Original Article

LEPTIN- a key player in chronic kidney disease

Ponnudhali D [1], Nagarajan P[2]

[1] Professor & HOD, Department of Biochemistry, VMKV medical college, Salem.
[2] Professor & HOD, Dept of Nephrology, GMKMCH, Salem.

Abstract:

Background: Leptin is an adipose derived protein hormone, involved in body weight regulation. It is found to play an important role in the development of chronic kidney disease (CKD) by various metabolic and inflammatory mechanisms.

Aim: To assess the serum leptin levels in chronic kidney disease and to analyze its correlation with GFR, BMI, insulin and insulin resistance.

Materials & methods: Serum leptin and insulin levels were measured in 45 non-diabetic CKD patients (group 1) and 45 healthy controls (group 2). Serum leptin and insulin were measured using DRG & Monobind ELISA kits. HOMA- IR &BMI were calculated and the values taken. The statistical analysisof Independent student t- test & Pearson's correlation were performed using SPSS 26 software.

Results: Serum Leptin levels were significantly increased in group 1 -CKD patients (15.8 ± 2.76ng/ml) compared with group 2 -healthy controls (6.31± 0.87 ng/ml) P=0.003. Serum insulin levels were also significantly increased in the CKD group (14.34 ± 8.23 µU/ml) from that of healthy individuals (6.40 ± 1.16 µU/ml), P= 0.000. There were positive significant correlations of serum leptin with BMI& Insulin (p=0.000)& negative correlation of leptin with GFR.

Conclusion: Leptin may independently contribute to GFR decline in the kidney and could have a nephrotoxic potential, resulting in CKD.

Key words: Leptin, chronic kidney disease, CKD, leptin resistance, insulin resistance.

Corresponding Author: Dr. Ponnudhali. D, Professor & HOD, Department of Biochemistry, VMKV medical college, Salem.
Email: ponnudhalid@gmail.com

Introduction:

Chronic kidney disease has been known to be associated with metabolic syndrome and insulin resistance and cardiovascular disease (1,2).Obesity is considered as an important risk factor for CKD and the relationship between obesity and CKD has been studied in detail. Impaired renal function in obesity is due to glomerular hyperfiltration and leptin mediated glomerular injury (3,4,5).

Leptin is an adipocyte derived hormone, abundantly produced by adipose tissue and is associated with obesity, metabolic syndrome and CKD. It is an 167 amino acid protein produced by Ob gene in adipocytes and secreted by the white adipose tissue, it is also produced from brown adipose tissue, stomach, placenta, mammary gland, ovarian follicles and some fetal organs (6). It causes decreased food intake, induces satiety and increases energy expenditure, by decreasing neuropeptide Y (7).

Leptin is a uremic toxin, postulated to be involved in the pathogenesis as well as progression of CKD. Leptin has been found to be inversely associated with eGFR and currently there are some studies, suggestingthat its levels are increased in patients with chronic kidney disease

(3,7,8). Hence we chose to assess serum leptin levels in our population, with an aim of understanding the relationship betweenserum leptin levels and CKD.

Materials & Methods:

It is a case-control study, conducted in patients attending the outpatient department of Nephrology, Government Mohan Kumaramangalam Medical College Hospital, Salem. We have recruited 45 non-diabetic patients with chronic kidney disease who were not on dialysis and another 45 healthy non-diabetic controls, for the study. Written consent was obtained from all the subjects after clearly explaining the study protocol with them. We had obtained ethical clearance from ethical committee of Govt Mohan Kumaramangalam Medical College Hospital.

We have divided the study subjects into 2 groups. Group1 :45 non-diabetic predialysis chronic kidney disease patients and group 2:45 non- diabetic healthy controls.

Group 1 individuals were with chronic Kidney Disease (CKD) were diagnosed and staged, based on NKF K/DOQI guidelines (9). The study group 1 included CKD patients, not on hemodialysis/ peritoneal dialysis. Patients with history of diabetes, metabolic syndrome, endocrine disorders, obesity, pregnancy, malignancy or any other terminal illness were excluded from the study.

The control group 2 individuals were healthy adults with normal renal function (GFR > 90 ml/min). Subjects with diabetes, hypertension, renal disease, chronic infections, pregnancy, systemic illness, endocrine disorders, malignancy or neuropsychiatric illness were excluded from the study. All subjects in both the control and study group were age and sex matched.

Group 1 comprised of 45 non diabetic patients with Chronic Kidney Disease (CKD). Group 2 acted as controls and consisted of 45 healthy adults with normal renal function (GFR > 90 ml/min).

Laboratory analysis:

Blood samples were collected from patients, after an overnight fast of 8 hrs, then fasting blood samples were collected from both CKD patients and healthy controls. Next the plasma /serum were separated soon after collection, and stored at -20°C , till the biochemical parameters were analysed.

Complete blood count, urine routine, blood glucose, urea and creatinine were estimated using the semi autoanalyzer-Microlab 300, in the clinical Biochemistry Laboratory, VMKVMCH in Salem. Serum Leptin was analyzed using DRG (sandwich) EIA 2395 ELISA kit (10). Serum Insulin was analyzed using Monobind's Insulin/ MAPS ELISA kit (11).

Calculated parameters: Homeostasis model assessment-Insulin Resistance (HOMA-IR) was calculated using the formula, HOMA-IR = fasting serum insulin (μIU/ml)* fasting plasma glucose (mg/ dl)/405 (12). GFR was calculated using the MDRD (Modification of Diet in Renal Disease) formula available online (13).

Statistical analysis: All the parameters were compared in both the groups 1& 2 using student independent't' test and Pearson's correlations were made using the SPSS 26 version software.

RESULTS:

We recruited 90non-diabetic individuals for the study, among them 45 were predialysis CKD patients and the remaining 45 were healthy controls. We analyzed the serum leptin, insulin levels in the individuals, along with measuring their GFR and BMI.

We found that serum Leptin levels were significantly increased in the chronic kidney disease patients (15.8 ± 2.76ng/ml) compared with their healthy counterparts

(6.31± 0.87 ng/ml) with P=0.003. Serum insulin levels were also significantly increased in the CKD group1 (14.34 ± 8.23 µU/ml) from that of the healthy individuals (6.40 ± 1.16 µU/ml), with a P-value of 0.000. The group1 participants had higher HOMA-IR scores (3.42 ± 2.17) compared to those in group2 (1.56 ± 0.41). There was a significant decrease in BMI in the CKD group from that of the healthy controls (P=0.02).There was also a significantly low GFR (53.78± 30.01ml/min) in CKD group compared to that of controls (113.62± 16.56 ml/min) P=0.000. All these values are shown in table 1.

We have correlated the serum leptin levels with BMI, GFR and insulin levels as shown in Table 2. We have found positive significant correlations between Leptin with BMI & GFR (P=0.000). And a negative significant correlation between Leptin &GFR (p=0.000).

Table 1: Comparison of serum Leptin & other parameters in Chronic kidney disease patients with normal healthycontrols

Parameters	Group 1 (CKD)	Group 2 (controls)	P value
LEPTIN (ng/ml)	15.8 ± 2.76	6.31± 0.87	0.003
BMI (Kg/m^2)	24.03 ± 0.91	25.47± 0.89	0.02
INSULIN(µU/ml)	14.34 ± 8.23	6.40 ± 1.16	0.000
HOMA-IR	3.42 ± 2.17	1.56 ± 0.41	0.000
GFR	53.78 ± 30.01	113.62 ± 16.56	0.000

Table 2: Correlation of Leptin with BMI, GFR and Insulin

Parameters	Correlation coefficient (r)	Sig. (2-tailed)
LEPTIN& BMI	0.569	0.000
LEPTIN & GFR	-0.720	0.000
LEPTIN & INSULIN	0.754	0.000
INSULIN & GFR	-0.652	0.000

Discussion:

The current study has been conducted in 90 non-diabetic subjects, of which 45 (group 1) were chronic kidney disease patients and the remaining 45 were healthy individuals with normal renal function (GFR > 90 ml/min).We were interested in assessing the serum Leptin levels in chronic kidney disease patients and compare it withhealthy individuals having normal renal function.

In our study we have identified an increase in leptin levels resulting in hyperleptinemia in the CKD patients. The findings of our study correlate with the results of many studies, who have expressed an increase in serum leptin levels in CKD (7,8,14,15).

Hyperleptinemia could be either caused by CKD on one of the spectrum and on the other end, or it could have played an important role in the development of CKD. Along with increase in serum leptin

levels in CKD patients, we found a negative significant correlation of leptin levels with GFR. This finding is similar to many studies, that have reported inverse correlation of leptin with GFR (3,7,14). Claudio Petone et al have reported an association of leptin with decline in GFR in women and not in men (3). Increased leptin levels have been positively correlated with BMI and also with metabolic syndrome (8,16)

Leptin is a uremic toxin which is retained in our body due to reduced renal clearance as in chronic kidney disease. It is mainly metabolized by the proximal tubular cells and cleared by kidney. Hence its concentration in blood could increase in impaired renal function with reduction in GFR. In CKD, there is reduced renal clearance of leptinresulting in hyperleptinemia (17,18). Increase in half-life of leptin due to reduced degradation by the kidney, have been a proposed mechanism of increased leptin levels in CKD.

Apart from renal clearance being proposed as a cause of increase in serum leptin levels in CKD, Leptin is also found to have a direct role in the pathogenesis of CKD (3).

Leptin is also known to mediate proinflammatory processes by interacting with the innate and adaptive immune system and this property of leptin could result in immune mediated renal injury. Leptin acts on the central and peripheral leptin receptors, which are of 2 types- Long form (Ob-Rb) & short truncated form (Ob-Ra). Kidney expresses abundant Ob-Ra receptors, but only very minor amounts of Ob-Rb, which is found mainly in the brain. Leptin binds to Ob- Ra receptors in the kidneys and stimulates the proliferation of glomerular endothelial and mesangial cells (17). Leptin activates excess synthesis of inflammatory markers like TNF-β1 which in turn activates collagen IV synthesis and cellular proliferation resulting in glomerulosclerosis, renal fibrosis and hypertrophy (18,20,21,22,23)

Leptin is also known to increase oxidative stress and decrease the nitric oxide bioavailability and disturbs the endogenous vasoactive response to acetylcholine, resulting in endothelial dysfunction linked to the development of renal injury (24).

One of the major effects of increased leptin production is the activation of sympathetic nervous system, which causes chronic elevation of blood pressure, resulting in renal dysfunction. Leptin also enhances natriuresis, that in turn causes increase in arterial pressure to maintain the sodium & water homeostasis (25,26).

Another interesting cause of hyperleptinemia could be LEPTIN RESISTANCE which is leptin insensitivity or failure of leptin to activate its receptor, resulting in hyperleptinemia (27,28,29). This could be due to the leptin receptor defect due to a mutation or polymorphisms in the leptin receptor gene, which is quite rare in humans (30). This leptin resistance could also be due to leptin gene polymorphisms (31,32)or may be due to or post receptor signalling defect (33).

All these mechanisms point to leptin being a potential key factor in the pathogenesis of CKD.We have found that insulin levels are significantly increased in the CKD group and leptin is positively correlated with insulin levels, which is similar to other studies(7,32). Insulin was found to have an inverse correlation with GFR like leptin.

Leptin receptors have been found on the pancreatic β cells and leptin directly inhibits the secretion of insulin from the βcells (35,36,37,38). Leptin receptors are present in liver cells and leptin is found to antagonize the insulin signalling, by decreasing the insulin induced tyrosine phosphorylation of IRS - 1 (39). Hence leptin is implicated in the development of peripheral insulin

resistance by both impaired secretion as well as by attenuating the insulin action.

This could be the cause of hyperinsulinemia in CKDpatients, which was identified in our study, along with increased insulin resistance. We also found higher HOMA -IR scores in CKD patients compared to the those with normal renal function, but leptin does not have any correlation with HOMA-IR scores.The correlation of leptin with insulin resistance have been found by some authors (40,41,42).

Conclusion:

We have demonstrated that plasma leptin levels areinverselyassociated with GFR and increased in chronic kidney disease patients. There is increasing evidence for involvement of increased plasma leptin levels in the pathogenesis of chronic kidney disease, by different mechanisms, including leptin resistance. Leptin could be a key player in CKD and reducing the plasma leptin levels could result in a better prognosis in CKD patients. So further studies have to be carried out in larger population, to establish the role of leptin in CKD and whether therapeutic lowering of plasma Leptin might prevent the progression of CKD and its co-morbidities.

Reference:

1. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J: The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med* 140: 167–175, 2004
2. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS: Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation 109: 42–46, 2004
3. Claudio Pedone1 et al. Longitudinal Association between Serum Leptin Concentration and Glomerular Filtration Rate in Humans.PLOS ONE;2015DOI:10.1371/journal.pone. 0117828
4. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive- leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 334: 292–295.PMID: 8532024
5. Menon V, Wang X, Greene T, Beck GJ, Kusek JW, Marcovina SM, et al. Factors associated with serum leptin in patients with chronic kidney disease. Clin Nephrol 2004; 61: 163–169. PMID: 15077866
6. Paul Trayhurn1* and John H. Beattie2 Physiological role of adipose tissue:white adipose tissue as an endocrine and secretory organ.Proceedings of the Nutrition Society .2001; 60: 329- 339
7. Amal A. El-Mahdy1 ,Eithar K. El-Adham1*, A. M. El-Waseef2, , M. A. Mosleh1Serum Insulin and Leptin Levels in Chronic Renal Failure Patients Using Radiometric Techniques.International Journal of Advanced Research (2014), Volume 2, Issue 11, 352-360
8. EDDINE MERABET, SAMUEL DAGOGO-JACK, DANIEL W. COYNE, SAMUEL KLEIN, JULIO V. SANTIAGO, S. PAUL HMIEL, AND MICHAEL LANDT.Increased Plasma Leptin Concentration in End-Stage Renal Disease*Journal of Clinical Endocrinology and Metabolism.1997;Vol. 82, No. 3:847-850
9. RateGraham RD Jones and Ee-Mun Lim. The National Kidney Foundation Guideline on Estimation of the Glomerular Filtration.ClinBiochem Rev. Aug 2003; 24(3): 95–98.
10. Nazish Rafique, Mohammad Nasir Afzal. Relationship of serum leptin levels with body mass index and gender.RMJ. 2009; 34(2): 164-166.

11. A Piyali das et al. Association of obesity and leptin with insulin resistance in type 2 diabetes mellitus in indian population. Indian J Physiol Pharmacol.2013; 57(1): 45-50.
12. Ali Movahed et al. Antihyperglycemic Effects of Short Term Resveratrol Supplementation in Type 2 Diabetic Patients. Evidence-Based Complementary and Alternative Medicine. Volume 2013, 1-11.
13. Wieneke Marleen Michels et al. Performance of the Cockcroft- Gault, MDRD, and New CKDEPI Formulas in Relation to GFR, Age, and Body Size. Clin J Am Soc Nephrol. 2010; 5:1003–1009.
14. Anoop Shankar,1 Shirmila Syamala,2 Jie Xiao,1 and PaulMuntner3Relationship between Plasma Leptin Level and Chronic Kidney Disease.Volume 2012, Article ID 269532: 1-6 doi:10.1155/2012/269532
15. Cynthia Ciwei Lim et al. Elevated Serum Leptin, Adiponectin and Leptin to Adiponectin Ratio Is Associated with Chronic Kidney Disease in Asian Adults.2015;PLOS ONE: 1-11 DOI:10.1371/journal.pone.0122009
16. Rodrigo Bueno de etal.The clinical impact of plasma leptin levels in a cohort of chronic kidney disease patients.Clin Kidney J (2013) 6: 63–70
17. Bossola M, Muscaritoli M, Valenza V, et al. Annorexia and serum leptin levels in hemodialysis patients. Nephron Clin Pract2004;97:76-82.
18. Wolf G, Hamann A, Han DC, Helmchen U, Thaiss F, Ziyadeh FN, et al. Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: potential role in glomerulosclerosis.Kidney Int 1999; 56: 860–872.
19. Wolf G, Ziyadeh FN. Leptin and renal fibrosis. Contrib Nephrol. 2006; 151: 175–183
20. Christiane Rüster and GunterWolf.Adipokines promote chronic kidney disease.Nephrol Dial Transplant (2013) 28 (Suppl. 4): iv8–iv14
21. G. Wolf, A. Hamann, D. C. Han et al., "Leptin stimulates proliferation and TGF-β expression in renal glomerular endothelial cells:potential role in glomerulosclerosis," Kidney International, vol. 56, no. 3, pp. 860–872, 1999.
22. G. Wolf, S. Chen, D. C. Han, and F. N. Ziyadeh, "Leptin and renal disease," American Journal of Kidney Diseases, vol. 39, no. 1, pp. 1–11, 2002.
23. G. Wolf and F. N. Ziyadeh, "Leptin and renal fibrosis," Contributions to Nephrology, vol. 151, pp. 175–183, 2006.
24. Beltowski J, Jamroz-Wisniewska A, Wojcicka G et al. Renal antioxidant enzymes and glutathione redox status in leptin-induced hypertension. Mol Cell Biochem 2008; 319: 163–174
25. E. K. Jackson and P. Li, "Human leptin has natriuretic activity in the rat," American Journal of Physiology, vol. 272, no. 3, pp. F333–F338, 1997
26. J. E. Hall, H. L. Mizelle, D. A. Hildebrandt, and M.W. Brands, "Abnormal pressure natriuresis. A cause or a consequence of hypertension?" Hypertension, vol. 15, no. 6, pp. 547–559, 1990.
27. The Biology of Leptin: A Review Karen L. Houseknecht*, Clifton A. Baile†, Robert L. Matteri‡, and Michael E. Spurlock§
28. Hamilton BS, Paglia D, Kwan AY &Deitel M. Increased obese mRNA expression in omental fat cells from massively obese humans. Nature Medicine 1995 1 953±956.
29. Caro JF, Sinha MK, Kolaczynski JW, Zhang PL & Considine RV. Leptin: the tale of an obesity gene. Diabetes 1996;45 :1455± 1462.
30. CleÂment K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D et al. A mutation in the human leptin

receptor gene causes obesity and pituitary dysfunction. Nature 1998 392 398±401.
31. Thompson DB, Ravussin E, Bennett PH & Bogardus C. Structure and sequence variation at the human leptin receptor gene in lean and obese Pima Indians. Human and Molecular Genetics 1997 6 675±679.
32. 30 Chung WK, Power-Kehoe L, Chua M, Chu F, Aronne L, Huma Z et al. Exonic and intronic sequence variation in the human leptin receptor gene (LEPR). Diabetes 1997 46 1509±1511.
33. MachteldWauters, Robert V Considine1 and Luc F Van Gaal Human leptin: from an adipocyte hormone to anendocrine mediator.European Journal of Endocrinology. 2000;143: 293±311
34. Obineche EN, Gillett MP, Abdulle A, Sulaiman M, Al-Rokhaimi M. Leptin and lipid metabolism related hormones in chronic renal failure in Arabia. Nephrology 2002;7:115-120.
35. Emilsson, V., Y. Liu, M. A. Cawthorne, N. M. Morton, and M. Davenport. 1997. Expression of the functional leptin receptor mRNA in pancreatic islets and direct inhibitory action of leptin on insulin secretion. Diabetes 46:313-316.
36. Kieffer, T. J., R. S. Heller, C. A. Leech, G. G. Holz, and J. F. Habener. 1997. Leptin suppression of insulin secretion by the activation of ATP-sensitive K+ channels in pancreatic b-cells. Diabetes 46:1087-1093.
37. Lostao MP, Urdaneta E, Martinez-Anso E, Barber A & Martinez JA (1998) Presence of leptin receptors in rat small intestine and leptin effect on sugar absorption. FEBS Letters 423, 302-306.
38. Nakata M, Yada T, Soejima N & Maruyama I (1999) Leptin promotes aggregation of human platelets via the long form of its receptor. Diabetes 48, 426-429.
39. Cohen B, Novick D & Rubinstein M. Modulation of insulin activities by leptin. Science 1996;274: 1185±1188.
40. Pelleymounter M, Cullen M, Baker M, Hecht R,Winters D, Boone T et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995 269 540±543.
41. StephensTW, BasinskiM, BristowPK, Bue-Vallesky JM, Burgett SG, Craft L et al. The role of neuropeptide Y in the antiobesity action of the obese gene product. Nature 1995 377 530±532.
42. Muzzin P, Eisensmith RC, Copeland KC & Woo SL. Correction of obesity and diabetes in genetically obese mice by leptin gene therapy. PNAS 1996 93 14804±14808.

Received: 25.10.2021 Revised: 20.11.2021 Accepted: 28.12.2021