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Original Article

Correlation of circulating inflammatory markers, ghrelin, adiponectin with obesity indices in subjects with metabolic syndrome

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ABSTRACT

Objective: The goal of this study was to evaluate the association of obesity indices with circulating inflammatory markers in subjects diagnosed Metabolic Syndrome (MetS).

Methodology: Random selection of individuals' samples from participants of Isfahan Cohort Study (ICS) was used. Only subjects who met the National Cholesterol Education Program's Adult Treatment Panel III (ATP-III) criteria were included in the study. All participants underwent a 30-minute face to face interview to complete validated questionnaires. A trained nurse measured obesity indices such as body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR) and waist to height ratio (WHtR). Serum total cholesterol, triglycerides, HDL, LDL, fasting blood glucose, interleukin-6 (IL-6), interleukin-10 (IL-10), adiponectin, ghrelin and CRP were also measured. The Mann- Whitney U test was used to compare the inflammatory markers in subjects with and without MetS. Correlation coefficients between inflammatory biomarkers and obesity indices were evaluated in participants with MetS using Pearson Coefficient correlation test.

Results: In subjects with MetS, WC and BMI were significantly higher compared to subjects without MetS ($P < 0.001$). We found the median Interquartile range (IQR) of CRP was significantly higher in subjects with MetS ($P < 0.001$). Adiponectin and ghrelin level showed no significant difference in subjects with or without MetS. Subjects with MetS had a statistically significant positive correlation between IL6 and WHtR ($r = 0.367$, $P = 0.015$). No significant correlation was found between IL-10, ghrelin, adiponectin and CRP with BMI, WHtR and WC. Negative correlation was observed for adiponectin and the WC ($r = -0.367$, $P = 0.026$) as well.

Conclusion: Our findings indicate that in subjects diagnosed with MetS, only IL6 had positive association with WHR and no significant correlation between all other inflammatory markers with Obesity Indices was found.

KEY WORDS: Inflammatory markers, Obesity, Metabolic syndrome.

doi: http://dx.doi.org/10.12669/pjms.291(Suppl).3513

How to cite this:

Gharipour M, Sadeghi M, Mansourian M, Andalib E, Talaie M, Mohamadifard N, et al. Correlation of circulating inflammatory markers, ghrelin, adiponectin with obesity indices in subjects with metabolic syndrome. Pak J Med Sci 2013;29(1)Suppl:264-268

doi: http://dx.doi.org/10.12669/pjms.291(Suppl).3513

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INTRODUCTION

Obesity plays a crucial rule in the development of the most common risk factors for diabetes, hypertension, atherosclerosis and metabolic syndrome (MetS).[1,2] MetS can easily be diagnosed by using clinical settings and threshold values for abdominal obesity, hypertension, high fasting

blood glucose, and dyslipidemia.[3] Systemic insulin resistance has been implicated as one possible factor that links visceral obesity to adverse metabolic consequences.[4] Previous studies showed that adipose tissue plays mediatory role between insulin resistance as a key risk factor for MetS and inflammatory markers.[5] Inflammatory markers have been shown to be inversely proportional to the severity of intra-abdominal adiposity.[6] Although, the mechanism of this relation has not been clarified but studies stated that adipose tissue is the main source for inflammatory markers secretion such as C-reactive protein (CRP), interleukin-6(IL-6), and adiponectin.[7] Several studies showed inflammatory markers production is altered in obesity, type 2 diabetes and MetS.[8] An acute inflammatory marker, CRP is a sensitive marker that is reported to predict the risk of developing CVD.[9]

Some interleukins such as IL-6 could increase liver CRP production.[10] In obesity IL-6 content of adipose tissue is higher hence, the CRP levels is also increased.[11,12] Ghrelin is a known marker of endothelial function and produces nitric oxide in the vessel wall endothelium. Lower serum levels of ghrelin have significant relationship with insulin resistance, type II diabetes and hypertension.[13]

Adiponectin is a protein that is produced primarily in the stomach. Adiponectin not only plays a role in hunger regulation but also in long-term body weight regulation and energy homeostasis. Adiponectin is a protein that is secreted by adipocytes and has been proposed to mediate obesity-related insulin resistance. Moreover, concentrations of adiponectin are reduced in individuals with obesity, insulin resistance and cardiovascular disease.

To our knowledge, a limited number of studies have been conducted to examine the correlation between inflammatory markers and obesity indices in subjects with MetS with some reporting reverse correlations. The mechanisms by which the MetS develops in certain individuals and not in others are not understood. Many controversies still exist regarding the effect of obesity on inflammatory markers. Adipose tissue, especially in the visceral area, is an active endocrine organ that produces various inflammatory markers.[14] Therefore, people with obesity who develop an intense inflammatory state may be more likely to develop MetS than those with lower levels of inflammation.

In our study we focused on testing the hypothesis that in subject with MetS whether obesity indices such as body mass index (BMI), waist circumference, waist-to-hip ratio (WHR) and waist to height ratio (WHtR) have any correlation with circulating inflammatory markers as well as adiponectin and ghrelin.

METHODOLOGY

We randomly selected individuals' samples from participants of Isfahan Cohort Study (ICSa a previously reported study which began in 2001 as part of baseline study of Isfahan Healthy Heart Program (IHHP).[15] Subjects (age ≥35 years) were selected through multi-stage cluster sampling. Selected subjects from phase I of IHHP were included in ICS. All subjects divided into two age and sex matched subgroups with or without MetS. Diagnosis of MetS was according to Adult Treatment Panel III (ATPIII) criteria where MetS is defined as having at least three of the following five criteria: 1- waist circumference(WC) >102cm in men and >88 cm in women, 2- serum triglyceride > 150 mg/dl, 3- high density lipoprotein (HDL) <40 mg/dl in men and < 50mg/dl in women, 4- fasting blood glucose (FBG)> 110 mg/dl, 5- Blood pressure>130/85 mmHg.[3] Inclusion criteria were as follows: Participating in ICS from 2001 and diagnosed with Mets. Exclusion criteria include: Participant's lack of interest in the study, history of stroke or other cerebrovascular diseases, pregnancy, history of carotid operation or carotid stent, cancers, inflammatory disease and consumption of anti-inflammatory drugs.

Written informed consent was obtained from all participants and the study was approved by the ethical committee of the Isfahan Cardiovascular Research Institute. All participants underwent a 30-minute face to face interview to complete a validated questionnaires including demographic data, CVD risk factors, history of diabetes, hypertension, smoking, hyperlipidemia and duration of these disease, any previous ailments or medication. In addition to fasting blood samples, Serum total cholesterol and triglycerides were measured using enzymatic colorimetric methods. HDL cholesterol was tested following dextran sulphate-magnesium chloride precipitation of non-HDL cholesterol. LDL cholesterol level was derived from the friedewald equation in the presence of increased triacylglycerol levels.[16] Ten milliliter of fasting blood sample of all participants centrifuged, preserved at -70 degrees of centigrade and kept in the laboratory of Isfahan Cardiovascular Research Institute for necessary laboratory tests such as IL-6, IL-10, Adiponectin, ghrelin, and CRP. Ghrelin was measured using ELISA method and BioVendorkits.

IL-6 and IL-10 were measured with ELIZA method using Medsystem kit (Bendermed-Austria). Adiponectin and ghrelin were measured with ELIZA method using Biovendor kit (Germany). Immunoturbidimetry method with autoanalyzer (Hitachi 902) with Pars Azmun kit (Iran) was used to measure CRP.

Throughout the whole study, all measurement such blood pressure (BP), body mass index (BMI), WC, waist to hip ratio (WHR) and waist to height ratio (WHtR) were taken by trained nurses.[17]

Statistical Methods: All the statistical analyses were performed using Statistical Package for Social Science 18.0 and statistical significance margin was defined a P value of less than 0.05 (P = 0.05). Subjects were divided into two age and sex matched subgroups based on their diagnosis of MetS. Due to a positively skewed distribution, an evaluation of normality was performed with a Kolmogorov-Smirnov test. Mean differences in continuous variables between subjects with Mets and without MetS were analyzed with unpaired t-test. The Mann-Whitney U test was used for comparisons between the level of inflammatory markers in the subjects with obesity with and without MetS. Inflammatory markers, ghrelin and adiponectin were described using the median ± interquartile range (IQR). A correlation coefficients between inflammatory markers and obesity indices were calculated by Pearson Correlation test in all selected subjects with MetS.

RESULTS

General characteristics and biochemical assessment of the subjects are summarized in Table-I. In subjects with MetS, WC and BMI were significantly higher (P<0.001). No statistically significant difference in the distribution of HDL and LDL -cholesterol, triglycerides, cholesterol, fasting blood sugar and diastolic blood pressure between groups were found. The level of serum IL-6, IL-10, adiponectin and ghrelin also showed no significant difference between groups with and without MetS. The median IQR of CRP was significantly higher in subjects with MetS (P < 0.001).

The correlation between inflammatory markers and obesity indices that was determined by non-parametric analysis in MetS group has shown in Table-II. In MetS group a significantly positive correlation between IL-6 and WHtR (r = 0.367*, P =0.015) was found.

No significant correlation was found between IL-10, ghrelin, adiponectin and CRP with BMI, WHtR and WC. Significant negative correlation was observed for adiponectin and WC (r = -0.367, P =0.026). In the group without MetS, we also found significant negative correlation between adiponectin with other obesity indices such as WHR (r=-0.509), WHtR (r=-0.454) and BMI (r= -0.475).

Table-I: Serum concentrations of lipids, obesity indices and components of metabolic syndrome (mean ± SD) and, inflammatory markers (Median ± IQR), in patients with and without MetS.

Variable	*Mets-*	*Mets+*
Age (Yr)	52.86±7.62	55.50±8.84
Waist (cm)	87.32±.10.82	94.98±.9.02*
BMI (kg/m2)	26.00± 3.75	29.77± 3.51*
WHR	0.90±0.09	0.91±0.06
WhtR	0.42±0.05	0.48±0.06*
HDL (mg/dl)	46.84±12.56	47.60±11.40
Triglycerides (mg/dl)	168.84±129.4	174.58±75.03
Cholesterol (mg/dl)	206.6±38.38	217.02±42.79
Fasting Blood Sugar (mg/dl)	90.47±41.76	97.62±42.17
SBP (mmHg)	115.96±13.8	126.62±15.48*
DBP (mmHg)	75.96±6.80	81.68±8.68*
LDL	119.90±23.66	122.48±25.21
IL6 (pg/ml)	0.8±0.7	0.8±0.90
IL10 (pg/ml)	0.8±2.35	1.1±2.00
Adiponectin (µg/ml)	11.50±8.50	10.0±9.00
Ghrelin (µg/ml)	110.0±149.25	96.0±68.8510
CRP (mg/l)5)	4.0±6.60	8.0±35.35*

CRP, C-reactive protein; IL-6, interleukin-6;
IL-10, Interleukin 10;
factor-a. Mean ±SD (all such values).
Significantly different from subjects with MetS(t test): P <0.001
Median; interquartile range in parentheses for skewed variables (all such values) *P<0.001

DISCUSSION

Our findings demonstrate that IL-6 has a significant correlation with WhtR in subjects with MetS. We have also shown significant correlation between IL-6 and WHtR. Significant negative correlation was observed between adiponectin and waist, WHR, WHtR and BMI among subjects without MetS.

Only a few studies have examined associations between measures of different obesity indices and markers of inflammation in subjects with MetS. A recent study has shown that MetS correlated with increased inflammatory markers in different population but they didn't focus on obesity indices.[18] Sam et al, demonstrated an association between adipose tissue and visceral fat with inflammatory

Table-II: Correlation between obesity indices and inflammatory factors in subjects with and without metabolic syndrome.

		MetS +				*MetS -*			
		WHR	*WhtR*	*BMI*	*Waist*	*WHR*	*WhtR*	*BMI*	*Waist*
IL-6	Pearson Correlation	0.167	0.367*	0.053	0.222	0.270	0.211	0.283	0.069
	P value	0.284	0.015	0.740	0.147	0.076	0.169	0.062	0.661
IL-10	Pearson Correlation	-0.290	-0.165	-0.165	-0.156	0.125	0.108	-0.080	-0.236
	P value	0.059	0.290	0.295	0.312	0.418	0.485	0.607	0.128
Adiponectin	Pearson Correlation	-0.229	0.031	0.006	-0.335*	-0.509**	-0.454**	-0.475**	-0.098
	P value	0.140	0.845	0.969	0.026	0.000	0.002	0.001	0.531
Ghrelin	Pearson Correlation	0.171	-0.102	-0.023	-0.296	-0.028	-0.002	-0.169	0.031
	P value	0.274	0.515	0.883	0.051	0.858	0.989	0.274	0.842
CRP	Pearson Correlation	-0.150	-0.072	-0.139	-0.142	0.141	0.191	-0.056	-0.138
	P value	0.337	0.648	0.380	0.359	0.361	0.215	0.719	0.379

**Correlation is significant at the 0.01 level.
* Correlation is significant at the 0.05 level (2-tailed).

markers.[19] Nevertheless, to date, there has been no published literature related to each different obesity indices and their correlation with inflammatory markers among Iranian population.

Obesity is characterized as an excess of adipose tissue, with consequent weight gain, and associated with several co-morbidities.[18] In our study, subjects who diagnosed with MetS have significantly higher anthropometric measurements (WC and BMI) compared to subjects without Mets (P<0.001).

We found strong correlation between IL-6 and WHtR in subjects with MetS. Previous findings in a large-scale cross-sectional study in US showed significant positive relation between obesity and CRP.[20] Unlike Cartier[21], we did not find any significant relationship between different indices of obesity and CRP.

It seems that inflammatory markers are related to decreased levels of adiponectin in individuals with obesity.[22] In individuals with obesity adiponectin levels are significantly reduced with negative correlation between BMI and adiponectin levels in plasma.[22] Similar to these studies we showed lower level of adiponectin among MetS subjects. But unlike other studies significant negative correlation has been seen between adiponectin and all type obesity indices.

Choi et al. indicated fasting plasma adiponectin and ghrelin levels are associated with central obesity.[23] This study as well as ours are in agreement showing a well known inverse relationship between obesity and circulating ghrelin concentrations.[22,23]

Limitation of our study: One of limitation of our study is that due to relatively small sample size we may not be able to show significant correlations between study variables therefore, the results could not be generalized. Due to the same reason, we failed to categorize inflammatory markers into elevated and normal levels. Second limitation includes the use of cross-sectional data, from which we were unable to prove a causal relation between obesity indices and inflammatory markers among subjects with MetS.

CONCLUSION

To conclude, the results of the present study indicate that the observed inflammatory markers concentration cannot be explained by type of obesity indices among subjects with MetS.

ACKNOWLEDGEMENT

This program was supported by a grant (No. 31309304) from the Iranian Budget and Planning Organization, as well as the Deputy for Health of the Iranian Ministry of Health and Medical Education and Iranian Heart Foundation. It was conducted by Isfahan Cardiovascular Institute in collaboration of Isfahan Provincial Health Center both affiliated to Isfahan University of Medical Sciences.

Conflict of interest: We declare no conflict of interest of those who were involved in the study.

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