Original Article

Chemerin Level and the Relation to Insulin Resistance in Chronic Kidney Disease

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ABSTRACT. Chemerin has been associated with different components of the metabolic syndrome, including hypertension, hyperlipidemia, and insulin resistance (IR). The aim of this study was to evaluate serum chemerin level in chronic kidney disease (CKD) patients and its relation to IR. This study was conducted on 80 participants who were classified into three groups: Group I (30 CKD patients with mean age 53 ± 12 years), Group II (30 patients with end-stage renal disease on regular hemodialysis with mean age 48 ± 14.8 years) and Group III having 20 healthy age- and sex-matched controls. Serum chemerin level, fasting blood sugar, fasting insulin, HOMA-IR index calculation, urea, creatinine, estimated glomerular filtration rate, total cholesterol, and triglyceride were measured. Body composition was assessed by dual-energy X-ray absorptiometry. In Groups I and II, we found a significantly higher mean chemerin level compared to healthy controls (P <0.001), a highly significant positive correlation between mean chemerin level and the HOMA-IR index [r = 0.56, P <0.001/(r = 0.53, P <0.001)], and a highly significant negative correlation between mean chemerin level and GFR (r = −0.51, P <0.001/r = −0.46, P ≤0.001). In Group I, there was also a highly significant positive correlation between mean chemerin and systolic blood pressure (r = 0.31, P <0.05), diastolic blood pressure (r = 0.39, P <0.05 and creatinine (r = 0.34, P <0.05). Chemerin might be considered a uremic IR adipokine marker in CKD Stages 3, 4, and 5.

Introduction

Chronic renal disease (CKD) is now recognized as one of the major worldwide pandemics. The underlying role of insulin resistance (IR), overt diabetes mellitus (DM), hypertension and dyslipidemia in initiation and progression of renal dysfunction is well established.¹⁻³ Early detection of IR may help to prevent or slow down the occurrence of CKD, and cardiovascular diseases.⁴ Adipocytokines are important biologically active compounds, present mainly in adipose tissue, and are concerned
with lipid metabolism, IR, and inflammation. One of the novel adipokines is a 16-kDa protein, known as chemerin- or tazarotene-induced gene 2 protein or retinoid acid receptor responder protein 2. It is mainly secreted by the adipose tissue and the skin and is expressed in the liver, platelets, placenta, and to a lesser extent, the kidney. Chemerin acts through three different G protein-coupled receptors. Chemokine-like receptor 1 (CMKLR1) carries most of the chemerin’s biological effects and both of them are highly expressed in the adipocytes especially during the differentiation of preadipocytes to adipocytes. Hence, they may be involved in the pathogenesis of obesity-related disorders. Different studies have reported elevated chemerin level in CKD as well as its strong link with different components of the metabolic syndrome including dyslipidemia, IR, and hypertension.

The aim of this study was to evaluate and compare serum chemerin level in patients with CKD Stages 3 and 4 and those on regular hemodialysis (HD) and its relation to IR.

**Patients and Methods**

This study was conducted on 80 participants. Group I included 30 CKD patients Stage 3 and 4 (22 males and 8 females) with a mean age of 53 ± 12 years. Group II included 30 patients (20 males and 10 females) with a mean age of 48 ± 14.8 years with end-stage renal disease (ESRD) on regular HD. Group III included 20 healthy controls (12 males and 8 females) with a mean age of 46.6 ± 15 years with GFR >90 mL/min. All patients were recruited from Kasr Al-Ainy nephrology department. Exclusion criteria included age <18 years and >70 years, presence of DM, human immunodeficiency virus, hepatitis B or hepatitis C infections, any evidence of acute or chronic infection and patients using immunomodulatory drugs.

After taking a written consent from all participants and approval of Ethical Committee of the Faculty of Medicine of Cairo University, the patients were subjected to full history taking, clinical examination, laboratory investigations including complete blood picture, fasting blood sugar (FBS), fasting serum insulin, serum urea, serum creatinine, total cholesterol, triglyceride (TG), and serum chemerin. Although the exclusion of DM can be made by measuring glycosylated hemoglobin (HbA1C), we excluded DM by FBS because the HbA1C level is affected by Hb level, which is affected in most CKD patients. Thus, to avoid this bias, we preferred to use FBS to ensure the generalizability of the data in all groups.

Serum creatinine, urea, total cholesterol, and TG were measured by colorimetric method using the Hitachi 912 autoanalyzer, fasting serum insulin was determined using radioimmunoassay, and IR was calculated according to the following equation [HOMA-IR = FBS (mg/dL) × fasting insulin (mIU/mL)/405]. The estimation of GFR was made using the Cockcroft-Gault equation. Serum chemerin was determined by sandwich enzyme immunoassay using the bio Vendor (Bio Vendor GmbH, Heidelberg, Germany) kit.

Body composition (total fat mass, trunk fat mass, and lean mass) was assessed by dual-energy X-ray absorptiometry using the DPX-L device with software that calculates the grams of fat tissue, fat mass percentage, grams of lean tissue, and grams of bone mineral mass. Fat-free mass is calculated as the sum of lean tissue plus bone mineral mass.

**Statistical Analysis**

Analysis of data was made by Statistical Package for the Social Sciences statistics for Windows version 12.0 (Chicago, IL, USA). A comparison of qualitative variables was done using Chi-square test, whereas the comparison of quantitative variables was done using unpaired t-test. When groups were compared, one-way ANOVA followed by post hoc least significant test was used when the comparison showed a significant difference. Kruskal–Wallis test is a nonparametric test used for comparing two or more independent samples of equal or different sample sizes. Spearman’s correlation was used to assess the relation...
between two quantitative parameters in the same group.

**Results**

Demographic, clinical, and laboratory data are represented in Tables 1 and 2. Correlation between mean chemerin level and all different studied variables in the three groups was performed. In the CKD group (Group I), a significantly positive correlation was found between mean chemerin level and systolic blood pressure (SBP) \((r = 0.31, P < 0.05)\), diastolic blood pressure (DBP) \((r = 0.39, P < 0.05)\), and creatinine \((r = 0.34, P < 0.05)\). A highly statistically significant positive correlation was found between mean chemerin level and the HOMA index \((r = 0.56, P < 0.001)\), and a highly significant negative correlation was found between mean chemerin level and GFR \((r = -0.51, P < 0.001)\) (Figures 1 and 2). No correlation was found between mean chemerin level and the other studied parameters.

In the ESRD group (Group II), a highly significant positive correlation between mean chemerin level and HOMA index \((r = 0.53, P < 0.001)\) and a highly significant negative correlation between mean chemerin levels and estimated glomerular filtration rate \((r = -0.46, P < 0.001)\) was found. Furthermore, a negative correlation was found between mean chemerin levels and both urea and TG. No correlation was found between mean chemerin level and the other studied parameters. In the control group (Group III), the only relationship was a negative correlation between mean chemerin level and Hb.

**Discussion**

Chemerin is a chemoattractant protein that has different functions related to glucose metabolism in the liver and muscle and regulation of adipocyte development and differentiation. Chemerin level was found to be elevated in DM with a positive correlation with obesity, IR\(^{11}\) and hypertension.\(^{11}\) It was found to increase with deterioration of renal functions\(^{13}\) and was considered an independent predictive marker of the presence of atherosclerosis in CKD.\(^{21}\)

We aimed in this study to evaluate serum chemerin level in patients with CKD and its relation to IR. When the three studied groups were compared, we did not find a significant difference in the body mass index (BMI) \((P > 0.05)\). Pfau et al found a lower BMI in

### Table 1: Demographic and clinical data of chronic kidney disease patients, regular hemodialysis patients and healthy controls.

| Variables          | Group I CKD \((n = 30)\) | Group II CKD on regular HD \((n = 30)\) | Group III Healthy \((n = 20)\) | \(F\) | \(P\) | LSD |
|--------------------|----------------------------|----------------------------------------|-------------------------------|------|------|-----|
| Age (years) (mean±SD) | 53±12                     | 48±14.8                                | 46.6±15                       | 1.9  | >0.05|      |
| BMI                | 27.9±6                     | 24.3±5                                 | 27.8±5                        | 3    | >0.05|      |
| Gender             |                            |                                        |                               | 0.9* | >0.05|      |
| Male               | 22 (73.3%)                 | 20 (66.7%)                             | 12 (60%)                      |      |      |      |
| Female             | 8 (26.7%)                  | 10 (33.3%)                             | 8 (40%)                       |      |      |      |
| SBP (mm Hg)        | 141±20                     | 145±18                                 | 111±10                        | 25   | <0.001|      |
|                   | Control versus both groups |                                        |                               |      |      |      |
| DBP (mm Hg)        | 83.7±11                    | 86±11.9                                | 71±9                          | 11   | <0.001|      |
|                   | Control versus both groups |                                        |                               |      |      |      |

*Chi-square test. One-way ANOVA test. Table 1 shows no significant difference between the studied groups as regard age, sex, and BMI but showed a significant difference between the control groups and both patients groups regarding both the systolic and the diastolic blood pressure. CKD: Chronic kidney disease, HD: Hemodialysis, LSD: Least significant difference \((post hoc\) test), BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation.
patients with CKD compared to control subjects and Abd Rabo et al found a higher BMI in patients with CKD compared to controls. This might be related to different socioeconomic statuses. In our study, the SBP and the DBP were statistically higher in Group I and Group II compared to Group III (P <0.001). This is matching with the report that up to 85% of patients with CKD were proved to have hypertension in the National Health And Nutrition Examination Survey (NHANES).

A significantly higher cholesterol, triglyceride levels, and HOMA index were found in Group I and Group II compared to the control group (P <0.001). This was partially in agreement with Shurraw et al. In their study, they found elevated TG but not cholesterol levels and increased IR in CKD and ESRD patients. No significant difference could be found in the total fat, trunk fat, or lean mass distribution between the three studied groups (P >0.05). This is contrary to Johansen and Lee observation of increased obesity and muscle wasting in patients with CKD with a negative influence on patient survival.

In our study, the mean chemerin level was

Table 2. Laboratory data of chronic kidney disease patients, regular hemodialysis patients, and healthy controls.

| Variables          | Group I (n=30) | Group II (n=30) | Group III (n=20) | F   | P     | LSD                                      |
|--------------------|---------------|----------------|-----------------|-----|-------|------------------------------------------|
| Hb (g/dL)          | 10.3±1.8      | 8.9±1.8        | 13.4±1.8        | 42  | <0.001| CKD versus ESRD Control versus both groups |
| TLC (mm$^3$)       | 9±2.6         | 8±3            | 7.9±2           | 0.9 | >0.05 | NS                                       |
| Platelets (mm$^3$) | 276±106       | 208±64         | 277±61          | 6   | <0.001| ESRD versus other two groups              |
| Creatinine (mg/dL)| 2.5±0.5       | 9.4±2          | 0.78±0.2        | 330 | <0.001| CKD versus ESRD Control versus both groups |
| Urea (mg/dL)       | 82.7±30       | 165±73         | 27.9±8          | 38  | <0.001| CKD versus ESRD Control versus both groups |
| Cholesterol (mg/dL)| 199±38        | 179±48         | 151±16          | 8.8 | <0.001| Controls versus other two groups          |
| TG (mg/dL)         | 188±56        | 155±57         | 129±27          | 8   | <0.001| Controls versus other two groups          |
| FBS (mg/dL)        | 102±12        | 95±6.9         | 92±11           | 5.3 | <0.05 | CKD versus other two groups               |
| eGFR (mL/min)      | 35±11         | 9±3            | 132±41          | 199 | <0.001| CKD versus ESRD Control versus both groups |
| HOMA index         | 1.79±0.6      | 1.68±0.4       | 1±0.3           | 14  | <0.001| Controls versus other two groups          |
| Total body fat (Kg)| 19.6±9        | 17.2±13        | 23±12           | 1.5 | >0.05 | DEXA: Dual-energy X-ray absorptiometry, LSD: Least significant difference (post hoc test), HB: Hemoglobin, CKD: Chronic kidney disease, ESRD: End-stage renal disease, TLC: Total leukocyte count, TG: Triglycerides, FBS: Fasting blood sugar, eGFR: Estimated glomerular filtration rate. One-way ANOVA test *Kruskal–Wallis test. Table 2 shows a significant difference between the studied groups as regards all variables except TLC, total body fat, trunk fat, and lean mass. DEXA: Dual-energy X-ray absorptiometry, LSD: Least significant difference (post hoc test), HB: Hemoglobin, CKD: Chronic kidney disease, ESRD: End-stage renal disease, TLC: Total leukocyte count, TG: Triglycerides, FBS: Fasting blood sugar, eGFR: Estimated glomerular filtration rate.
significantly higher in all patients (Group I and Group II) compared to the healthy controls (Group III). This was supported by different studies that documented elevated chemerin level in adults with CKD compared to controls.\textsuperscript{9,13} Mean chemerin level in our study was, however, even significantly higher in Group I compared to the other two groups ($P < 0.001$) contrary to Abd Rabo et al, who found significantly higher serum chemerin level in the ESRD patients compared to CKD patients.\textsuperscript{22} and Pfau et al, who reported more than two-fold elevation of chemerin level in the regular HD patient compared to controls.\textsuperscript{12} Our finding may be explained by the reduction of high serum chemerin by the HD procedure noticed by Blaszak et al.\textsuperscript{10} We did not find a significant difference in the mean

Figure 1. Correlation between HOMA index and mean chemerin levels in Group I patients. There was a positive correlation between HOMA index and chemerin level in CKD patients.

Figure 2. Correlation between glomerular filtration rate and mean chemerin levels in Group I patients. There was a negative correlation between chemerin level and glomerular filtration rate in chronic kidney disease patients.
We found a chemerin level between males and females among the three groups \( (P > 0.05) \). This is similar to Pfau et al, who did not find a gender difference in the chemerin level.\(^{12}\) The significant positive correlation between mean chemerin level and creatinine in Group I and the highly significant negative correlation between mean chemerin level and GFR in Group I and Group II reported by our study was also documented by Blaszak et al and Zylla et al.\(^{10,26}\)

Elevated chemerin level with progressive renal dysfunction can be attributed to reduced clearance with reduction of GFR as the level of serum adipokines are affected by GFR and renal degradation.\(^{13}\) Another way of renal contribution to elevated chemerin level is through its synthesis. The expression of chemerin and CMKLR1 is up-regulated in the kidney of model rats with progressive diabetic nephropathy,\(^{27}\) as well as in renal biopsies of patients with severe lupus nephritis who had marked tubulointerstitial plasmacytoid dendritic cell infiltration which express CMKLR1 and respond to chemerin through chemotaxis.\(^{28}\) Studies evaluating the role of adipose tissue being the main source of circulating chemerin\(^{29}\) in elevated chemerin level in CKD, ruled out subcutaneous adipose tissue as a source for its elevation but the role of the visceral adipose tissue remains debatable.\(^{30}\) We found a significant positive correlation between mean chemerin level and both SBP and DBP in Group I and a highly significant positive correlation between mean chemerin level and HOMA index in both Group I and Group II. This is in agreement with Zylla et al, who addressed a strong link between serum chemerin and hypertension and with IR.\(^{11}\) Abd Rabo et al also found a significant positive correlation between chemerin level and IR in both CKD and ESRD patients on HD.\(^{22}\) Chemerin seems to have different effects on glucose uptake as agreed by Sell and Eckel who found a positive correlation between chemerin level and IR and assumed that chemerin induces IR in peripheral tissues and reduces glucose uptake by skeletal muscle.\(^{31}\) Weigert et al, assumed that the level of chemerin rises as a compensation to IR due to its opposite effect on the adipocytes, where it increases insulin-stimulated glucose uptake.\(^{32}\)

Regarding the lipid profile, we did not find a correlation between the chemerin level and TG in Group I, a negative correlation was found in Group II and no correlation was found between the chemerin level and cholesterol in both groups. This was contrary to Abd Rabo et al’s finding of significant positive correlation between chemerin level and both TG and total cholesterol in patients with CKD.\(^{22}\) In our study, we did not find a correlation between the chemerin level and the BMI, which is in agreement with Abd Rabo et al.\(^{22}\) On the other hand, Dorte et al found a positive correlation between serum chemerin and BMI in HD patients.\(^{12}\) No correlation between the chemerin level and total body fat, trunk fat or lean mass was detected in our study. Bozaoglu et al noted increased chemerin mRNA expression in white adipose tissue that may be responsible for elevated serum chemerin with renal impairment.\(^{8}\) However, Blaszak et al found no difference between subcutaneous adipose tissue chemerin mRNA expression in CKD patients and healthy controls.\(^{10}\) Visceral adipose tissue was found to be responsible for higher chemerin release than subcutaneous adipose tissue, but its role in elevated serum chemerin in patients with renal impairment needs evaluation.\(^{12}\)

Our study is one of the rare studies comparing chemerin level in different stages of CKD and attempting to find a relation to IR in CKD. The study should be viewed with limitations; it was done on a small number of patients. We chose age-matched groups to limit the variables controlling the chemerin level. The levels of chemerin may be different in different age groups. The duration of dialysis as a factor controlling chemerin level has not yet been investigated. To conclude, the strong positive correlation of chemerin with HOMA index in CKD patients may allow its use as an IR adipokine marker in CKD. The study revealed that there is a strong correlation between serum level of chemerin and both creatinine and GFR in patients in CKD.
**Conflict of interests:** None declared

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