Original Article

Assessment of the correlation between Plasma level of Chemerin and inflammatory markers in end-stage renal disease patients undergoing Hemodialysis

Mehdi Mahmudpour[1], Mohsen Ghasemi[2], Khadijeh Ghasemi[3]*

[1] Assistant Professor of Nephrology, The Persian Gulf Tropical Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran, [2] General Practitioner., The Persian Gulf Tropical Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran, [3] Assistant Professor of Pediatric Nephrology, Department of Pediatrics, School of Medicine, Persian Gulf Shohada hospital, Bushehr University of Medical Sciences, Bushehr, Iran

Correspondence: Khadijeh Ghasemi. Department of Pediatrics, School of Medicine, Persian Gulf Shohada hospital, Bushehr University of Medical Sciences, Bushehr, Iran. Email: ghassemi61 @ yahoo.com

ABSTRACT

Background of the study: One of the major complications of renal failure is inflammation. It is revealed that inflammatory milieu in uremic patients correlates with the increased risk of cardiovascular mortality, anemia, and bone diseases. Therefore, finding any marker with precise prognostic or diagnostic value can have valuable clinical impacts. This study was conducted to investigate the correlation between chemerin levels and inflammatory markers as the indicators of inflammation. **Material and methodology:** This was a cross-sectional study. Sixty-two hemodialysis patients from 2 hemodialysis centers who aged more than 18 years old enrolled in this study. Linear logistic regression analysis was used to test the correlation between serum phosphate, hs-CRP, and TNF-alpha with chemerin. A comparison between the mean value of groups in different cut-off points of phosphorus with chemerin was performed with an independent sample t-test. **Results**: There was a direct correlation between chemerin level and hs-CRP (P= 0.013), without any correlation between chemerin and TNF-alpha (P=0.058). Also, there was a direct correlation between hyperphosphatemia and chemerin levels when phosphorus increased to more than 6.5 mg/dl (P=0.039) and more than 7 mg/dl (P=0.001). **Conclusion:** The current study`s data revealed that the plasma level of chemerin directly correlated with inflammation. Therefore, this adipokine can be proposed as a valuable diagnostic and prognostic tool with clinical impact in hemodialysis patients.

Keywords: Chemerin, Inflammation, Uremia, Hemodialysis patients

Introduction

Chemerin, a 16_KDa protein, is a chemo-attractant for chemokine-like receptor-1 expressing cells[1] that was detected at first in body fluids of cancer and rheumatoid arthritis patients[2]. This adipokine, which is highly expressed in liver, adipous tissue, fibroblast, and platelets[3-6], is a product of the enzymatic process on pro-chemerin[7].

Chemerin plays a major role in adipocyte differentiation and insulin signaling[8]. This cytokine is associated with metabolic syndrome, systemic inflammation[1] and increased level of CRP[9, 10]. On the other hand, it is supposed that this molecule has anti-inflammatory properties[11].

Increased risk of cardiovascular disease and inflammation are major complications of uremia. Therefore, identifying new risk factors that induce inflammation or any indicator that had a diagnostic or prognostic role in the diagnosis of inflammation or cardiovascular disease in hemodialysis patients can be valuable.

Several studies indicated that chemerin level is increased in chronic kidney disease (CKD) patients. One of the proposed mechanisms is the renal dysfunction and decreased urinary

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excretion of chemerin independent of adipose tissue production[12- 15].

It was believed that renal dysfunction not only can lead to an increased level of chemerin, but also the level of inflammation in hemodialysis patients can influence the level of chemerin. Hence, this study was conducted to investigate the correlation between chemerin levels and inflammatory markers in ESRD patients who underwent hemodialysis.

Materials and Methods

Patient setting and data description: This study was a cross-sectional study that was approved by Bushehr University of Medical Sciences Ethics Committee. Eighty-eight hemodialysis patients attending the two major hemodialysis centers in Bushehr were included in the study and were evaluated. After obtaining informed consent, all patients who aged more than 18-year-old, and had undergone hemodialysis for at least 3 months, enrolled in this study. Individuals who had PTH more than 600 pg/ml, platelet count more than 500000, active infections, active inflammatory disease, were under antibiotic or statin therapy, had taken NSAID or corticosteroids during recent one month, and smokers, as well as those who had morbid obesity, were excluded (n=26). Demographic data were assessed from the questionnaire. Measured anthropometric and biochemistry were performed at the beginning of the study. Blood samples from patients were collected from the arterial line before starting dialysis and were centrifuged and frozen at -70 ℃ prior to be measured. Biochemical parameters included Complete Blood Count (CBC), level of serum creatinine (Cr), Blood Urea Nitrogen (BUN), calcium (Ca), phosphorus (P), parathyroid hormone (PTH), high sensitive CRP (hs-CRP), Tumor Necrotizing Factor-alpha (TNF-α), and Chemerin (Bio Vendor, Czech).

Statistical analysis: SPSS version 25.0 was used for all statistical analyses. Descriptive statistics were expressed as mean ± standard deviation. Variables were tested for normal distribution by the Shapiro-Wilk W test. Data were log-transformed to approximate normal distribution. Linear logistic regression was used to test the correlation between serum phosphate, hs-CRP and TNF-alpha with chemerin. A comparison between the mean value of groups in different cut-off points of phosphorus with chemerin was performed with an independent sample t-test.

Results

As shown in Table 1, the median circulating level of chemerin was 349.5±72.6 ng/ml. After being adjusted with age, sex, and BMI, Chemerin was significantly (P=0.013) correlated with hs-CRP, but was not correlated with TNF-α (P=0.058) and phosphorus level (P=0.139).

Table 1. Chemerin level and its correlation with hs-CRP, TNF-α and phosphorus after being adjusted with age, BMI and sex.

variable	TNF-α	hs-CRP	phosphorus
Total (N=62)	3.08±3.5	11.26±14.02	5.49±1.61
Chemerin	β Std.er	β Std.er	β Std.er
	0.12 0.006	0.21 0.008	0.24 0.16

When patients were divided into two groups based on the plasma level of phosphorus at different cut-off levels, chemerin had a significant correlation in cut off levels of 6.5 mg/dl (P=0.039) and 7 mg/dl (P=0.001) (Table 2).

Table 2. Correlation between chemerin with phosphorus in different phosphorus levels.

Phosphorus level	chemerin	P-value
≥5.5 (n=35)	343.3±60.2	0.601
<5 (n=27)	375.6±71.5	
≥6 (n=41)	343.9±64.4	0.79
<6 (n=21)	383.8±64.9	
≥6.5 (n=43)	344.5±63.7	0.039
<6.5 (n=19)	386.6±65.9	
≥7 (n=51)	346.7±62.6	0.001
<7 (n=11)	407.1±65.5	

Discussion

The aim of this study was to investigate whether there is any correlation between increased level of chemerin and inflammatory markers in End-Stage Renal Disease patients who underwent hemodialysis regardless of the direct impact of renal function on chemerin. In this study, it was found that although in ESRD patients chemerin level increased as compared to normal population[14, 16-19], whenever there was propagated inflammatory milieu, this elevation was aggravated independently.Previously, it was proposed that impaired clearance or catabolism of chemerin in the kidney may lead to an increased level of chemerin in hemodialysis patients[8, 14, 20]. Another proposed mechanism was the inflammation of adipose tissue that occurred in obesity, leading to increased production of chemerin[21]. However, the current study showed that after adjustment with BMI, chemerin directly correlated with hs-CRP. Weigert et al. postulated that chemerin had opposite effects in adipose tissue, where it was increased to compensate a milieu that insulin resistance was induced[10].

The origin of chemerin is a 163 amino acid pre-pro-protein, which then converts to a 143 amino acid pro-protein, following enzymatic cleavage of a signal peptide[22, 23]. This pro-protein should undergo further extracellular c-terminal processing by plasmin, different carboxypeptidases, and serine proteases that

are involved in inflammatory cascades[24-27]. Based on the origin of chemerin production and the milieu that induce chemerin production, this c-terminal cleavage can be different[28, 29]. On the other hand, proteolytic activity is mandatory for the inactivation of chemerin that is mediated by a neutrophil-derived serine protease, mast cell chymase, and angiotensin-converting enzyme [30, 31].

There are three main types of chemerin receptors: An orphan G protein-coupled receptor chemokine-like receptor (CMKLR)1 also known as ChemR23, in which biological activities of chemerin is mediated by the receptor[32]; there are two other chemokines (c-c motif) receptors-like (CCRL)2 and G protein-coupled receptor(GPR)[27, 33, 34]. Chemerin is elevated in different inflammatory diseases. ChemR23-expressing cells are recruited in several chronic inflammatory diseases such as ulcerative colitis and Crohn's disease[10].

In addition, the expression of ChemR23 is increased in infiltrating plasmacytoid dendritic cell (pDC) in multiple sclerosis that is accompanied by the detection of chemerin in cerebrovascular endothelial cells[35]. In severe lupus nephritis, the expression of chemerin in proximal tubular cells and recruitment of ChemR23-expressing pDC to the kidney parenchyma is shown[36]. All these data are implied in the pro-inflammatory role of chemerin in inflammatory conditions.

In contrast, there has been other evidence that showed the anti-inflammatory effect of the chemerin-ChemR23 system. In the animal model, chemerin and chemerin derived peptide C15 could suppress the production of some inflammatory mediators. Additionally, C15 could induce microbial and apoptotic cell phagocytosis by ChemR23$^{+/+}$ macrophage[37]. In the acute lung injury model, due to lipopolysaccharide, chemerin could ameliorate the production of chemokines (CXCL1) and some cytokines such as TNF alpha, IL-1β, and IL-6[38]; and recruitment of neutrophil to the lung was higher in ChemR23$^{-/-}$ mice in comparison to wild-type mice[39]. Based on these data, it can be proposed that the chemerin-ChemR23 system can have anti-inflammatory activities.

Whether chemerin be an inflammatory mediator or its increase be due to anti-inflammatory effects of this molecule in uremic context for compensation, there is a question that needs further investigations. The current study`s findings also showed that there was a direct correlation between chemerin level and hyperphosphatemia when the plasma level increased to more than 6.5 mg/dl.

Some data reported that chemerin concentration threshold of more than 240 µg/L can be used as an indicator of metabolic syndrome with the sensitivity and specificity of 75% and 67%, respectively[40]. Similarly, the chemerin level can be used as an indicator of inflammation in uremic patients with some clinical impacts such as differentiating anemia of chronic disease from iron deficiency anemia or predicting cardiovascular disease or for a therapeutic approach to hyperphosphatemia. All of these aspects are potential clinical fields that need further investigations to determine the clinical impact of this interesting molecule.

Conclusion:

In conclusion, plasma levels of chemerin with inflammatory properties increased in chronic kidney disease. The level of this molecule may be directly correlated with inflammation in the hemodialytic patient. Therefore, the plasma level of adipokin can be used in the uremic patient as an indicator for differentiation between iron deficiency anemia and anemia of chronic disease, cardiovascular disease prediction, or hyperphosphatemia treatment approach. All the results of this research need further investigation with larger sample size.

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