Original Article

Assessment of serum chemerin level in an Iranian population with metabolic syndrome and healthy individuals in 2016

Zanganeh Sh, BSc[1], Roostaei F, BSc[1], Shafiepour MR, PhD[2], Mahmoodi M, PhD[3], Khoshdel A, PhD[4], Hajizadeh MR, PhD[4*]

1- MSc Student of Clinical Biochemistry, Dept. of Clinical Biochemistry, Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. 2- Assistant Prof., of Internal medicine, Dept. of Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. 3-Prof., of Clinical Biochemistry, Molecular Medicine Research Center and Dept. of Clinical Biochemistry, Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. 4- Assistant Prof., of Clinical Biochemistry, Molecular Medicine Research Center and Dept. of Clinical Biochemistry, Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

Abstract

Background: Chemerin is and adipokine produced and secreted by adipose tissue and is associated with functions such as insulin resistance, inflammation, and blood pressure regulation. The purpose of the present study was the determination of serum chemerin level in an Iranian population with metabolic syndrome and its comparison with healthy individuals.

Materials and Methods: The study subjects consisted of 31 individuals with metabolic syndrome and 25 healthy individuals (control group). Serum chemerin level was measured and its relationship with indices of metabolic syndrome, obesity, and insulin resistance was determined. The collected data were analyzed using independent two-sample t-test and the Pearson correlation coefficient in SPSS software.

Results: Serum chemerin level was significantly higher in the metabolic syndrome group compared to the control group ($P = 0.009$). The mean of the measured indices of BMI ($P < 0.001$), waist circumference ($P < 0.001$), systolic blood pressure ($P = 0.001$), diastolic blood pressure ($P < 0.001$), insulin resistance ($P = 0.001$), and triglyceride ($P < 0.001$) was significantly higher in the metabolic syndrome group compared to the control group. However, HDL level was significantly higher in the control group compared to the metabolic syndrome group ($P = 0.007$).

Conclusions: Serum chemerin level was higher among patients with metabolic syndrome compared to healthy individuals. Thus, it can be concluded that serum chemerin level measurement can be effective in the diagnosis of this syndrome and determination of appropriate treatment methods.

Received: June 2016, **Accepted**: October 2016

Keywords: Chemerin, Obesity, Insulin Resistance, Metabolic Syndrome

Introduction

Today, obesity, as one of the consequences of the modern lifestyle (increased food intake and a sedentary lifestyle), has become an international concern (1). Inflammation caused by adipose tissue, which increases with obesity, increases the risk of incidence of many diseases such as fatty liver and metabolic syndrome (2). Metabolic syndrome consists of a series of metabolic abnormalities such as central obesity, insulin resistance, hyperglycemia, hypertension, and dyslipidemia which increase the risk of diabetes and cardiovascular diseases (CVD) (3, 4). Regardless of the difference in the prevalence of this disease in different areas due to factors such as race and climate, it has been reported that one-fourth of the world population suffer from metabolic syndrome (5, 6).

[*] **Corresponding author:** Mohammad Reza Hajizadeh, Molecular Medicine Research Center and Dept. of Clinical Biochemistry, Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.
E-mail: hajizadehus@yahoo.com

According to the World Health Organization (WHO) reports, metabolic syndrome is the new pandemic of the 21st century and it is anticipated that approximately half of the world population will be suffering from this disease in the span of the next 20 years. In Iran, the incidence of this disease has had an increasing trend; its prevalence increased from 30.1% in 2002 to 34.7% in 2009 (7).

Adipokines (e.g., Leptin, adiponectin, and chemerin) are polypeptide produced and secreted by adipose tissue and are associated with functions such as insulin resistance, inflammation, and blood pressure regulation (7, 8). Chemerin, also known as tazarotene-induced gene 2 protein (TIG2) and retinoic acid receptor responder protein 2 (RARRES2), is an adipokine. This adipokine plays a role in different functions through adipocyte and immune cell surface receptors. Chemerin acts as a chemotactic factor, and using its receptors on the surface of immune cells, causes the movement of these cells toward adipose tissue, and thus, inflammation. It also has a role in the differentiation, homeostasis, and enlargement of fat cells. In addition, it affects the expression of genes such as glucose transporter type 4 (GLUT4). Chemerin is a chemical absorption protein which regulates the activity of dendritic cells (DCs) and macrophages through the G protein-coupled receptor of CMKL1. Chemerin is secreted in an inactive form and as prochemerin, and is activated through connection with C-terminal domain and by inflammation and coagulation serine proteases (4, 9, 10). The results of some human subject researches have shown a relationship between chemerin and metabolic syndrome, obesity, insulin resistance, and inflammation. Jialal et al. found that the level of this adipokine in plasma and adipose tissue was higher among individuals with metabolic syndrome compared to healthy individuals, and was correlated with insulin resistance and inflammation factors, and lipid profile (11). Moreover, Ali et al. reported that the level of this adipokine was higher in those with metabolic syndrome compared with healthy individuals, and was related with lipid profile, insulin resistance, and risk of CVD incidence (4). However, results regarding the relationship of chemerin with many metabolic syndrome parameters such as age, lipid factors, and blood pressure are contradictory (4, 10).

Coimbra et al. found that serum chemerin and leptin levels in elderly individuals with type 2 diabetes have a correlation with obesity and duration of illness, and increase with increased BMI and illness duration; however, adiponectin has an inverse relationship with obesity and illness duration (12). Elsebai et al., in their study on patients with type 2 diabetes, reported that serum chemerin and beta-2 microglubulin levels in these patients were related to incidence of diabetic nephropathy (13). They concluded that adipokine and beta-2 microglublin can be predictive markers for incidence of nephropathy among individuals with diabetes (13). Aksan et al. showed that serum chemerin level was higher and was related with increased risk of CAD in individuals with metabolic syndrome and coronary artery disease (CAD) compared to individuals with metabolic syndrome alone (14).

The present study was conducted with the aim of determining serum chemerin level in individuals with metabolic syndrome in comparison to healthy individuals in Rafsanjan, Iran.

Material and Methods

The statistical population of the present descriptive study consisted of individuals with metabolic syndrome referring to physicians in Rafsanjan in 2016. Their condition was affirmed through clinical examination by a specialist and measurement of metabolic syndrome indices (waist circumference, systolic and diastolic blood pressure, triglyceride, fasting glucose level, and HDL). Healthy individuals were selected from among students and personnel of

Rafsanjan University of Medical Sciences through convenience sampling after referring to the laboratory of the School of Medicine and based on the results of experiments and a physician's diagnosis. These individuals were entered into the study after signing a consent form. The number of participants and sample volume of each group were calculated based on the study by Jialal et al. (11) and using the following equation. The number of 22 participants per group was determined; however, due to possibility of sample loss, a greater number of individuals were entered into the study.

$n_2 = k \times n_1, \ldots n_1 = [(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times (\sigma_1^2 + \sigma_2^2/k)]/\Delta^2$

In the above equation:

$\alpha = 0.05 \rightarrow Z_{1-\alpha/2} = 1.96$

$\beta = 0.20 \rightarrow Z_{1-\beta} = 0.85$

$\sigma_1 = 64$ ng/ml

Based on this equation, the standard deviation of serum chemerin level in individuals with metabolic syndrome (σ_2) was determined as 53 ng/ml, and standard deviation of serum chemerin level in individuals without metabolic syndrome (K) as 1. Moreover, an equal sample volume was determined for the two groups (Δ = 50 ng/ml).

The minimum difference in mean serum chemerin level in the two groups which was clinically significant was 22 ($n_{Case} = n_{Control} \approx 22$). The exclusion criteria consisted of presence of CVD, acute pulmonary disease, hepatitis B and C, Cushing's syndrome, polycystic ovary syndrome (PCOS), and HIV/AIDS, and use of lipid-lowering drugs, glucocorticoids (GCs), and antipsychotics (15, 16). Metabolic syndrome was diagnosed based on the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III). Based on this guideline, 3 of the following 5 criteria must be true for the individual (17).

1- Systolic blood pressure equal to or higher than 135 mmHg, diastolic blood pressure of equal to or higher than 85 mmHg, or use of antihypertensive drugs
2- Central obesity: This criterion has been defined as waist circumference and must be more than 102 cm in men and 88 cm in women.
3- Fasting serum triglyceride level of higher than 150 mg/dl (1.7 mmol/l)
4- Fasting serum HDL level of lower than 40 mg/dl (1 mmol/l) in men and lower than 50 mg/dl (1.3 mmol/l) in women
5- Fasting glucose level of more than 110 mg/dl

The control group, who were matched in terms of age and gender with the metabolic syndrome group, did not have metabolic syndrome based on the NCEP/ATP III, or any of the illnesses listed in the exclusions criteria based on a physician's approval. First, written informed consents were obtained from all participants. Then, their name, surname, age, and gender were recorder. The factors of height, weight, waist circumference, hip circumference, and systolic and diastolic blood pressure were measured by a physician. After 12 hours of fasting, 10 ml blood samples were obtained from the participants and placed in a centrifuge (3000 rpm) for 5-10 minutes in order to separate serum from coagulated blood. Then, the transparent liquid on the surface was removed using a pipette, and placed in microtubes and stored in -20 °C for further examinations (4, 8, 11).

Assessment of biochemical factors: Lipid factors of HDL, LDL, triglyceride, and blood sugar were measured using the BT4500 (Biotechnica, Italy).

Assessment of serum chemerin and insulin levels: ELISA kits were used to measure serum chemerin (Zellbio, Germany) and insulin level s)Monobind, USA).

Assessment of insulin resistance index: This index was calculated using the relevant equation (18).

All data collected in the questionnaires were entered into SPSS software (version 18, SPSS Inc., Chicago, IL, USA). Results of quantitative variables are represented as mean ± SD and qualitative variables as number (%). Independent two-sample t-test was used to compare mean of quantitative variables between individuals with metabolic syndrome and healthy individuals. Moreover, the Pearson correlation coefficient was used to assess the relationship between quantitative variables in individuals with metabolic syndrome. The significant level in all tests was determined as 0.05.

Results

The study participants consisted of 31 individuals with metabolic syndrome (11 men and 20 women) with mean age of 42.10 ± 12.06 years and 25 controls (14 men and 11 women) with mean age of 37.52 ± 8.96 years. Statistical tests showed no significant difference between mean age of the two groups (P=0.109). Furthermore, chi-square test did not show a significant difference in the gender prevalence distribution of the two groups (P = 0.125).

The results of statistical tests are presented in table 1. Based on the results, serum chemerin level was significantly higher in the metabolic syndrome group compared to the control group (P = 0.009). Moreover, mean BMI (P < 0.001), waist circumference (P < 0.001), systolic blood pressure (P = 0.001), diastolic blood pressure (P< 0.001), insulin resistance (P = 0.005), and triglyceride (P < 0.001) was significantly higher in the metabolic syndrome group compared to the control group. However, mean HDL was significantly higher in the control group compared to the patient group (P = 0.007).

Table 1: The level of the studied factors in the metabolic syndrome and control groups (Mean ± SD)

Variable	Metabolic syndrome group	Control group	P-value*
Height (cm)	165.32 ± 9.68	169.32 ± 10.21	0.140
Weight (Kg)	89.23 ± 16.29	77.20 ± 15.17	0.006
Body mass index (Kg/M^2)	32.71 ± 5.93	26.76 ± 3.47	< 0.001
Waist circumference	113.10 ± 14.09	94.88 ± 10.72	< 0.001
Hip circumference	120.61 ± 15.94	105.64 ± 8.70	< 0.001
Waist to hip circumference ratio	0.94 ± 0.07	0.90 ± 0.07	0.018
Systolic blood pressure (mmHg)	126.87 ± 12.06	114.96 ± 12.91	0.001
Diastolic blood pressure (mmHg)	81.61 ± 8.20	73.04 ± 8.86	< 0.001
Serum insulin level (mg/dl)	7.57 ± 1.86	6.59 ± 1.77	0.049
Fasting serum glucose level (mg/dl)	106.00 ± 13.63	91.88 ± 10.29	< 0.001
High-density lipoprotein (mg/dl)	44.29 ± 7.74	49.92 ± 7.03	0.007
Triglyceride (mg/dl)	191.90 ± 74.11	104.20 ± 55.22	< 0.001
low-density lipoprotein (mg/dl)	100.10 ± 27.26	96.44 ± 22.27	0.590
Insulin resistance index (HOMA-IR)	2.01 ± 0.67	1.52 ± 0.56	0.005
Chemerin (ng/ml)	806.83 ± 153.63	180.46 ± 194.88	0.009

* Independent two-sample t-test with significant level of < 0.05

Table 2 presents the Pearson correlation coefficient of serum chemerin level and metabolic syndrome indices in individuals with metabolic syndrome. Based on the results, serum chemerin level had no significant relationship with any of the studied factors (P >0.05).

Table 2: The relationship between serum chemerin level and metabolic syndrome indices in individuals with metabolic syndrome

Variable	Pearson correlation coefficient (r)	P-value
Height	0.061	0.744
Weight	0.319	0.080
Body mass index	0.253	0.169
Waist circumference	0.356	0.051
Hip circumference	0.261	0.156
Waist to hip circumference ratio	0.185	0.320
Systolic blood pressure	0.088	0.636
Diastolic blood pressure	0.028	0.880
Serum insulin level	0.155	0.404
Fasting serum glucose level	0.191	0.302
HDL	0.305	0.096
TG	0.133	0.475
LDL	0.240	0.193
HOMA-IR	0.175	0.399
Age	0.046	0.804

HDL: High-density lipoprotein; TG: Triglyceride; LDL: Low-density lipoprotein; HOMA-IR: Insulin resistance index

Discussion

Adipokines are polypeptides produced and secreted by adipose tissue and are associated with functions such as insulin resistance, inflammation, and blood pressure regulation (7, 8). Some human subject studies have reported a relationship between chemerin and metabolic syndrome, obesity, insulin resistance, and inflammation (4). However, some other studies have dismissed the presence of this relationship (19). Thus, the aim of the present study was the determination of serum chemerin level and its relationship with obesity and insulin resistance in individuals with metabolic syndrome in Rafsanjan.

The present study was conducted on 31 individuals with metabolic syndrome and 25 healthy individuals (control group). The two groups did not differ significantly in terms of age and gender. BMI, waist circumference, systolic and diastolic blood pressure, insulin resistance index, serum insulin and triglyceride levels, and fasting serum glucose level were significantly higher in the metabolic syndrome group compared to the control group. Nevertheless, HDL was higher in the control group in comparison with the patient group. There was no significant difference between the groups in terms of LDL and mean height. Data analysis showed that serum chemerin level was significantly higher in the metabolic syndrome group compared with the control group.

These findings are consistent with the results of many previous studies which have reported higher serum chemerin levels in individuals with metabolic syndrome in comparison to a control group (11, 20, 21). Bozaoglu et al. found that serum chemerin level was higher in individuals with metabolic syndrome compared to healthy individuals in a Mexican-American population and was related to many indices of this syndrome such as triglyceride, HDL, and fasting

insulin level (18). They also found that the level of this adipokine was higher in obese individuals than thin individuals.

Jialal et al. also showed that serum chemerin level was higher in individuals with metabolic syndrome compared to healthy individuals (11). They found that it was related to increase in factors such as fasting triglyceride and insulin levels; however, it had an inverse relationship with omentin level and HDL level in individuals with metabolic syndrome (11). Chu et al. showed that serum chemerin level was higher in individuals with metabolic syndrome compared with healthy individuals and was related to factors such as BMI and triglyceride (19). However, they found that it had an inverse relationship with adiponectin and acute-phase proteins, and no relationship with pantraksin enzyme 3, which is an anti-inflammatory agent (19).

Obesity is one of the most important outcomes of the modern lifestyle and increases the risk of many diseases (17). There are many markers for obesity such as BMI and waist circumference. Obesity is accompanied with increased body fat, and in humans, this adipokine is produced by immune cells and adipose tissues; thus, increased cell count and adipose tissue results in an increase in the production of this adipokine (22).

Some studies have suggested that chemerin is involved in increased insulin resistance in individuals with metabolic syndrome (4, 11). Nevertheless, no relationship was observed between chemerin level and insulin resistance in these individuals in the present study. The lack of relationship between serum chemerin level and insulin resistance may be due to the presence of different hormones which play a role in insulin resistance. The insulin resistance effect of chemerin is insignificant in comparison to these hormones (15).

The present results suggest that no significant relationship exists between serum chemerin level and triglyceride, LDL, and HDL. This finding is not in agreement with the results of some previous studies in this field (11, 20, 21). Based on the results of these studies, chemerin has an important role in increased LDL and HDL; this adipokine affects the hepatic cells and increases the level of VLDL which is a precursor of LDL (16).

Conclusion

Based on the results of the present study and previous studies, serum chemerin level increases in individuals with metabolic syndrome. Therefore, changes in serum chemerin level can be used as a criterion for diagnosis and confirmation of metabolic syndrome, and the assessment of this adipokine can be effective in the determination of appropriate treatment methods.

Acknowledgements

The authors would like to thank the Deputy of Research of Rafsanjan University of Medical Sciences for the funding of this study and all who participated in this study.

Conflict of interest: None declared

References

1. Fatima SS, Bozaoglu K, Rehman R, Alam F, Memon AS. Elevated chemerin levels in Pakistani men: an interrelation with metabolic syndrome phenotypes. PLoS One 2013; 8(2):e57113.
2. .Balistreri CR, Caruso C, Candore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. Mediators Inflamm 2010; 2010:802078.
3. Wang D, Yuan GY, Wang XZ, Jia J, Di LL, Yang L, et al. Plasma chemerin level in metabolic syndrome. Genet Mol Res 2013; 12(4):5986-91.
4. Ali TM, Al Hadidi K. Chemerin is associated with markers of inflammation and predictors of atherosclerosis in Saudi subjects with metabolic syndrome and type 2 diabetes mellitus. Beni-Suef

University Journal of Basic and Applied Sciences 2013; 2(2):86-95.

5. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014; 2014:943162.
6. Emanuela F, Grazia M, Marco DR, Maria Paola L, Giorgio F, Marco B. Inflammation as a link between obesity and metabolic syndrome. J Nutr Metab 2012; 2012:476380.
7. Delavari A, Forouzanfar MH, Alikhani S, Sharifian A, Kelishadi R. First nationwide study of the prevalence of the metabolic syndrome and optimal cutoff points of waist circumference in the Middle East: the national survey of risk factors for noncommunicable diseases of Iran. Diabetes Care 2009; 32(6):1092-7.
8. Osman MM, El-Mageed AIA, El-Hadidi E, Shahin RSK, Mageed NAAA. Clinical utility of serum chemerin as a novel marker of metabolic syndrome and type 2 diabetes mellitus. Life science journal 2012; 9(2):1098-108.
9. Mattern A, Zellmann T, Beck-Sickinger AG. Processing, signaling, and physiological function of chemerin. IUBMB Life 2014; 66(1):19-26.
10. Li Y, Shi B, Li S. Association between serum chemerin concentrations and clinical indices in obesity or metabolic syndrome: a meta-analysis. PLoS One 2014; 9(12):e113915.
11. Jialal I, Devaraj S, Kaur H, Adams-Huet B, Bremer AA. Increased chemerin and decreased omentin-1 in both adipose tissue and plasma in nascent metabolic syndrome. J Clin Endocrinol Metab 2013; 98(3):E514-7.
12. Coimbra S, Brandão Proença J, Santos-Silva A, Neuparth MJ. Adiponectin, leptin, and chemerin in elderly patients with type 2 diabetes mellitus: a close linkage with obesity and length of the disease. Biomed Res Int 2014; 2014:701915.
13. Elsebai AA, Saad WE, Mahdy MM. Serum chemerin and beta 2-microglobulin in type 2 diabetes: assessment of diabetic nephropathy. Life science journal 2014; 11(8):992-1000.
14. Aksan G, İnci S, Nar G, Soylu K, Gedikli Ö, Yüksel S, et al. Association of serum chemerin levels with the severity of coronary artery disease in patients with metabolic syndrome. Int J Clin Exp Med 2014; 7(12):5461-8.
15. Koç F, Tokaç M, Kocabaş V, Kaya C, Büyükbaş S, Erdem S, et al. Ghrelin, resistin and leptin levels in patients with metabolic syndrome. European Journal of General Medicine 2011; 8(2):92-7.
16. Aquilante CL, Kosmiski LA, Knutsen SD, Zineh I. Relationship between plasma resistin concentrations, inflammatory chemokines, and components of the metabolic syndrome in adults. Metabolism 2008; 57(4):494-501.
17. Lin CC, Liu CS, Li CI, Lin WY, Lai MM, Lin T, et al. The relation of metabolic syndrome according to five definitions to cardiovascular risk factors-a population-based study. BMC Public Health 2009; 9:484.
18. Shirai K. Obesity as the core of the metabolic syndrome and the management of coronary heart disease. Curr Med Res Opin 2004; 20(3):295-304.
19. Takahashi M, Takahashi Y, Takahashi K, Zolotaryov FN, Hong KS, Kitazawa R, et al. Chemerin enhances insulin signaling and potentiates insulin-stimulated glucose uptake in 3T3-L1 adipocytes. FEBS Lett. 2008; 582(5):573-8
20. Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, et al. Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population. J Clin Endocrinol Metab 2009; 94(8):3085-8.
21. Chu SH, Lee MK, Ahn KY, Im JA, Park MS, Lee DC, et al. Chemerin and adiponectin contribute reciprocally to metabolic syndrome. PLoS One 2012; 7(4):e34710.
22. Sadashiv, Tiwari S, Paul BN, Kumar S, Chandra A, Dhananjai S, et al. Over expression of resistin inadipose tissue of the obese induces insulin resistance. World J Diabetes 2012; 3(7):135-41.