S
IL-18 (pg/ml)	389.2 ± 143.7	226.0 ± 89.2	150.2 ± 53.3	< 0.001

NN.S: Non significant ; *P*: Comparison between control and both MetS and pre-MetS groups n=number; FBS: fasting blood sugar; IL; interleukin

In metabolic group, there are significant increase in fasting blood glucose (FBG), cholesterol, triglyceride and IL-18 levels and significant decrease in HDL as compared to healthy control group. There is no difference in LDL cholesterol levels between MetS

ISSN: 2319-9865

and pre-MetS patients. The results also show that, patients with premetabolic conditions had higher concentrations of IL-18 when compared with healthy subjects.

Correlation between IL-18 and clinical and laboratory parameters are presented in table 3. Significant correlations are observed with waist circumference, blood sugar, blood pressure and HDL.

Table 3: Correlations between IL-18 and basic characteristics of both patients groups

Parameters	r (*p*-value)	
	MetS/ Pre-MetS (*n*=50)	Control (*n*=25)
BMI (kg/m²)	0.08 (N.S)	0.22 (N.S)
Waist Circumference (cm)	0.34 (<0.01)	- 0.02 (N.S)
Systolic Blood Pressure (mmHg)	0.32 (<0.02)	- 0.001 (N.S)
Diastolic Blood Pressure (mmHg)	0.31 (<0.03)	- 0.27 (N.S)
Fasting Blood Sugar (mg/dL)	0.39 (<0.01)	- 0.10 (N.S)
Triglycerides (mg/dL)	0.21 (N.S)	- 0.04 (N.S)
Cholesterol (mg/dL)	- 0.09 (N.S)	0.33 (N.S)
HDL (mg/dL)	- 0.50 (<0.001)	0.15 (N.S)
LDL (mg/dL)	- 0.14 (N.S)	0.22 (N.S)

N.S: Non significant ; BMI: body mass index

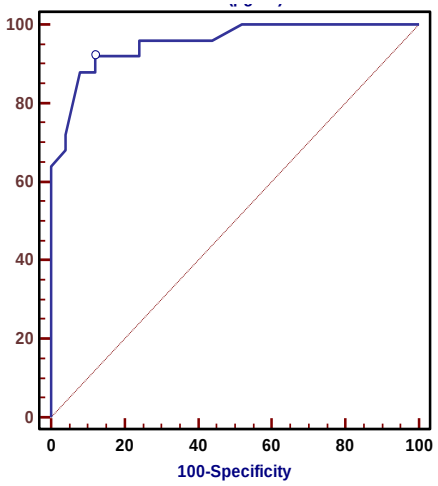
Cut-off values of IL-18 (pg/ml) and ROC curves for the cut-off value of IL-18 (pg/ml) are presented in table 4 and figure 1. A cut off value of > 210 pg/dL provided 92.0% sensitivity and 88.0% specificity for screening of patients with pre-metabolic syndrome. While a cut off value of > 250 pg/dL provided 72.0% sensitivity and 96.0% specificity for diagnosis of patients with metabolic syndrome.

Table 4. Cut-off values of IL-18 (pg/ml) for diagnosis of metabolic syndrome (n=50)

Cut-off value	Sensitivity % (95% CI)	Specificity % (95% CI)	+PV % (95% CI)	-PV % (95% CI)
> 210 pg/ml [a]	92.0 (74.0 - 99.0)	88.0 (68.8 - 97.5)	88.5 (69.8 - 97.6)	91.7 (72.4 - 99.0)
> 250 pg/ml [b]	72.0 (50.6 - 87.9)	96.0 (79.6 - 99.9)	94.7 (74.0 - 99.9)	77.4 (58.9 - 90.4)

[a] Screening cut-off value ; [b] diagnostic cut-off value
+PV: positive predictive value ; -PV: negative predictive value

Figure 1: ROC curves for the cut-off value of IL-18 (pg/ml) for diagnosis of metabolic syndrome (n=50)



ISSN: 2319-9865

DISCUSSION

In the current study, the increased levels of IL-18 were observed more frequently in patients with MetS than in those who were pre-MetS and still higher in both than healthy subjects. Hung et al. results as well agreed with these data [12,13]. They reported for the first time that elevated IL-18 levels were an independent risk for the metabolic syndrome in the absence of diabetes history in a large community population sample.

In metabolic and premetabolic groups, IL-18 levels in this study showed significant positive correlations with waist circumference, systolic and diastolic blood pressure. The results are agreed with a previous one which showed that serum levels of IL-18 were slightly, but significantly, correlated with the waist circumference in patients with MetS [14]. Moreover, Zirilik et al. reported that levels of IL-18 correlated significantly with measures of obesity, such as BMI, total fat mass, total lean mass, and waist circumference. These data suggest that IL-18 may reflect visceral fat deposition.[15] The results support the concepts that, human adipose tissue produces IL-18 and thereby contributes to systemic IL-18 concentrations. In adding up, the adipocytes behave as primitive immune cells and that IL-18 may mediate some of the detrimental complications of obesity such as cardiovascular disease and type 2 diabetes [8].

IL-18 levels in premetabolic and metabolic groups had significant positive correlations with fasting blood sugar. In a follow- up of the participants from the Oslo Diet and Anti-smoking Study carried out in 1972-1977, comprising 1,232 men with a high risk of CVD IL-18 strongly predicted cardiovascular events in subjects with metabolic syndrome, and the prediction was even more pronounced in the sole presence of elevated fasting glucose [17,18]. Furthermore, IL-18 founded to be even more predictive in the presence of diabetes with positive correlation to the FBG levels. Such observation Suggests, hyperglycemia is not only the cardiovascular risk in metabolic syndrom, but also the potentially harmful effects of a given cytokine level through the subsequent IL-18 increase. These findings introduce the possibility of a mutually potentiating effect of IL-18 and elevated fasting glucose.

Correlation between IL-18 and the two the lipids component of metabolic syndrome had revealed a negative correlation with HDL, a result which stated by other study [6]. However, no correlation was recorded with the other atherogenic triglycerides.

Using Receiver Operating Characteristic (ROC) analysis, a cut off value of > 210 pg/dL provided 92.0% sensitivity and 88.0% specificity in pre- metabolic syndrome. While a cut off value of > 250 pg/dL provided 72.0% sensitivity and 96.0% specificity in metabolic syndrome. Therefore, measurement of IL-18, in combination with other parameters, may be useful in evaluating the metabolic syndrome.

The main limitation of the study is that, in addition to the limited sample size, the current study was not designed to evaluate the possible role of IL-18 in the assessment of concomitant cardiovascular complications of metabolic syndrome. Further studies are necessary in order to elucidate whether this marker has any further value in this aspect and if those patients with pre-MetS progress to MetS.

CONCLUSION

IL-18 has been be elevated in subjects with the metabolic syndrome and to increase in parallel with an increasing number of components of the syndrome. Its level can be used as an additional predictive risk factor for development of pre-metabolic syndrome with a cutoff value greater than 210 pg/ml, while a cutoff value greater than 250 pg/ml can be used for diagnosis of patient with metabolic syndrome.

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