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Research Article

LEPTIN LEVEL RELATIONSHIP WITH NUTRITIONAL, INFLAMMATORY AND CARDIOVASCULAR RISK FACTORS IN NON-DIABETIC ESRD IRAQI PATIENTS

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ABSTRACT

Background: Recent studies have shown a positive correlation between Inflammatory markers and anorexia in CKD patients, which is a direct contributor to higher hospitalization rates, and higher death rates in hemodialysis patients. In addition, the impairment of renal function exhibits significant alterations in lipoprotein metabolism, which result in the development of severe dyslipidemia, that leads to the development of CVD. Objective: To evaluate the relationship between serum leptin with nutritional inflammatory and cardiovascular risk factors in non-diabetic ESRD Iraqi patients. Subjects & methods: Determination of serum leptin in 51 non-diabetic end stage renal disease patients and comparing it to the serum leptin in 47 healthy controls by ELISA. In addition, determination of serum hsCRP as a most important inflammatory factor, serum albumin and serum cholesterol as nutritional and atherosclerotic factor respectively. Results: serum leptin level is significantly higher in the patient group than the healthy control group (75.9± 23.7 *vs* 32.5±16.6). In addition, the serum leptin level is positively correlated with serum has CRP level ($r = 0.45$, $p < 0.01$), serum cholesterol ($r = 0.29$, $p < 0.05$) respectively. Conclusion: Leptin can be considered as a nutritional and inflammatory marker in non-diabetic ESRD Iraqi patients.

Key word: Leptin, hsCRP, dyslipidemia, end stage renal disease, cardiovascular disease

INTRODUCTION

Malnutrition is one of the most common clinical problems in end-stage renal disease (ESRD) patients. It may be associated with restricted diet, loss of appetite and reduced intake of dietary energy and leads to weight loss which contributes to anorexia and malnutrition progression, in addition to the effect of medications, inflammation, and their uremia status. All these factors lead to an increase in morbidity and mortality in haemodialysis patients [1-3]. A significant decline in nutritional parameters such as the serum albumin levels because of low energy and protein intake was found to be associated with increased risk of morbidity and mortality in advanced chronic kidney disease (CKD) patients [4]. A decrease in food intake occurs spontaneously during a progressive decline in kidney function, and this is due to the accumulation of uremic toxins which stimulate the disorders of the central nervous system and adipose tissue and affect diminished appetite [3]. Recent studies have shown a positive correlation between Inflammatory markers and anorexia in CKD patients, which is a direct contributor to higher hospitalization rates, and higher death rates in hemodialysis (HD) patients [5,6,7].

Leptin is adipocytokine, which is a 16-kDa protein hormone made up of 167 amino acids that acts on the hypothalamus to regulate food intake and energy expenditure[1]. The kidney is responsible for about of 80% of leptin clearance in healthy individuals; it is cleared from the circulation by glomerular filtration followed by metabolic degradation in renal tubules. This decrease in renal clearance may be the main reason which explains hyperleptinemia in ESRD patients on maintenance dialysis. Leptin has been shown to be related to several metabolic, inflammatory, and hemostatic factors involved in the development of hypertension and cardiovascular disease [8]. The stimulation of leptin release from adipocytes may be caused by cytokines mediating the inflammatory response, which frequently occur in ESRD patients on dialysis [9]. It has been suggested that leptin plays an important role in inducing anorexia and malnutrition in ESRD patients but the mechanism of its effects on the progressive malnutrition in kidney failure and its clinical significance are not clearly understood [3]. There are many postulated mechanisms of involvement of leptin in both development, and progression of CKD either by increasing blood pressure through its stimulation of the sympathetic nervous system and promoting renal sodium reabsorption [9,10] or through inducing renal injury by stimulating renal endothelial cell proliferation and increased mesangial cell production, leading to renal scarring through the production of collagen (type I and type IV). This will lead to renal fibrosis and proteinuria [11].

The dyslipidemia in ESRD patients is linked to the risk of cardiovascular disease. Usually there is an increase in triacylglycerol-rich lipoprotein concentration (VLDL) and decreased high density lipoprotein concentration (HDL-C), while total cholesterol and low-density lipoprotein (LDL-C) concentrations are not increased. The impairment of renal function exhibits significant alterations in lipoprotein metabolism, which may result in the development of severe dyslipidemia. However, the exact role of these alterations in the pathogenesis of atherosclerosis in individuals with CKD is still controversial [12-14].

The aim of this study was to study the relationship between leptin levels and inflammation, nutritional and cardiovascular factors in non-diabetic ESRD Iraqi patients on maintenance hemodialysis.

MATERIALS AND METHODS

Subjects: This study included ESRD patients, (n=51) (20 females, 31 males) all patients were undergoing hemodialysis (3 times week). The range of age was between 30-60 years. They were from Kidney disease and Transplantation Unit at Baghdad Teaching Hospital during the period from November 2016 to feburay2017. The study also included healthy control (n= 47) of matching age and weight (27 females, 20 males). Exclusion criteria include ESRD with diabetes mellitus.

Ethical clearance certificate: That study is carried out as per International conference of Harmonization-Good Clinical Practices Guidelines (ICH-GCP) or as per Declaration of Helsinki guidelines. The number of ethical permissions (5471) issued by Baghdad College of medical sciences.

Methods: Fasting venous blood (10ml) was withdrawn from both patients and controls. The blood samples were collected from the patient pre-hemodialysis. After the blood samples were collected in a plain tube and centrifuged for 15 minutes at 3000 r pm after being allowed to clot at room temperature for 30 minutes. The separated serum was divided into aliquots and stored frozen at (-20 c°) to be used later for leptin, hsCRP, Cystatin -c determination by Enzyme-Linked Immune Sorbent Assay (ELISA). While blood glucose, lipid profile, urea and creatinine analysis were done immediately after separation of the serum. The quantitative determination of Glomerular filtration rate is calculated by CKD EPI Calculator - four variables MDRD CKD EPI equation With SI Units using standardized serum creatinine, age, race, gender, white or another race male [15]. Body mass index was calculated as body weight in Kg/Sq height (meter) [2 16].

Statistical study

All values were expressed as mean ± standard deviation (mean ±SD). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version23.0). Independent student t-test was performed to assess differences between two means. The Pearson correlation coefficient was used to determine the correlation between quantitative data. P value < 0.05 was considered significant.

DISCUSSION

The results of the present study have shown significantly higher serum leptin levels in patients with advanced CKD, particularly in those undergoing dialysis in comparing with the control group ($p < 0.01$).There is a close agreement with results reported by two previous studies [17,18]. There was a significant negative correlation between leptin level and e GFR as shown in figure 1and positively correlated with creatinine ($r=0.38$,$p<0.010$) and cystatin c, ($r= 0.31$ $p<0.05$) which are the most important markers for the assessment of renal function in CKD patients [19]. In addition, there seem to be other factors that affect leptin levels in heamodialysis patients. One of these factors is the metabolic acidosis that reduces the release of leptin from adipocytes. Moreover, uremic factors of unclear origin reduce leptin gene expression in adipocytes as a negative feedback due to decreased elimination [20-22]. On the other hand, and according to a previous study, which concluded that leptin in renal disease is responsible for the systemic inflammatory response modification and may be associated with elevation of leptin gene expression due to stimulation of leptin mRNA [23].

The present study had shown a significant positive correlation between serum leptin levels and serum hsCRP in ESRD patients as shown in figure 2. There is a significant agreement of these results with other studies which observed that ESRD patients with high leptin levels had more inflammatory activation ,which is represented by high levels of serum hsCRF [24- 26], this may increase the rate of mortality in ESRD patients who are on maintenance haemodialysis due to cardiovascular disease (CVD) based on the critical role of hsCRP in endothelial injury, and pathogenesis of atherosclerosis[27]. hsCRP is an important inflammatory marker that plays a role in cytokine release, was associated with increased rate of mortality in ESRD patients [17,28,29]. Bonanni et al in their study had concluded that the increase in inflammatory marker levels in HD patients, may be related to the exposure of blood to bio incompatible dialysis membranes [30.]

Other important risk factors that play role in CVD in hemodialyized patients is the obesity which leads to dyslipidemia. In this study there was significant correlation between leptin level and BMI ($r=0.29$, $p < 0.05$) as in figure 3. Many studies showed similar results[31-33.] Evidence from recent studies concluded that dyslipidemia is the strongest risk factor of CVD [26,34]. In addition, in the present study the leptin levels were correlated positively and significantly with cholesterol levels in ESRD patients ($r= 0.291$, $p< 0.05$), while there were no significant correlations between leptin and other lipid profile parameters in the patient group. In accordance with the finding of this study. Svobodova *et al,* in their study, reported that the serum leptin level was correlated positively with serum cholesterol and triglyceride levels in heamodialysis patients [35]. There were many previous studies with different results e.g. Fox et al in their study had detected that dialysis patients with higher serum cholesterol have lower mortality rates, depict that hemodialysis patients have a high risk of atherosclerotic cardiovascular disease [36]. Another study had shown that the one of the reasons of the development of protein-energy malnutrition has been attributed to the increase in the serum leptin level that may reduce nutrient intake manifested by the decrease in cholesterol level[37]. Another hypothesis considered that hyper cholesterolemia is a one risk factor for all causes of CVD mortality in ESRD patients and that this association is masked among individuals with inflammation and/or malnutrition. Several studies support the notion that a high cholesterol level contributes to a higher risk of CVD or mortality in dialysis patients[14,38-40]. Both malnutrition and hypoalbuminemia, which are important clinical features in advanced CKD are the most powerful predictors of morbidity and mortality of ESRD patients undergoing dialysis [41]. In this study there was a significant difference in albumin level between ESRD patients and control groups ($p< 0.001$). On the other hand, a negative correlation was identified between leptin level and albumin level, but not significant. Other studies showed different results; the findings of two previous studies showed significant negative correlation [42,43] while a recent study in 2015 showed a positive significant correlation between them [26]. Kayardi et al in their study did not reveal a correlation between serum leptin levels, and albumin [44].

Another finding of this study is hsCRP levels were negatively correlated with the albumin levels in the patient group ($r= -0.28$, $p< 0.05$). In heamodialysis patients the serum albumin generation is inhibited due to the increase in serum CRP. Hypo albuminemia may be a powerful marker of anorexia and can be used in the diagnosis of malnutrition in advanced renal failure patients. Since the hsCRP is an acute - phase response which decreases hepatic synthesis of albumin and increases its catabolism, thus much of the observed association of albumin level with outcomes may be attributed to inflammation rather than malnutrition in the ESRD population [45].

Table 1: Comparison between serum variables in chronic kidney disease (CKD) patients (stage 5) and their controls

Parameter	CKD (stage 5) (n= 52)	Control (n=47)	P value
Age (year)	42.4±13.6	41.1± 13.7	> 0.05
Body mass index (Kg/m^2)	26± 3.1	26.3±3.4	> 0.05
leptin (ng/ml)	75.9± 23.7	32.5±16.6	< 0.01
hsCRP (µg/ml)	9.2±2.5	1.3±0.65	< 0.01
Cys-c (ng/ml)	9.6±4.9	5.2±1.3	< 0.01
eGFR (mL/min/1.73 m^2)	7.7±3.7	122.7±31	< 0.01
FBS (m.mol/l)	5.6±0.6	5.7±0.68	> 0.05
Urea (m.mol/l)	48.2±21.7	11±1.9	< 0.01
Creatinine (µmol/l)	820.6± 304.3	69.6±10	< 0.01
Triglyceride (m.mo/l)	2.1±0.3	1.7±0.16	< 0.01
Cholesterol (m.mo/l)	5.0±0.7	4.6±0.4	< 0.01
Albumin (mg/dl)	3.3±.36	4.2±0.61	< 0.001

Significant p< 0.01, highly significant p< 0.001, not significant p> 0.05

Table 2: Correlation between serum leptin and serum cystatin-c and serum creatinine and between hsCRP and serum albumin in CKD patients (stage 5)

Parameter	r value	P value
Leptin *Vs* cystatin-c	0.31	< 0.05
Leptin *Vs* creatinine	0.38	<0.01
hs CRP *Vs* albumin	-0.28	<0.05

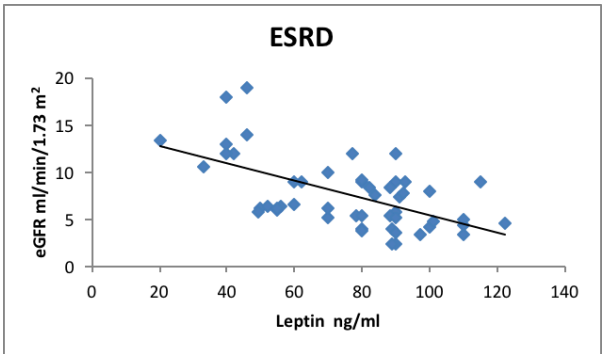

Fig 1: **Correlation between serum leptin and eGFR (r = - 0.58, p <0.01) in CKD patients (stage5)**

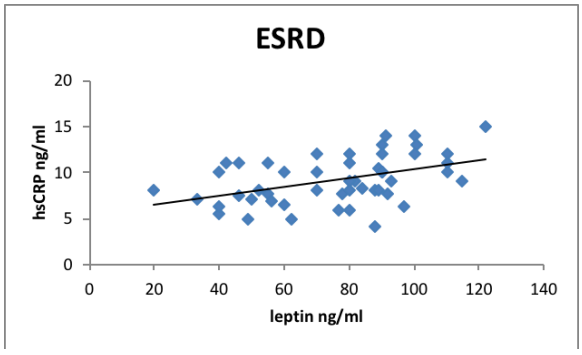

Fig. 2: **Correlation between serum leptin and hsCRP (r = 0.45, p <0.01) in CKD patients (stage5)**

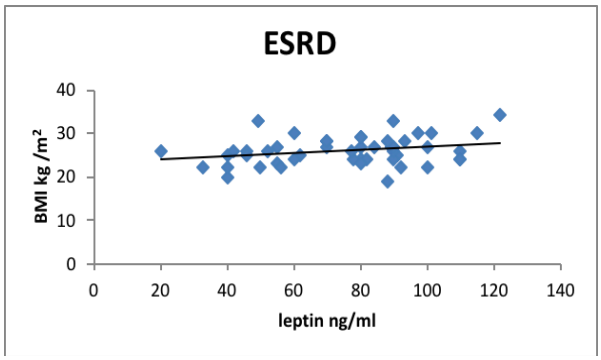

Fig. 3: **Correlation between serum leptin and BMI (r = 0.3, p <0.05) in CKD patients (stage5)**

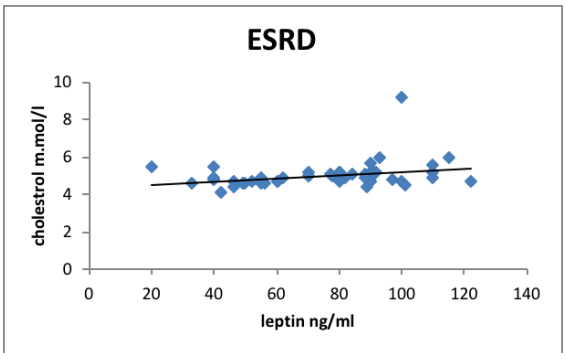

Fig. 4: Correlation between serum leptin and cholesterol (r = 0.29, p <0.05) in CKD patients (stage5)

CONCLUSION

From the results of the present study, the elevation of serum leptin levels in ESRD patients appears to be associated with impairment of nutritional markers, e.g. Albumin, and cholesterol, and with weight changes in patients (BMI), and this could be due to the leptin effect on metabolic processes, including appetite and nutritional status, if there is no down - regulation in leptin receptors. So, the chronic increase in leptin levels can be one of the factors that play a role in anorexia and protein energy wasting in the ESRD population. In addition to its correlation with hsCRP which contributed to CVD complications in ESRD patients. Leptin can be considered as a nutritional and inflammatory marker in non-diabetic ESRD Iraqi patients on maintenance dialysis.

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