Role of Leptin and dyslipidemia in chronic kidney disease

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Abstract: Chronic kidney disease (CKD) patients are at an increased risk of cardiovascular complications and plasma leptin level is elevated in cardio renal syndrome. We wanted to explore leptin levels in patients with different stages of CKD and find its association with risk of cardiovascular disease. This cross-sectional study was conducted in Nephrology Department of Jinnah Post Graduate Medical Centre (JPMC) from January 2014 to September 2014. Group I comprised of controls (GFR=116±8.3, n = 44) acquired from general population, CKD patients were grouped as II, III and IV respectively with GFR; 85.77±9.9 (n = 42), 53.84±9.9 (n=42) and 20.22±8.4 (n = 42).CKD patients with any inflammatory disease, Diabetes Mellitus and on steroid therapy were excluded. Serum leptin, lipid profile and C reactive proteins (CRP) were measured. Leptin and CRP levels increased significantly with progression of CKD. High density lipoproteins (HDL) to low density lipoproteins (LDL) ratio was significantly high in control as compared to CKD groups (p<0.001). A positive correlation of leptin was observed with CRP and HDL/LDL ratio (r= 0.994,p<0.001 and r=-0.403 p<0.001) respectively. Hyperleptinemia observed with progression of CKD contributed to pathogenesis of cardiovascular disease by decreasing HDL/LDL ratio.

Keywords: Chronic Kidney disease, C reactive protein, Leptin, HDL/LDL ratio.

INTRODUCTION

End-stage renal disease (ESRD) is a complication of impaired renal function and chronic kidney disease (CKD) associated with increased morbidity, mortality, and increases the risk of cardiac disease (CVD). The prevalence of CKD is high in Pakistani population, since incidence of hypertension and diabetes in our inhabitants is one of the highest in the world.

CKD is linked to a series of multiple toxic physiological and metabolic functions. Diabetes and hypertension as being its complication are concomitant with lethal outcomes. An increased risk of CVD in these patients can lead to mortality(Locatelli et al., 2003) which is attributed to inflammatory and oxidative stress, erythropoietin(EPO) resistance leading to anemia(Kazory and Ross 2009), vitamin D deficiency (Levin and Li 2005) and vascular calcification (Mizobuchi et al., 2009). Adipocytokines such as leptin, are also potentially involved in the pathogenesis of metabolic syndrome (e.g. dyslipidemia) in End-stage renal disease (Mak and Cheung 2007).

Leptin is an adipose tissue-derived hormone that has been associated to numerous metabolic and inflammatory factors involved in the pathogenesis of hypertension and cardiovascular disease (Wannamethee et al., 2007). Increased leptin levels are in response to high energy deposition in the form of adipocytes and obesity, irrespective of the degree of BMI (Fatima et al., 2013). In renal disease the scenario is much different, as the initially CKD may be altered with change in grades of obesity; and therefore increasing leptin levels and resistance (fig. 1). Hyperleptinemia is observed in patients during CKD progression and potentially anorexic-cachectic syndrome. However, histological changes in the basement membrane from initial to end stage disease may also contribute to the decreased levels of leptin at the end stage of CKD (Becker et al., 2005). Leptin is known to be important in the regulation of food desire, body composition and might also be responsible for metabolic changes during CKD leading to inflammation and loss of lean body mass (Mak et al., 2006).

Fig. 1: This diagram shows the illustration of the hypothetical mechanism of etiology of Chronic Kidney Disease.

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The etiology of kidney dysfunction may initially be associated with long-standing obesity and insulin resistance, like the metabolic syndrome (MetS). Leptin is predominantly washed out from the circulation by the kidneys after the metabolic degradation in the renal tubules (Cumin et al., 1996). Shamsuzzaman et al. (2004) established an association between serum levels of leptin and C-reactive protein (CRP) in healthy young adults. Leptin plays a role in stimulating the sympathetic system and C-reactive protein (CRP) in healthy young adults. A study established an association between serum levels of leptin and inflammatory disease and patient on steroid therapy. Total 170 were divided into four groups as: Group I control subjects (GFR=116±8.3, n = 44), recruited from BBS, Aga Khan University. Group II, III and IV were CKD patients with GFR; 85.77±9.9 (n = 42), 53.84±9.9 (n = 42) and 20.22±8.4 (n = 42), respectively were enrolled from Nephrology department of JPMC.

Ethics statement
The research protocol was approved by the Institutional Review Board of the Basic Medical Science Institute, Jinnah Postgraduate Medical Centre (NO.F.1-2/2013/BMSI-E.COMT/003/ JPMC). Written informed consents were attained from study subjects and all investigations were conducted in accordance with the principles expressed in the Declaration of Helsinki. Consent for the publication of the clinical details was also obtained.

Study participants
This cross-sectional study was conducted in the Department of Biological and Biomedical Sciences (BBS), Aga Khan University in collaboration with the Nephrology Department of J.P.M.C. during the period of January 2014 to September 2014. Two hundred patients were recruited for the study out of which 170 subjects were enrolled in present study. CKD patients between the ages 35- 45 years without any known cardiovascular disease were recruited. We excluded the patients with Diabetes Mellitus, liver disease, acute or chronic inflammatory disease and patient on steroid therapy. Total of 170 were divided into four groups as: Group I control subjects (GFR=116±8.3, n = 44), recruited from BBS, Aga Khan University. Group II, III and IV were CKD patients with GFR; 85.77±9.9 (n = 42), 53.84±9.9 (n = 42) and 20.22±8.4 (n = 42), respectively were enrolled from Nephrology department of JPMC.

MATERIALS AND METHODS

Data collection
At the time of enrollment questionnaire was employed to record the baseline demographic and clinical data of the study subjects from their medical records. All study participants were requested to come with 10-12 hours overnight fasting for sample collection. The analysis of biochemical parameters including Cholesterol, Triglycerides and HDL-c were measured by spectrophotometry using commercially available Merck kits. Low density lipoprotein (LDL-c) was measure by Friedwal’s formula (Friedwald et al., 1972). CRP (mg/dl) were determined by Enzyme Linked Immuno-Sorbent Assay kit method Glomerular filtration rate (GFR) was estimated by Cockcroft & Gault equation(Cockcroft and Gault 1976). Serum leptin levels were measured by commercially available ELISA kits method. Serum HDL-cholesterol was determined by kit manufactured by Merck, France. LDL-cholesterol was calculated according to Friedewald’s formula (Friedewald et al., 1972). Triglycerides were determined by using Glycerol-3-Phosphate Oxidase Phenol Aminophenanzone (GPO-PAP) method, by Merck, France. Serum cholesterol was estimated by enzymatic colorimetric (CHOD-PAP) method, manufactured by Merck, France (Rifai and Warnick 2006).

STATISTICAL ANALYSIS
In this study SPSS (version 11; SPSS Inc., Chicago, IL, USA) was used to statistically analyze the descriptive data of continuous variables including age, height, weight, BMI and blood pressure along with serum Cholesterol, Triglycerides, HDL-C and LDL-c mean ± standard deviation (SD). Statistical comparisons were calculated using a student t-test and Mann Whitney U test for continuous/quantitative variables. Pearson’s coefficient of correlation (r) was used for the determination of the correlation of GFR levels with and lipid profile. In all statistical analysis performed p-values <0.05 were considered significant.

RESULTS
Total of 170 subjects had mean BMI of 22.32±0.9 Kg/m² and mean leptin levels 8.26±4.6 ng/ml. Leptin levels increased significantly with progression of CKD. CRP was significantly increased in CKD groups as compared to group I (table 1). In lipid profile, cholesterol, triglyceride and LDL were significantly high in CKD groups (p<0.001), while HDL was significantly low.
The HDL/LDL ratio was significantly reduced with progression of CKD. A positive correlation was observed between leptin and CRP as shown in fig. 2 (r=0.994, p<0.001). Correlation of Leptin with HDL/LDL ratio showed an inverse correlation r=-0.403 with p<0.001.

**DISCUSSION**

There have been various studies exploring the serum leptin levels in different conditions but none points out it’s relation to metabolic dysfunction in CKD Pakistani population. To fill this gap we designed this study to assess the levels of leptin and CRP in CKD patients.

Generally, high plasma concentrations of cholesterol, LDL, and to some extent high total triglyceride concentrations with low concentrations of HDL, are associated with increased atherosclerotic CVD risk (Kwan et al., 2007, Thomas et al., 2008). Same pattern of uremic lipid profile has been evident in our CKD population with gradual shift towards altered cholesterol, triglyceride and HDL. Various elements are concomitant with the development of dyslipidemia in chronic renal impairment (Kwan et al., 2007).

Inflammation probably plays a key role in the initiation and progression of the atherosclerotic process (Ross 1999). High serum concentrations of systemic inflammatory markers such as CRP have been associated with atherosclerosis (Stenvinkel et al., 2008).

It has been observed that increased BMI of CKD patients mediate link between obesity and CVD by its effects on arterial pressure (Menendez et al., 2000), inflammatory vascular response (Konstantinides et al., 2001, Bodary et al., 2002), and platelet aggregation (Chaldakov et al., 2001, Cooke and Oka 2002). Several studies advocate that adipose tissue releases leptin (Friedman and Halaas 1998) which possesses cytokine-like properties which is responsible for elevated IL-6 and C reactive proteins. The research of ours study highlight the role of Leptin in patients of normal BMI. Our study is strengthened by other studies in CKD patients where CRP was found to be associated with renal disease explained by the reactive oxygen specie being activated and causing an inflammatory condition. This inflammation under such conditions might cause altered lipid profile, thus increase risk for cardiovascular involvement (Briffa et al., 2013).

**CONCLUSION**

Hyperleptinemia in progressive CKD patients of our population demonstrated high CRP with low HDL/LDL ratio. This association explains the relationship of raised Leptin levels and CRP in progression of CKD as well as metabolic dysregulation that may lead to pathogenesis of cardiovascular disease in advanced CKD patients.

**Implication of the study**

Future longitudinal studies are required to explicate the possible mechanisms by which leptin causes metabolic dys regulations in cardiovascular diseases.
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