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Serum Chemerin and Cardiovascular Risk Factors in Diabetic Subjects without Established Vascular Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Author EMA designed the research. Author NAA provided cases. Author SRH conducted the research. Author EMA analyzed data and wrote the paper. Author GAF revised the manuscript. Author EMA had primary responsibility for final content. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The current study aims to investigate serum chemerin as a potential cardiovascular marker in diabetic patients without established vascular diseases.
Study Design: Case-Control study.
Place and Duration of Study: The outpatients clinic, King Abdulaziz University Hospital in Jeddah, Saudi Arabia, between January 2013 and June 2014.
Methodology: Ninety consecutive diabetic patients and 90 age- and sex-matched controls were recruited from King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Demographic, anthropometric and biochemical variables were estimated.
Results: Overall and central obesity were highly prevalent among both groups. Serum chemerin

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was correlated with glycated hemoglobin (r= -0.207, p<0.05) and with C reactive protein (CRP) (r= 0.171, p<0.05). Moreover, serum chemerin was correlated with prothrombin time (r = -0.278, p<0.05) in control subjects and with diastolic blood pressure (r = -0.233, p<0.05) in diabetic subjects.

Conclusion: We concluded that only glycated hemoglobin was significantly and independently correlated with serum chemerin levels.

Keywords: Chemerin; diabetes mellitus; insulin resistance; inflammation; C reactive protein.

1. INTRODUCTION

Adipose tissue is recognized as an endocrine organ that produces several hormones and adipokines that are pro-inflammatory [1]. Adipocytes also express receptors for some adipokines (e.g. TNF-α, adiponectin, leptin) that appear to modulate insulin sensitivity, the inflammatory process and lipid and glucose metabolism [2,3]. The inflammatory response associated with obesity has been proposed as a potential contributory mechanism by which obesity increases insulin resistance and may eventually lead to the onset of diabetes mellitus [4]. Chronic subclinical inflammation can lead to endothelial dysfunction and hypercoagulability, both of which enhance the development of cardiovascular disease [5]. Inflammatory markers, such as high white blood cells count, increased levels of high sensitivity- C reactive protein (hs-CRP), and markers of hemostasis, such as activated partial thromboplastin time (APTT) and prothrombin time (PT), have also been related to the development of type 2 diabetes [6,7].

The pathophysiologic link between obesity and diabetes mellitus type 2 is not entirely clear, but adipokines appear to be involved. Chemerin regulates adipocyte differentiation and modulates the expression of adipocyte genes, such as glucose transporter-4, adiponectin and leptin, which are involved in glucose and lipid homeostasis [8]. It has also been shown to be associated with insulin resistance and inflammatory markers [9].

The purpose of this present study was to investigate serum chemerin as a potential cardiovascular marker in diabetic patients without established vascular diseases.

2. MATERIALS AND METHODS

Ninety consecutive diabetic patients as defined by hemoglobin A1c cutoff level of ≥6.5% [10] were recruited from the outpatients clinic, King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia. Exclusion criteria included documented history of cardiovascular diseases, renal diseases, hepatic diseases, or chronic inflammatory disease. Ninety age- and sex-matched controls without diabetes were recruited from the same catchment site. None of the patients were receiving any medication that could interfere with our results (e.g., antioxidants supplements, anti-inflammatory drugs, anti-obesity therapies). The study was approved by the ethical approval committee of KAUH.

Demographic data, height, weight, waist circumference, hip circumference and medical history were recorded. Body Mass Index (BMI) and Waist to Hip Ratio (WHR) were calculated as indicators for the distribution of total body fat and central body fat respectively [11]. In addition, ethnic-specific cutoff values for waist circumference were also used to define central obesity [12]. Blood pressure readings were obtained by a mercury sphygmomanometer in both arms with the patients in supine position, after 5 minutes of rest. A minimum of three readings were taken. Smoking habits and physical activity level were estimated for all study subjects.

Venous blood samples were collected from all study participants, after 12-14 hrs fasting, in sodium heparin vacutainers (Becton-Dickinson, Franklin Lakes, NJ). Blood was centrifuged for 15 min at 3,000 × g and the plasma was stored at -80℃ until analysis. Glucose, insulin, glycated hemoglobin (HbA1c), and hs-CRP were determined by standard methods (Dimension Vista System, Siemens, Germany). Quality control was assessed daily for all determinations. Insulin sensitivity measures were calculated by the Homeostasis Model Assessment- Insulin Sensitivity (HOMA)-IS and Insulin Sensitivity Index (ISI) formulas [13,14]. HOMA-IS was derived using the HOMA calculator (http://www.dtu.oc.ac.uk). Cardiac biomarkers (Troponin I and CK MB) were measured by electrochemiluminescence assays on Elecsys (Roche Diagnostics). PT and APTT were

estimated by the coagulation method using Dade Behring reagents (Dade-Behring, Marburg, Germany). The levels of plasma chemerin were using an enzyme-linked immunosorbent assay (ELISA), following the manufacturer's instructions (Biovendor-Laboratorni medicina, Czech Republic). The ELISA intra-assay and inter-assay coefficients of variation were <5% and <10%, respectively. All of the samples were measured in duplicate.

Continuous data were expressed as mean ± standard deviation and categorical data as number (percentage). Mann-Whitney test and chi-square test were used for continuous and categorical variables, respectively. The correlation analysis was performed by calculating the Pearson's or Spearman coefficient correlation for parametric and nonparametric variables respectively. A multiple stepwise linear regression analysis was used to determine the contribution of various factors to serum chemerin. Statistical analysis was performed using SPSS 17.0 statistical package.

3. RESULTS AND DISCUSSION

The diabetic patients and controls were matched for gender and age. Clinical data are presented in Table 1. The control group included 90 subjects (63 female: 26 male) with a mean age of 57.5±0.7 and was matched with 90 asymptomatic diabetic patients (63 female: 26 male), who were 58.5±0.8 years old.

Mean values of BMI among asymptomatic diabetics and their matching controls were above the recommended cutoff value for obesity (31.5±0.7 and 32.8±0.7 respectively). Two thirds of the study population was obese according to their BMI values being ≥30 Kg/m^2. Central obesity was also highly prevalent among both groups as determined by waist circumferences values above 80 cm in females and above 94 cm in males (94% of controls verses 97% of cases) and by WHR values ≥0.80 in females and ≥0.95 in males (84% of controls verses 85% of cases). Both groups were comparable with respect to blood pressure readings, smoking status and physical activity habits. Nevertheless no significant differences were observed between both groups except for FBG and insulin sensitivity measures (P<.001). Also, 25% of the diabetics were of intermediate coronary risk, as categorized by serum hs-CRP levels (1-3 mg/dl), in comparison with 12% of their matched controls (P= .05). Univariate analysis are depicted in Fig. 1 between serum chemerin and HbA1c (r= -0.207, P= .05) and in Fig. 2 between serum chemerin and hs-CRP (r= 0.171, P= .05). Moreover, serum chemerin was inversely correlated with PT (r = -0.278, P= .05) in control subjects and with DBP (r = -0.233, P= .05) in the diabetic subjects.

Multivariate analysis, considering all variables with P value up to 0.1, showed that only HbA1c was significantly associated with serum chemerin levels (β =-0.217; 95% CI: -34.4: -0.03; P= .05).

Adiposity and altered adipokine secretion appear to predispose to the development of type 2 diabetes [2,3]. It has been proposed that lower circulating levels of chemerin might be a marker of higher diabetes risk and of higher cardiovascular risk [8].

Other studies have reported elevated circulating chemerin in obese subjects but not in type 2 diabetic patients [15]. Although the reason for this discrepancy is unclear. These reports may require validation in larger study groups. Our data show similar circulating levels of chemerin in both groups. This might be partly attributed to the high prevalence of overall and central obesity in the study cohort.

Visceral fat may contribute to the chronic inflammation observed in obese individuals, but only a few studies documented adipokine secretion as a potential mechanistic link between visceral fat and systemic inflammation in people with abdominal obesity [16]. Unlike reported associations between chemerin and BMI, WHR and adipocyte volumes in some studies [9,17], our data failed to show any relationship between chemerin and anthropometric measures and/or surrogate measures of insulin sensitivity. This has also been reported by other studies [15,18].

We have shown that chemerin has a modest correlations with HbA1c (Fig. 1) and hs-CRP (Fig. 2). Clinical studies demonstrated that chemerin modulates inflammation [19]. Mechanisms linking chronic inflammation to the development of diabetes remain elusive, but it can be assumed that any effects may be exerted via insulin secretion, insulin resistance, or both. Given the slightly higher serum levels of hs-CRP among the diabetics than their matched controls (0.61±0.1 mg/dl vs. 0.74±0.1 mg/dl) and that more diabetics had a serum hs-CRP levels between 1-3 mg/dl (the reference value of intermediate coronary risk) than the controls (P= .05), might indicate that chemerin is more

likely to be a marker for inflammation than obesity [20].

To determine the factor most strongly associated with serum chemerin levels in the study cohort, a multiple stepwise linear regression test was performed. Only HbA1c was significantly associated with serum chemerin and independent of several other cardiovascular risk factors. Nevertheless, it should be noted that the associations as shown do not necessarily reflect causality. Since chemerin is an adipokine with insulin-sensitizing effects [21], it might explain this relationship but the significance of increased chemerin serum concentrations in impaired insulin sensitivity remains to be elucidated. Of note is the fact that some studies have reported that serum chemerin may not be a predictive marker of diabetes mellitus [19,22].

Table 1. Clinical characteristics of the study population (N=180)

	Controls without diabetes (n=90)	Asymptomatic diabetic subjects (n=90)	p
Weight (Kg)	79.9±1.9	83.9±2.0	NS
Height (cm)	159.2±0.9	159.8±0.9	NS
BMI (Kg/m^2)	31.5±0.7	32.8±0.7	NS
BMI classes			
Normal (18.5-24.9 Kg/m^2)	18 (20)	9 (10)	
Overweight (25-29.9 Kg/m^2)	18 (19)	26 (26)	NS
Obese (≥30 Kg/m^2)	54 (61)	56 (63)	
Waist circumference (cm)	105.9±1.4	109.3±1.4	NS
Waist circumference >80 cm in females and >94 cm in males	84 (94)	87 (98)	NS
Hip circumference (cm)	112.5±1.6	115.5±1.4	NS
WHR	0.95±0.0	0.95±0.0	NS
WHR ≥0.80 in females and ≥0.95 in males	75 (84)	76 (85)	NS
SBP (mmHg)	131.3±1.8	138.8±2.3	NS
DBP (mmHg)	80.8±1.4	79.4±1.3	NS
Smoking status			
Non-smokers	74 (82)	76 (84)	
Ex-smokers	9 (10)	7 (8)	NS
Smokers	7 (8)	7 (8)	
Physical activity Level			
≥ 3times/ week	1 (1)	0 (0)	
1-2 times/week	20 (23)	13 (15)	NS
<1 time/week	69 (76)	77 (85)	
FBG (mmol/L)	5.66±0.1	9.45±0.3	<0.0001
Fasting insulin (µU/ml)	13.9±0.9	17.9±1.7	NS
HOMA-IS	140.0±10.4	65.1±5.4	<0.0001
ISI	181.9±13.2	96.1±6.6	<0.0001
hs-CRP (mg/dl)	0.61±0.1	0.74±0.1	NS
hs-CRP levels			
low coronary risk (<1.0 mg/dl)	79 (88)	68 (75)	<0.05
intermediate coronary risk (1-3 mg/dl)	11 (12)	22 (25)	
CK-MB (µg/L)	1.11±0.2	1.4±0.2	NS
cTnI (µg/L)	0.04±0.0	0.05±0.0	NS
PT (sec)	31.2±0.9	29.8±0.9	NS
APTT (sec)	32.4±1.9	31.1±1.8	NS
Chemerin (ng/ml)	398.0±14.7	393.9±13.6	NS

Data are given as the mean ± SD or as the number of subjects with percentages given in parentheses, as appropriate. Categorical data are compared by χ2 test, continuous variables are compared by Mann-Whitney U test. APTT: activated partial thromboplastin time, BMI: Body mass index, CK-MD: creatin kinase-MB, cTnI: cardiac troponin I, DBP: Diastolic Blood Pressure, FBG: Fasting Blood Glucose, HOMA-IS: homeostasis model assessment of β-cell insulin secretion, hs-CRP: high sensitivity-C reactive protein, ISI; insulin sensitivity index, NS: non-significant, PT: prothrombin time, SBP: Systolic Blood Pressure, WHR: Waist- hip Ratio

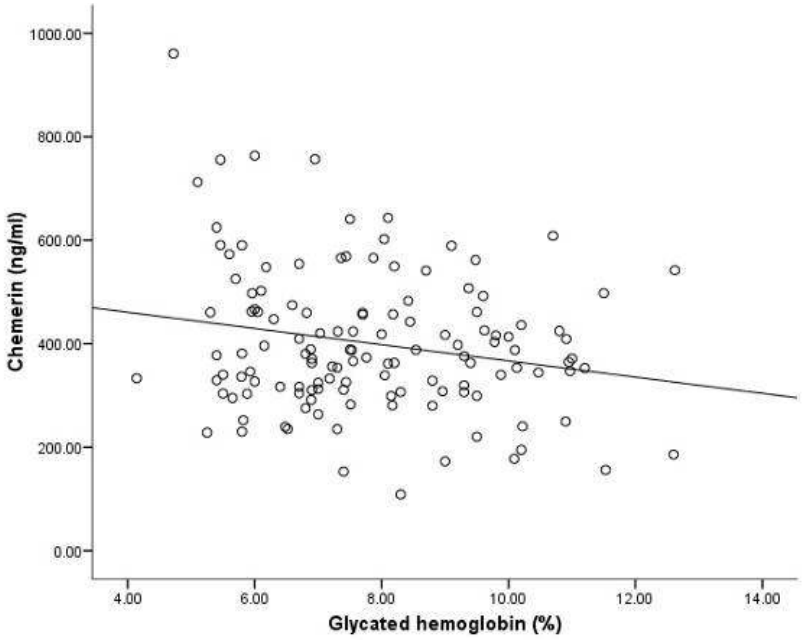

Fig. 1. Scatter plot showing correlation between serum levels of chemerin and glycated hemoglobin (%) among the 180 study participants (r= -0.207, *P*= .05)

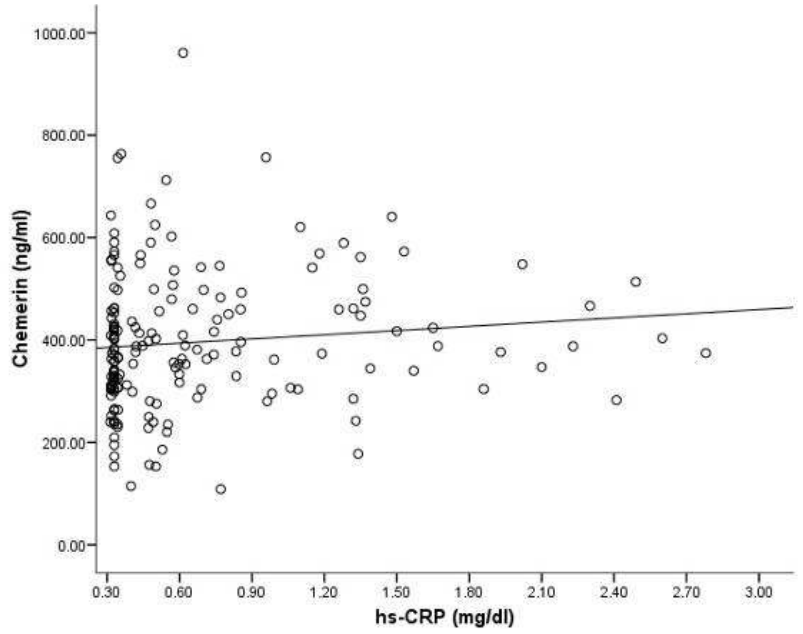

Fig. 2. Scatter plot showing correlation between serum levels of chemerin and high sensitivity-C reactive protein among the 180 study participants (r= 0.171, *P*= .05)

Table 2. Stepwise multiple regression analysis of serum chemerin level with all variables with p value up to 0.1 entered into the model among the study population (N=180)

Independent variables	β	95% CI limit of β		*p*
Total R^2 = 3.5%				
HbA1c (%)	-0.217	-34.4	-0.025	0.049

95% CI: 95% confidence interval, HbA1c: glycated hemoglobin

By contrast, chemerin levels were negatively correlated with PT among non-diabetic controls [15]. PT is most affected by the blood levels of clotting factor VII. Factor VII coagulant activity levels were found to be higher in type 2 diabetes patients and metabolic syndrome individuals [23]. Previous studies have suggested that serum chemerin is associated with the features of metabolic syndrome such as blood pressure, DBP was associated with chemerin among asymptomatic diabetic patients [15,24].

Although our study had some limitations, it provides important new data about the relationship between chemerin and inflammation in diabetics without overt macrovascular disease. Nevertheless, a causal relationship could not be established because of the cross-sectional nature of the study. The possibility of residual confounding factors could not be excluded even though the results were adjusted for multivariate covariates. Also, our relatively small sample size is another limitation of this study.

4. CONCLUSION

Obesity, either overall or central, was highly prevalent among the study cohort. A high proportion (25%) of patients with type 2 diabetes have intermediate coronary risk based on their serum hs-CRP levels. Of the biochemical markers studied, only HbA1c was significantly and independently correlated with serum chemerin levels.

Further longitudinal studies among different set of populations are needed to be conducted for better understanding of the precise mechanism linking chemerin and inflammation in diabetic subjects.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that the research design has been examined and approved by the ethics committee at KAUH and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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