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Original Article

Association of adiponectin and metabolic syndrome in women

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Abstract

BACKGROUND: An inverse association between serum adiponectin level and metabolic syndrome was seen in few studies. The aim of this study was to assess the association between serum adiponectin levels and metabolic syndrome in a sample of Iranian women from Kerman.

METHODS: In a cross-sectional study 946 subjects were studied to determine the prevalence of metabolic syndrome and in a case control study (170 subjects for each group) the association between serum adiponectin levels and metabolic syndrome were investigated. Metabolic syndrome was defined using International Diabetes Federation (IDF) criteria. Socio-demographics factors and measures of waist circumference, blood pressure and lipid profiles were collected. Serum adiponectin level was measured by ELISA method.

RESULTS: The prevalence of the metabolic syndrome was 36.7%. Mean of serum adiponectin level in individuals with metabolic syndrome was lower than individuals without it (10.5 ± 4.1 and 13.45 ± 5.6 µg/ml, respectively, $p < 0.001$). Low level of adiponectin was a good predictor for metabolic syndrome (a range of β coefficients out of -2.03 to -2.85 according to five models). Systolic blood pressure, body mass index (BMI) and diastolic blood pressure were independent predictors of serum adiponectin (p values were 0.001, 0.009 and 0.034, respectively).

CONCLUSIONS: We found that adiponectin is negatively associated with metabolic syndrome. Systolic and diastolic blood pressure and BMI were identified as independent predictors.

KEYWORDS: Metabolic Syndrome, Adiponectin, Body Mass Index, Blood Pressure, Women.

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Metabolic syndrome is a collection of multiple metabolic disorders such as central obesity, low high-density lipoprotein (HDL), high triglyceride, high blood pressure and hyperglycemia/insulin resistance. Many studies have been shown that when these disorders occurred together, risk of development of some major diseases such as diabetes mellitus and cardiovascular disease (CVD) increase.[1-6] The prevalence of obesity in all societies is increasing and it is known as one of the main causes of increase in the prevalence of metabolic syndrome. The results of recent studies have revealed that the pattern of metabolic syndrome prevalence is completely different in Asians especially in Iran than Europe and U.S.[7-12]

Adiponectin is known as an anti-inflammatory cytokine which is a potent insulin sensitizer.[13] Adiponectin is a novel adipocytokine produced exclusively by adipocytes which has a high concentrations in human serum rising up to 0.05% of total serum's protein.[14] Studies showed an association between adiponectin concentration and insulin resistance and also other metabolic syndrome elements in patients who have type 2 diabetes. Recent studies have suggested that the adipo-

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cyte-derived hormone adiponectin may be a predictor factor for metabolic syndrome.[15] Higher serum adiponectin levels are associated with decreased risk for development of obesity,[16] type 2 diabetes,[17] insulin resistance,[18] dyslipidemia[17] and CVD.[19,20] Adiponectin levels are varied according to some factors such as sex, age, race and ethnicity.[21-24] Evidences have proposed that there are a relation between serum adiponectin and metabolic syndrome in different ethnic groups such as whites,[25] Asian Indians,[26] Koreans[27] and Japanese.[28] However, there have not been further studies conducted on serum adiponectin levels and its association with some complications particularly metabolic syndrome in Iran.[29-33]

According to some studies, the prevalence of metabolic syndrome is high in Iran. Azizi et al. in 2003 showed that the prevalence of metabolic syndrome was more than 30% in adults, which it was more prevalent in women than men (42% vs. 24%).[9] Zabetian et al. in 2007 revealed a 40% age-adjusted prevalence of metabolic syndrome in urban Tehranian women (≥20 years old).[10] This prevalence in Delavar et al. study[11] in 2009 was approximately 30%, and in Gharipour et al. study in 2006 among 50-59 years old female rural residences in Isfahan was approximately 70%.[12] These studies have highlighted the importance of the study on metabolic syndrome in Iranian population. Ethnicity plays key role in the association of adiponectin levels and metabolic syndrome,[23,24] however, little is known regarding the role of adiponectin on metabolic syndrome in Iranian population. The present study was aimed to assess the prevalence of metabolic syndrome and the association between serum adiponectin levels and metabolic syndrome among women in Kerman, Iran.

Methods

Participants:

This study was done in 2009 and was conducted in two steps. The first step was done to determine the prevalence of metabolic syndrome based on a cross-sectional study design. There was a Women Health Committee in Kerman Province which evaluates cardiovascular risk factors and screens breast cancer in these women. In this step a number of 946 women aged 25-53 years were selected randomly. This study was approved by ethical committee of Kerman University of Medical Sciences (KUMS). The importance of this study and metabolic syndrome was described for all participants. An informed written consent was obtained from all participants in the study.

After determining the prevalence of metabolic syndrome according to International Diabetes Federation (IDF) criteria,[34] to determine the association of serum adiponectin levels and metabolic syndrome, 170 subjects were randomly selected from two groups with and without metabolic syndrome (totally, 340 subjects were recruited). Women with Cushing disease or its clinical signs, secondary obesity, hypothyroidism, disabling diseases, cancer and also pregnant and nursing women were excluded.

Definition of the Metabolic Syndrome:

Metabolic syndrome was defined according to IDF criteria.[34] in this definition, unlike World Health Organization (WHO)[35] and National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III)[36] criteria, waist circumference (WC) as indicates central obesity, is an essential component for metabolic syndrome. WC shall be obtained by ethnic- and sex-specific cut-off point. In IDF consensus for Caucasian people, this cut-off point was ≥ 94 cm for men and ≥ 80 cm for women. Along with WC, the presence of at least two of the following abnormalities comprised the metabolic syndrome:

1. Triglycerides level ≥ 150 mg/dl, or drug or specific treatment for this abnormality
2. HDL cholesterol < 40 mg/dl, or drug or specific treatment for this abnormality
3. Fasting plasma glucose (FPG) ≥ 100 mg/dl, or previously diagnosed type 2 diabetes, or drug or specific treatment for this conditions
4. Blood pressure ≥ 130/85 mmHg, or previously diagnosed hypertension or specific treatment for this abnormality

Data collection:
A questionnaire to collect some information such as age and etc. was completed for all participants. Weight was measured to the nearest 0.1 kg with a calibrated physician's office scale and height was measured to the nearest 1 mm with a tape meter. Body mass index (BMI) was a number calculated by dividing the body weight (in kilograms) by the height squared (in meters). Waist Circumference was measured using an unstretched tape meter, located directly on the skin while the subject stood balanced with legs parallel, and was recorded to the nearest 0.1 cm. To minimize errors, all measurements were performed by one nurse. To measure blood pressure, systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured by a trainee nurse twice in a seated position. There was at least a 30 min interval between these two measurements, and then the mean of the two measurements was set as blood pressure of participants.

Laboratory measurements:
A blood sample (10 ml) was taken out of left brachial vein of these participants and FPG was measured by enzymatic colorimetric method using glucose oxidase (Pars Azmoon Inc. Iran). For lipid profiles, total cholesterol and triglyceride (TG) kits (Pars Azmoon Inc., Iran) were used. Total cholesterol (TC) and TG were analyzed using enzymatic colorimetric tests with cholesterol esterase and cholesterol oxidase, and glycerol phosphate oxidase, respectively. HDL-C was measured after precipitation of the apolipoprotein β containing lipoproteins with Phosphotungstic acid. Low-Density Lipoprotein (LDL) concentration was indirectly calculated as the Friedewald formula: LDL=TC-HDL- (TG/5).[37]

Participations with and without metabolic syndrome were distinguished on the basis of IDF (2005) criteria and case and control groups were selected accordingly. Five milliliter of blood sample was taken from brachial vein of both two groups in order to determine serum adiponectin levels at 8 Am. Serum was separated and kept in -70^{0}C and adiponectin concentration was measured by ELISA method (DIASORIN Inc. kit).[38]

Statistical Analysis:
Data were presented as mean ± standard deviation (SD) for continuous variables and absolute and relative frequency for categorical variables. Two groups of participants with and without metabolic syndrome were compared using Student's t-test. Univariate and multivariate (to adjust the potential confounders such as age, BMI and each components of metabolic syndrome) linear regression were used to determine the association between metabolic syndrome and adiponectin. Beta coefficients (β) with standard errors (S.E.) and coefficient of determination (R^2) were presented. Multivariate forward stepwise linear regression analysis was used to determine the independent predictors' variables affecting serum adiponectin level. All statistical analyses were performed using SPSS version 15 statistical software package (SPSS Inc. Chicago, IL). P value less than 0.05 was considered as statistically significant.

Results
The prevalence of metabolic syndrome according IDF criteria was 36.7%. Baseline and clinical characteristics of women with and without metabolic syndrome are presented in table 1. Participants with metabolic syndrome had higher age, BMI, waist and hip circumferences and waist to hip ratio ($p < 0.001$), lower systolic and diastolic blood pressure ($p < 0.001$), higher FPG, cholesterol, triglyceride and LDL ($p < 0.001$). There was a highly significant difference in adiponectin level between the two groups. Adiponectin level in women with metabolic syndrome was lower than that in those without metabolic syndrome (10.5 ± 4.1 vs. 13.45 ± 5.6 μg/ml, $p < 0.001$).

Univariate linear regression analysis of serum adiponectin level in women with metabolic syndrome is presented in table 2. Waist to hip ratio ($\beta = -8.80$, $p = 0.039$) and triglyceride ($\beta = -0.014$, $p < 0.001$) were negatively

Table 1. Clinical and baseline characteristics of metabolic and non metabolic syndrome

Characteristics	Participants with Metabolic Syndrome (n=170)	Participants without Metabolic Syndrome (n=170)	P value
Age (year)	38.5 ± 6.3*	34.02 ± 5.8	< 0.001
Body Mass Index (kg/m^2)	29.1 ± 4.7	26.9 ± 4.8	0.57
Waist Circumference (cm)	101.8 ± 12.5	84.9 ± 8.6	0.041
Hip Circumference (cm)	109.4 ± 13.3	94.8 ± 12.1	0.045
Waist to Hip Ratio	0.93 ± 0.05	0.90 ± 0.07	< 0.001
Adiponectin (µg/ml)	10.5 ± 4.1	13.45 ± 5.6	0.68
Systolic Blood Pressure (mmHg)	11.1 ± 0.92	11.6 ± 0.91	< 0.001
Diastolic Blood Pressure (mmHg)	6.8 ± 0.97	7.2 ± 0.88	< 0.001
Fasting Plasma Glucose (mg/dl)	102.2 ± 29.5	92.3 ± 16.1	< 0.001
Total Cholesterol (mg/dl)	215.6 ± 42.7	187.7 ± 45.1	< 0.001
Triglyceride (mg/dl)	219.6 ± 81.1	123.5 ± 69.5	< 0.001
High-Density Lipoprotein (mg/dl)	42.2 ± 20.3	46.9 ± 31.8	0.06
Low-Density Lipoprotein (mg/dl)	137.4 ± 37.9	117.01 ± 35.1	< 0.001

* Mean ± standard deviation

correlated with serum adiponectin level, while FPG (β = 0.025, p = 0.033) was positively correlated with serum adiponectin level. BMI had a borderline negative correlation with adiponectin in cases with metabolic syndrome (β = -0.13, p = 0.056).

Multivariate linear regression analysis is presented in table 3. In the unadjusted model, adiponectin was negatively associated with metabolic syndrome (β = -2.85, p < 0.001). In the model adjusted by BMI and waist to hip ratio, the result was similar (β = -2.11, p = 0.008). The model adjusted by FPG, TG, TC, HDL and LDL, SBP and DBP also produced similar results as unadjusted model (β = -2.26, p = 0.001). When the variables in models 2 and 3 were adjusted with age, the result was similar (β = -2.037, p = 0.038).

Table 2. Univariate linear regression analysis of serum adiponectin with baseline and clinical variables

Variables	β_{Crude}	S.E	R^2	P value
Metabolic Syndrome (yes)	-2.85	0.55	0.076	< 0.001*
Age	-0.005	0.045	0.001	0.91
Waist Circumference	-0.33	0.02	0.008	0.11
Body Mass Index	-0.13	0.07	0.017	0.056
Hip Circumference	0.008	0.02	0.001	0.66
Waist to Hip Ratio	-8.80	4.5	0.013	0.039*
Systolic Blood Pressure (mmHg)	0.23	0.28	0.002	0.41
Diastolic Blood Pressure (mmHg)	0.45	0.31	0.007	0.13
Blood Pressure (> 140/85)	0.78	0.89	0.002	0.43
Fasting Plasma Glucose	0.025	0.012	0.014	0.033*
Total Cholesterol	0.001	0.006	0.001	0.85
Triglyceride	-0.014	0.003	0.065	< 0.001*
High-Density Lipoprotein	-0.008	0.011	0.002	0.42
Low-Density Lipoprotein	0.005	0.007	0.002	0.46

Table 3. Multivariate linear regression analysis of baseline and clinical characteristics in 4 adjusted models

Linear regression models	β	R^2	P value
Model 1 (unadjusted, only metabolic syndrome)	-2.85	0.076	< 0.001
Model 2 (metabolic syndrome, adjusted for BMI and waist to hip ratio)	-2.11	0.079	0.008
Model 3 (metabolic syndrome, adjusted for FPG, TG, TC, HDL, LDL, SBP, and DBP)	-2.26	0.118	0.001
Model 4 (metabolic syndrome, adjusted for age and variables in models 2 and 3)	-2.037	0.177	0.038

BMI: Body Mass Index, FPG: Fasting Plasma Glucose, TG: Triglyceride, TC: Total Cholesterol, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein , DBP: Systolic Blood Pressure, SBP: Systolic Blood Pressure

Multivariate forward stepwise linear regression analysis of the variables showed that systolic blood pressure (β = -1.36, p = 0.001), BMI (β = -0.18, p = 0.009) and diastolic blood pressure (β = 0.92, p = 0.034) were independent predictors of serum adiponectin level and explained approximately 41.4% of the whole variance (Table 4).

Discussion

The results of the present study showed that the prevalence of metabolic syndrome based on IDF definition in women employees in Kerman was approximately 37%. Serum adiponectin levels of subjects with and without metabolic syndrome were completely different in both univariate and multivariate models. Women with metabolic syndrome had lower serum adiponectin, which it was statistically significant Systolic and diastolic blood pressure and also BMI were identified as independent predictors for serum adiponectin level.

Prevalence of metabolic syndrome in our study was more than what had been reported in developed countries such as U.S, America, Illinois province, Europe, Chinese adults and Korean adults that were varied from 15% to 25%.[39-44] However, a study by Ervin[24] in U.S (2009) recently showed that the prevalence of metabolic syndrome was approximately 35%. This finding was similar to our study and the other studies in developing countries. Our findings was also in line with the findings of studies which showed higher prevalence of this syndrome in Middle East countries rather than other countries specially Europe. According to IDF definition, the prevalence of metabolic syndrome in the present study also was so close to Tehran Lipid and Glucose Study (TLGS) which it was 30% in total of men and women participants.[9,45]

Our study revealed that in most participants with metabolic syndrome, there was significant relationship between metabolic syndrome and serum adiponectin level. There is a consistency with the results of recent studies that have studied low serum adiponectin levels in participants with metabolic syndrome.[46-48] Wang et al. in a study in China showed that the participants in the lowest adiponectin

Table 4. Multivariate forward stepwise linear regression analysis of baseline and clinical characteristics: correlation to serum adiponectin level among cases with metabolic and non-metabolic syndrome

Linear regression models	β	R^2	P value
Metabolic syndrome	-2.33	0.064	0.001
Systolic Blood Pressure	-1.36	0.111	0.001
Body Mass Index	-0.18	0.164	0.009
Diastolic Blood Pressure	0.92	0.139	0.034

quartile had a significant increased risk for obtaining metabolic syndrome (Odds ratio was 3.38 for lowest adiponectin quartile vs. highest adiponectin quartile).[49]

In a case study, Kumagai et al.[50] showed that level of serum adiponectin decreases in people with metabolic syndrome, and adiponectin to serum leptin ratio can be a suitable marker for determining the prevalence of metabolic syndrome. In another study, after adjusting the age and sex variables, it was shown that concentration of serum adiponectin had a reverse relationship with BMI, waist to hip circumference ratio, diastolic blood pressure, triglyceride, glucose and fasting insulin, and a direct relationship with HDL level; in people with the lowest adiponectin level, metabolic syndrome increased significantly.[51] In our study, lower serum adiponectin was associated with higher systolic blood pressure and BMI but lower diastolic blood pressure.

The results of one of these studies showed that increased level of circulating adiponectin in blood inhibits the prevalence of inflammations related to lipid tissue, insulin resistance and metabolic syndrome in obese people.[52] In a study carried out on Caucasian people aged 8-19 years, it was shown that people with metabolic syndrome may experience high levels of visceral fat, fasting insulin, low sensitivity to insulin and low level of adiponectin. In these people, level of inflammatory biomarkers was high too.[53] Performing a study in the same field, Tabara et al. revealed that adiponectin concentration with high molecular weight (HMW adiponectin) decreased significantly in plasma with regards to all elements of metabolic syndrome except for high blood pressure.[54] In the present study a significant negative association was found between serum adiponectin and metabolic syndrome.

Our study showed a negative association between adiponectin and systolic blood pressure and BMI and a positive correlation with diastolic blood pressure. Patients with hypertension appear to have significantly lower plasma adiponectin levels than normotensive patients,[55] but there has been no difference in adiponectin level between patients with and without CVD. While CVD was significantly associated with hypertension and this association was stronger in men than in women, this effect was more significant than the effect of other elements of metabolic syndrome such as LDL cholesterol and diabetes.[56] In this study, the correlation between blood pressure and adiponectin level was not mentioned.

One of the limitations of our study was that the sample size was low and limited to female employees. Another limitation of our study was that its cross-sectional design which is not an appropriate design for examination of the relationship between adiponectin as a causing factor and metabolic syndrome.

As the major importance of metabolic syndrome is its contribution to CVD and as our study showed the effect of BP on adiponectin, it is recommended to pay more attention to the effect of blood pressure on adiponectin level and CVD.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

Study design: MSa, MK; data analysis: MSh; literature review: MSa, MSh, MK; laboratory test: AG; Manuscript preparation: MSa, MSh.

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