Evaluation of serum Chemerin level in non-diabetic, Hemodialized patients

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Abstract

Background: Chronic Renal Failure (CRF) or chronic kidney disease (CKD) is the state which results from a permanent and usually progressive reduction in renal function and leads to many complications over a period of time. The most common complications include cardiovascular, cerebrovascular and peripheral vascular diseases. Most common causes of CRF are diabetes mellitus (diabetic nephropathy) and hypertention. Adipose tissue is now considered as an active endocrine gland secretes many metabolically active adipocytokines such as chemerin, visfatin, resistin and others that have important roles in complications and progression of metabolic diseases such as diabetes mellitus and other diseases like CRF and cardiovascular diseases (CVD). **Aim:** The aim of this study was to evaluate serum chemerin level and other biochemical and clinical markers in non-diabetic hemodialized patients, to determine the risk of CVD in non diabetic hemodialyzed patients. **Materials and methods:** This study was conducted for a sample composed of 50 patients with end stage renal disease (ESRD) or on hemodialysis (HD) and a control group consists of 50 apparently normal healthy subjects. Estimation of serum chemerin level by ELIZA, lipid profile, Blood urea, serum creatinine, serum albumin, serum electrolytes, serum uric acid and serum malondialdehyde (MDA) were done for both patients and control. Body mass index (BMI) and glomerular filtration rate (GFR) were calculated for both patients and control. Atherogenic index, CAD risk %, were also calculated for both HD patients and control. **Results:** The results of this study showed that the level of serum chemerin was significantly increased in CKD patients on hemodialysis compared to control. Blood urea, creatinine , TG, T-C, LDL-C,VLDL-C, MDA, uric acid, K^+, BMI and atherogenic index of plasma (AIP) levels were significantly increased in diabetic nephropathy patients compared to control, while, HDL-C, CAD risk %, Na^+, Ca^{+2}, PCV%, Hb and albumin levels were significantly decreased in ESRD patients compared to control. There was a non- significant difference of blood glucose for HD patients and control.

Key words: Chronic renal failure; Chronic kidney disease; End stage renal disease; Haemodialysis; Chemerin.

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الخـــلاصـــة

الفشل الكلوي المزمن هي الحالة التي تنتج عن انخفاض دائم وتدريجي عادة في وظائف الكلى ويؤدي إلى العديد من المضاعفات على مدى فترة من الزمن.المضاعفات الأكثر شيوعا تشمل أمراض القلب والأوعية الدموية. الأسباب الأكثر شيوعاً لمرض الفشل الكلوي المزمن هي مرض السكري و إرتفاع ضغط الدم. الأنسجة الدهنية في الوقت الحاضر تعتبر كغدد صماء نشطة تفرز العديد من المواد الالتهابية التي تسمى السايتوكينات (cytokines) مثل الكيميرين (chemerin) والفيسفاتين (visfatin) والريسستين (resistin) وغيرها.هذه السايتوكينات تتداخل مع حساسية الأنسولين ، الجلوكوز ، الايض الخلوي للدهون ومع العملية الالتهابية و لها أدوار هامة في مضاعفات وتطور الأمراض الأيضية مثل داء السكري وأمراض أخرى مثل الفشل الكلوي وأمراض القلب والأوعية الدموية. أجريت هذه الدراسة في مستشفى كركوك العام. وقد تم اختيار المرضى من وحدة غسيل الكلى في مستشفى كركوك العام وتضمنت الدراسة اخذ 50 عينة للمرضى المصابين بالفشل الكلوي المزمن في حين تم اخذ 50 عينة للأصحاء كمجموعة سيطرة للمقارنة. وكان الهدف من هذه الدراسة هو تقييم مستوى الكيميرين (chemerin) في مصل دم المرضى المصابين بالفشل الكلوي المزمن ، وكذلك دراسة اضطراب شحوم الدم، والإجهاد التأكسدي، ومؤشر كتلة الجسم، وفقر الدم، وحالة التغذية، وحمض اليوريك وغيرها في كل من هؤلاء المرضى والأصحاء.و تم استبعاد

مرضى السكري من هذه الدراسة. وأظهرت النتائج التي تم الحصول عليها وجود ارتفاع معنوي ($p \leq 0.05$) في مستويات الكيميرين في مصل دم المرضى المصابين بالفشل الكلوي المزمن عند المقارنة مع مجموعة الأصحاء. وأظهرت كذلك وجود ارتفاع معنوي ($p \leq 0.05$) في تركيز كل من اليوريا والكرياتنين وتركيزحامض اليوريك والبوتاسيوم والمالونديالديهايد ومؤشر تصلب الشرايين لدى مرضى الفشل الكلوي المزمن عند المقارنة مع مجموعة الأصحاء. كما كان هناك انخفاض معنوي في تركيز كل من الكالسيوم والصوديوم والالبومين والهيموغلوبين وعامل خطورة امراض القلب لدى مرضى متلازمه السكري الكلوي عند المقارنة مع مجموعة الأصحاء، في حين لم يكن هناك إختلاف معنوي في مستوى الكلوكوز لدى مرضى الفشل الكلوي المزمن عند المقارنة مع مجموعة الأصحاء. وخلصت الدراسة الى أن زيادة هرمون الكيميرين (chemerin) واضطراب شحوم الدم والإجهاد التأكسدي، وفقر الدم، و سوء التغذية لدى مرضى الفشل الكلوي المزمن يعزز تطور مرض الكلى ويمكن أن يسهم في تسريع تصلب الشرايين وأمراض القلب والأوعية الدموية ويمكن أن يزيد من معدلات الاعتلال والوفيات في مرضى الفشل الكلوي المزمن.

Introduction

Chronic renal failure (CRF) or also called chronic kidney disease (CKD) is the progressive loss of function of kidney and patient requires a long treatment in the form of renal replacement therapy. Haemodialysis is one of the renal replacement therapy, during which body's waste products, including creatinine, urea and excess water, are removed[(1)]. Chronic renal failure induces a slow and progressive decline of kidney function. It is usually a result of complications from another serious medical condition[(2)]. In chronic renal failure there is a steady and continued decrease in renal clearance or glomerular filtration rate (GFR), which leads to the gathering of urea, creatinine and other chemicals in the blood. CKD describes abnormal kidney function and/or structure[(1,2)]. Treatment of CRF includes medications and diet limitations, renal replacement therapy (that includes hemodialysis and peritoneal dialysis) and renal transplantation. Drug therapy for CRF including anti-hypertensive for hypertension, diuretics for oedema and hypertension, phosphate binders for hyper-phosphatemia, antibiotics, anticonvulsants for seizures, anti emetics (drugs that prevent vomiting) for nausea, laxatives for constipation, calcium for bone disorders and recombinant human erythropoietin for anemia[(3)]. There is evidence that treatment can prevent or delay the progression of CKD, reduce or prevent the development of complications, and reduce the risk of cardiovascular disease (CVD)[(4)]. CRF leads to many complications over a period of time. The most common include cardiovascular, cerebrovascular and peripheral vascular diseases[(5)]. CVD is the leading cause of morbidity and mortality in CKD patients, occurring even at the earliest stages of CKD without manifest vascular disease[(6)]. The cardiovascular mortality risk is substantially higher in dialysis patients than in an age-matched general population, CVD being the leading cause of death in individuals on dialysis[(7)]. Adipose tissue is an active endocrine organ that secretes several inflammatory cytokines, namely, adipokines, which interfere with insulin sensitivity, with glucose and lipid metabolism, and with the inflammatory process[(8)]. Adipokines contribute to renal and cardiovascular complications. In renal damage, various adipokines are involvedthrough mediating endothelial dysfunction, inducing oxidative stress and inflammation as well as stimulating renal sympathetic nervous activity, and it reduces cancellous bone but conversely increases cortical bone. Adipokines may also be involved in the development of renal anaemia[(9)]. Chemerin has been identified as a novel recently discovered adipocytokine that regulate adipocyte differentiation, modulate the expression of adipocyte genes, and play an important role in the pathogenesis of nephropathy[(10)]. Recent study revealed that levels of circulating chemerin was associated with a significant positive association with markers of inflammation and dyslipidaemia[(11)]. Chemerin is found to be highly expressed in adipose tissue and the liver, as well as by cells of the innate immune system, where it modulates the function of innate immune cells. As a result, chemerin may represent a link between obesity and inflammation and may be playing a potential role in the pathogenesis of atherosclerosis and cardiovascular complications[(12)].

Materials and Methods

This study was carried out in Kirkuk General Hospital. The patients of CRF were selected from Dialysis Unit in Kirkuk General Hospital. A total number of 50 patients were included in this study. They were clinically diagnosed by nephrologist as ESRD patients (on

hemodialysis), based on their history, clinical examination, renal function tests and other laboratory tests. Their ages range between (34-68) years with mean age of (50.18 ± 9.76), 25 of patients were male and 25 were female. For standardization and comparison, 50 apparently healthy individuals, neither smokers nor alcoholics, matched for sex, age and weight with the patient groups, were taken as controls, whose ages ranges (34 - 68) years with mean age of (48.86 ± 10.21), 26 were male and 24 were female.

Sample collection :- A fasting blood sample was collected to determine serum chemerin, lipid profile which includes triglycerides (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol(VLDL-C) for both patients and control. Atherogenic index and CAD risk %, were also calculated for both patients and control. Blood urea , creatinine, glucose, albumin, electrolytes, uric acid and MDA were also estimated for both patients and control. BMI and GFR were also calculated for patients and control group .

- Determination of serum chemerin was done using Human Chemerin ELISA Kit from CUSABIO.
- The BMI was calculated according to the equation[13]:

  BMI= weight (kg) / (height in meter) ^{2} (m^2)
- CAD-risk percentage was calculated by the following formula[14] :-

  CAD-risk (%) = HDL-C/TC %
- Atherogenic Index of plasma (AIP) can be calculated by the following formula[15] :-

  AIP = Log (Triglyceride/HDL-C)
- Serum MDA was determined using TBA assay[16].
- GFR was estimated using Cockcroft-Gault Formula[17]:-

$$\text{GFR} = \frac{(140 - \text{Age}) \times \text{Mass (in Kilograms)} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine (in mg / dl)}}$$

- Other biochemical parameters were determined using colorimetric methods.
- The data obtained in the current study was analyzed using SPSS program (version 18) .

Results

Table (1):- Clinical and biochemical parameters of HD patients compared to control groups

Parameters	Mean ± SD	
	HD patients	Control
S.Chemerin (ng/ml)	177.85 ± 20.19*	135.65 ± 15.66
B.Urea (mg/dl)	163.86± 43.51 *	34.52 ± 2.86
S.Creatinine (mg/dl)	7.26±1.97 *	0.81±0.092
S.Albumin (mg/dl)	3.46 ±0.75 *	4.23 ± 0.71
S.T-C (mg/dl)	221.24±23.89 *	191.83 ± 21.88

S.TG (mg/dl)	191.62±31.64*	143.51 ± 12.74
S.HDL-C (mg/dl)	39.55±7.91*	48.56 ± 11.12
S.LDL-C (mg/dl)	143.46±9.66*	114.57 ± 8.22
S.VLDL-C (mg/dl)	38.32±6.32*	28.7 ± 2.54
MDA (µmol/L)	2.31 ± 0.25*	1.38 ± 0.12
CAD risk (%)	17.87*	25.31
AIP	0.68*	0.47
Calcium(mmol/l)	1.92 ± 0.34*	2.33 ± 0.27
Sodium(mmol/l)	137.69 ± 4.86*	143.71 ± 3.52
Potassium(mmol/l)	5.87 ± 0.51*	4.36 ± 0.35
S.glucose (mg/dl)	98.76±12.57	94.34 ± 10.25
S.uric acid (mg/dl)	7.82±0.79*	5.27 ± 0.46
BMI (Kg/m^2)	27.87±3.46*	23.64 ± 2.35
GFR($ml/min/1.73m^2$)	9.64±4.23*	92.76 ± 7.48
PCV %	27.34±3.75*	40.73 ± 4.12
Hb (g/dl)	8.28±1.13*	12.34 ± 1.24

* *Significant*
($p \leq 0.05$) , non-significant ($p > 0.05$)

Table (2):- Correlation of serum chemerin levels with other clinical and biochemical parameters in HD patients

Parameters	Serum Chemerin (ng/ml)	
	r	*P value*
B.Urea (mg/dl)	0.721	0.019
S.Creatinine (mg/dl)	0.841	0.002
S.Albumin (mg/dl)	0.637	0.043
S.T-C (mg/dl)	0.718	0.019
S.TG (mg/dl)	0.915	0.000

S.HDL-C (mg/dl)	**- 0.986**	**0.000**
S.LDL-C (mg/dl)	**0.713**	**0.021**
S.VLDL-C (mg/dl)	**0.876**	**0.001**
MDA (µmol/L)	**0.776**	**0.008**
Atherogenic Index	**0.862**	**0.007**
CAD risk (%)	**- 0.805**	**0.005**
S.Ca^{+2} (mmol/l)	**0.341**	**0.335**
S.Na^{+} (mmol/l)	**- 0.323**	**0.363**
S.K^{+}(mmol/l)	**- 0.160**	**0.660**
S.glucose (mg/dl)	**-0.502**	**0.139**
S.uric acid (mg/dl)	**0.703**	**0.023**
BMI (Kg/m^2)	**0.974**	**0.000**
GFR($ml/min/1.73m^2$)	**- 0.966**	**0.000**
PCV %	**- 0.062**	**0.864**
Hb (g/dl)	**0.074**	**0.839**

Significant ($p \leq 0.05$) , non-significant ($p > 0.05$), r : Pearson's correlation coefficients

Discussion

In this present study, it was found a prevalence of high levels of serum chemerin in CKD patients on HD or end stage renal disease (ESRD). These results were in accordance with the results of other previous and recent studies done in other areas and countries[18-20]. The reasons of this observed increase are obscure, but may be due to enhanced tissue production and substantial chemerin gene expression that was found in various tissues[21,22]. However, the results of some previous and recent studies indicated that the regulatory factors mainly affect on chemerin gene expression are located in adipose tissue and thus, the increased chemerin production by visceral adipose tissue, subcutaneous adipose tissue and/or other tissues contribute to its high serum level observed in patients with CKD, and this is probably the main source of circulating chemerin level[20,23,24]. Therefore, this study and other studies demonstrated a statistically significant positive correlation of S.chemerin level with BMI that is mainly influenced by the amounts of fat mass that is considered as a major source of chemerin secretion[25,26]. Other recent studies found a strong association between circulating chemerin and kidney function. These studies suggested a connection between high chemerin concentrations and a progression of impaired kidney function and that high plasma chemerin is predictive of renal impairment and thus, patients with elevated chemerin levels are more prone to impaired GFR. A lower GFR was linked to high chemerin levels. These studies also demonstrated that patients with high plasma chemerin levels are at a significantly higher cardiovascular risk[19,26,27]. Therefore, this present study

revealed a significant negative correlation of S.chemerin level with GFR including a consistent increase in chemerin levels in patients with CKD, and thus recent study demonstrated that in patients with end stage renal disease after kidney transplantation, the GFR increased and reached a value higher than 50 ml/min and the serum chemerin concentrations decreased to the values observed in healthy subjects[19]. This study revealed a significantly positive correlation of S.chemerin with both B.urea and S.creatinine.These results were in accordance with other studies[20,28]. These results indicated that serum chemerin found to be elevated in CKD patients with the advancing stages of CKD, and that progressive loss of renal excretion capacity may be involved in the pathogenesis of chemerin accumulation[20]. Hence, chemerin was considered as uremic toxin and may be partially responsible for the metabolic disorders observed in renal failure[29]. This study presented a significantly positive correlation of serum chemerin level with serum albumin level. These results were in agreement with results of other studies[30,31]. These findings indicate the association between serum chemerin levels and nutritional status. Regarding the findings that malnutrition leads to worse cardiovascular outcomes and death in prevalent HD patients, and that HD patients with higher chemerin levels would have a superior nutritional condition and as a result, more favourable cardiovascular outcomes[31,32]. This study showed a significantly positive correlation of S.chemerin with S.T-C, S.TG, S.VLDL-C and S.LDL-C, while, it revealed a significantly negative correlation between S.chemerin and S.HDL-C. These results are in agreement with the results of other researchers[18,20]. These results denote that S.chemerin is associated with dyslipidemia in HD patients. This dyslipidemia that involves increased S.TG, increased S.T-C, increased S.VLDL-C, increased S.LDL-C and reduced S.HDL-C, is responsible for increased atherosclerotic cardiovascular complications in CKD patients with ESRD in addition to progression and pathogenesis of renal disease[33]. This study demonstrated a significant positive correlation of S.chemerin with AIP, whereas there was a significant negative correlation of S.chemerin with CAD risk percentage. This reveals a strong association between circulating chemerin with lipid ratio, AIP and CAD risk % that are considered as cardiovascular risk factors, denoting that circulating chemerin is a predictive marker of the occurence of atherosclerosis and coronary artery disease (CAD)[34,14].This study exhibited a significant positive correlation of S.chemerin with BMI in HD patients. This result was in accordance with the results of other studies[20,35]. This indicates that increased BMI and thus, the increased amount of adipose tissue itself could have been responsible for the enhanced chemerin release and contributing to its high serum concentration[20]. BMI has been considered as a common, strong, and potentially modifiable independent risk factor for CKD. Obesity is also a risk factor for progressive renal function loss in patients with known renal disease. In addition, a high BMI is associated with glomerular hyperperfusion and hyperfiltration, resulting in renal injury with proteinuria obesity-related glomerulopathy[36]. This present study exhibited a significant positive correlation of S.chemerin with S.uric acid level.This result was in agreement with results of other study[37]. Increased serum uric acid level or hyperuricemia in patients with CKD associated with an increased risk for cardiovascular mortality. Arterial stiffness may be one of the possible mechanisms by which hyperuricemia increases the risk of CKD and CVD through a pathway that involves changes in vascular elastic properties, hypertension and organ damage[38].This study exhibited that S.chemerin levels are positively correlated with S.MDA that is an oxidative stress marker. This result was in accordance with the result of other study[39]. Elevation of oxidative stress levels contribute to increased morbidity and mortality in CKD patients by enhancing atherosclerosis and cardiovascular complications, and may also promote the progression of renal disease in these patients[40].This present study showed a significant negative correlation of S.chemerin with GFR. This result was in agreement with the results of other recent studies [25,26,39]. A significant negative correlation of S.chemerin with GFR, indicates that the reduction of renal function may have a significant impact on serum chemerin concentrations and that circulating levels of chemerin are related inversely to GFR. Therefore, even in CKD patients with mild renal dysfunction, had significant accumulations of

chemerin. This denotes that the progressive loss of renal excretion capacity could be involved in the pathogenesis of circulating chemerin accumulation and that increased chemerin levels are predictive markers for renal impairment[20,26].

Conclusion

From this present study, we conclude that elevated circulating chemerin in non diabetic hemodialyzed patients probably enhances progression of renal disease and accelerates the atherosclerosis and cardiovascular disease and may increase the morbidity and mortality in CKD patients with ESRD.

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