

International Journal of Medical Science and Current Research (IJMSCR) Available online at: www.ijmscr.com Volume1, Issue 2, Page No: 68-73 July-August 2018



Study of Serum Leptin, Adiponectin Levels, leptin adiponectin ratio and their Correlation with Carotid Intima Media Thickness in Indian Predialysis Chronic Kidney Disease Patients

Dr. Dipankar Das¹, Dr. Prabal Rajvanshi², Dr. Rahul Arya³

¹ Post graduate resident, ² MD, FIACP, FIACM, Professor and Consultant, ³ Post graduate resident Department of Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi- 110029

Corresponding Author:

Dr. Dipankar Das Department of Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi- 110029

Type of Publication: Original Research Paper Conflicts of Interest: Nil

ABSTRACT

Background: Atherosclerosis is a well-established cause of cardiovascular events in adults with CKD. Even subtle chronic kidney disease (CKD) increases the risk of cardiovascular events. Atherosclerosis unless in a severe form is often asymptomatic. In adults, CIMT measurement is considered a valid and reliable surrogate marker for assessment of atherosclerosis.

Role of adipokines as an essential part of chronic kidney disease (CKD) has been recognized. In non-CKD populations adiponectin has significant anti-inflammatory and antiatherogenic vasculo-protective actions. Patients with CKD behave very differently from the general population. Plasma levels of adiponectin in patients with CKD are increased up to threefold the physiological level. Leptin the "satiety hormone", a proinflammatory cytokine is also elevated in CKD. Leptin(L) and adiponectin(A) are adipokines with respective pro-atherogenic and anti-atherogenic properties, the L: A ratio is a powerful marker for predicting Carotid intima media thickness (CIMT) thickness and, possibly cardiovascular outcome. There are sparse and conflicting results on association serum leptin, adiponectin levels and CIMT with no well published Indian studies on this aspect.

AIM: To study correlation between serum adiponectin, serum leptin, leptin adiponectin ratio and Carotid intima media thickness (**CIMT**) in Indian Predialysis CKD patients.

Materials and methods: Prospective case control study on total 130 patients (65 cases ,65 controls) over 1 year, was conducted in patients with chronic kidney disease as defined by KDIGO guidelines. Serum adiponectin and serum leptin level was measured by commercially available enzyme linked immunosorbent assay (ELISA) kits and their ratio calculated. The CIMT was measured using B-mode ultrasound and a 7.5 MHz transducer. Comparisons were done between the cases and control groups with special emphasis on the serum leptin, serum adiponectin level and carotid intima media thickness, correlations between these parameters was analyzed in detail.

Results: A significant positive correlation of serum Leptin and BMI was found. Leptin: adiponectin ratio is found to be increased according to the severity of CKD. Both multivariate and univariate regression analysis showed that serum leptin (ng/ml), s. adiponectin(μ g/ml), Leptin/adiponectin ratio all three are well predictors of CIMT, and among them Leptin having the highest level of correlation.

Conclusions: Serum leptin, adiponectin, and leptin adiponectin ratio correlate with significantly increased atherosclerotic risk and CVD as measured by CIMT in a stepwise fashion across decreasing categories of eGFR in Indian Predialysis CKD patients.

Keywords: Serum leptin, Serum adiponectin, CIMT, CKD, eGFR.

INTRODUCTION

CKD is associated with increased morbidity and mortality, decreased quality of life and increased healthcare expenditures. Chronic kidney disease was the cause of 956,000 deaths globally in 2013, up from 409,000 deaths in 1990. This is an underestimate as patients with CKD are more likely to die of cardiovascular disease (CVD) than to reach end-stage renal disease (ESRD). With increasing prevalence of CKD, CKD related excess CVD, ESRD and the consequent financial burden of renal replacement

International Journal of Medical Science and Current Research | July-August 2018 | Vol 1 | Issue 2

therapy (RRT), the importance of CKD and its risk factors must be realized to implement timely prevention and treatment.

There has been an exponential growth of interest in inflammation in CKD and end-stage renal disease (ESRD). In health, adiponectin has significant antiinflammatory and antiatherogenic vasculo-protective action Patients with CKD behave very differently from the general population. Plasma levels of adiponectin in patients with CKD are increased up to threefold the physiological levels. Abdallah e. Et al $^{(4)}$ Zoccali et al ⁽³⁾. Iwashima et al ⁽⁵⁾ found adiponectin levels to have a potential protective role against the development of CVD in patients with kidney disease. However, Hayashi m et al showed that adiponectin is associated with increased risk of carotid atherosclerosis in a predialysis CKD population ⁽⁶⁾. Multicentric cohort study finding suggests low adiponectin level is associated with increased CIMT in both diseased and non-diseased populations $(^{(7,8)})$.

Leptin the "satiety hormone" is a proinflammatory cytokine is predominantly cleared from the circulation via kidney. In the non-obese population, levels typically range from 5 to 10 ng/ml., its levels rise progressively with decreasing GFR. Mak RH⁽¹³⁾ found increased leptin level in CKD patients to positively correlate with inflammatory markers like interleukin-6 and CRP. Anoop Shankar et al ⁽¹⁴⁾ in a multi-ethnic, study found that higher plasma leptin levels were positively associated with CKD. High leptin levels induce activation of the sympathetic nervous system that causes chronic elevation of BP and renal dysfunction, serving as cofactor of TGF beta activation, promoting renal endothelial proliferation and subsequent glomerulosclerosis. ⁽²⁾.At present results are conflicting regarding serum leptin in CKD patients, in whom both beneficial and detrimental effects on uremia have been found. Scholze et al ⁽⁹⁾ found that high leptin levels are associated with better outcomes. Similarly, a study by kalantar Zadeh et al (10) suggested that being obese (having more leptin, in other words) is a survival advantage in hemodialysis patients. Data on leptin's role in early stages of CKD and its correlation with metabolic syndrome (MS) and CIMT are scarce.

Chronic kidney disease (CKD) increases the risk of cardiovascular events in humans. Vascular calcification, arterial remodeling and increased arterial stiffness have been described also in earlier stages of CKD. Carotid intima media thickness measurement is reliable, noninvasive, feasible, inexpensive method and free of radiation risk for assessment of atherosclerotic burden.

According to Giuseppe danilo norata et al (11) the L: A ratio is a powerful marker for predicting CIMT thickness and, possibly, cardiovascular outcome. The ratio of leptin to adiponectin (LAR) has been shown to be a better predictor of adverse outcomes including CVD and mortality in the general population as well as in ESRD patients than either leptin or adiponectin alone. No solid ranges of normal L: A values have yet been reported in the Asian population. A recent study showed that the mean L: A ratio was 0.85 for non-obese men in the general population; in obese patients, the mean L: A ratio was 2.81.^{(12).} Whether modification of the L: A ratio after lifestyle and/or pharmacological treatment could result in beneficial effects in terms of cardiovascular outcome; further studies are warranted to clarify these..

Findings on the association between serum leptin, adiponectin levels & CIMT in predialysis chronic kidney disease are contradictory. In CKD patients, an inverse correlation, no association or positive correlation between CIMT & adiponectin have been reported⁽¹⁾. There are conflicting results on association serum leptin, adiponectin levels and CIMT with no well published Indian studies on this aspect so this study aims to evaluate correlation between serum leptin, serum adiponectin level, leptin adiponectin ratio and Carotid intima media thickness (**CIMT**) in predialysis CKD patients.

Materials And Methods: This was a Prospective case control study on total 130 patients(65 cases ,65 controls) conducted in patients with predialysis chronic kidney disease as defined by KDIGO guidelines. Staging of the patients was done by using the MDRD formula (Modification of diet in renal disease). The patients were then subjected to various biochemical and radiological investigations including ultrasonography. The Study was conducted in VMMC and Safdarjung hospital, New Delhi. Serum Adiponectin ELISA kit. The Normal reference range were taken as 2-15 µg/ml. Serum leptin was assessed by DBC Leptin ELISA kit. Normal reference range for serum leptin was taken as 2-5.6ng/ml in males

and 3.7 -11.1ng/ml in females. The CIMT was measured using B-mode ultrasound and a 7.5 MHz transducer. Intimal-medial thickness was defined as the distance between the leading edge of the first echogenic line (lumen-intima interface) and the second echogenic line (media-adventitia interface) of the far wall. Three measurements were taken at 0.5, 1 and 2 cm below the carotid bifurcation of the common carotid artery on each side, and their arithmetic averages was calculated

INCLUSION CRITERIA: Patients were considered for valid study if they satisfied following criteria- 18 years or older, Patients with GFR<60 ml/min/1.73 m2, Chronic kidney disease not requiring renal replacement therapy, Sex -all genders EXCLUSION CRITERIA: Following patients were excluded from the study-Patients having history of carotid surgery, Patients on hypolipidemic drugs or hepatotoxic drugs, Pregnant females, Patients of metabolic syndromes as per IDF criteria, Patients known to have collagen vascular disorders or vasculitis, patients with history of malignancy, Patients with known coexisting liver disease.

Observation and Results

After using appropriate statistical methods for both continuous and discrete variables, the following results were obtained.

CKD Stage wise distribution of cases:

Maximum cases were of CKD stage 4 & 5 (46.15% and 35.38%) respectively.



Figure1: Distribution of cases according to CKD stages.

Serum Leptin levels according to severity of CKD in cases:

The change in serum leptin levels in different stages of kidney with p value <0.0001 is significant. The mean leptin values are 12.58 ± 11.17 , 21.55 ± 9.63 , 33.87 ± 16.17 in ng/ml in CKD stages 3,4 & 5 respectively.



Figure2: Mean serum leptin values in different stages of CKD



Figure3: Comparison of Serum adiponectin levels in different stages of CKD kidney

Comparison of Leptin: adiponectin ratio in different stages of CKD:

The leptin adiponectin ratio found to be 1.36 ± 1.14 , 1.87 ± 0.75 , 2.4 ± 0.96 in CKD stage 3, 4,5 respectively, suggesting the ratio increased as the severity of CKD progressed. The P value here is very significant (0.0002).



Figure4: Comparison of Leptin: adiponectin ratio in different stages of CKD

Page /



Figure5:_Comparison of CIMT average in different stage of CKD

Correlation Of Carotid Intima Media Thickness(Cimt) With Leptin, Adiponectin And L:A Ratio:

Relationship between CIMT and other variables:

Correlation coefficient \mathbf{r} was calculated to test the strength of association between carotid intima media thickness and other variables like Age, hemoglobin, serum sodium, serum potassium, serum calcium, serum phosphate, blood urea, fasting sugar, post prandial sugar, serum creatinine, Triglycerides, cholesterol, blood pressure, eGFR, BMI.

There was significant correlation between CIMT and eGFR (p value <0.0001 and r = -0.789). likewise, other variable, which had significant correlation with CIMT are B. Urea, Blood Pressure, BMI, Body Weight, Hb(gm/dl), Leptin/adiponectin ratio, s. adiponectin(μ g/ml), s. calcium, s. leptin(ng/ml), s. phosphorus, s creatinine(mg/dl)

Discussion & Conclusion

1. The mean value of average CIMT in CKD patients were 0.8 ± 0.12 mm as compared to 0.62 ± 0.05 mm in control groups and CIMT values on right and left side were comparable to each other. CIMT rises progressively with decreasing GFR.

2. There was significant correlation between CIMT and eGFR (p value <0.0001 and r = -0.789).

3. Mean value of serum adiponectin levels in CKD group were found to be $11.74 \pm 3.38 \ \mu g/ml$, significantly higher than that of control groups $9.63 \pm 2.71 \ \mu g/ml$. Also, as the severity of CKD increased serum adiponectin levels is found to be increased accordingly in them.

4.Serum adiponectin is found to be increased irrespective of age groups and gender.

5. In present study BMI value of the patients showed significant positive correlation with serum adiponectin concentration. (correlation coefficient is 0.4 and the p value 0.001). In non-CKD control group BMI was inversely correlated with serum adiponectin (Correlation Coefficient -0.445, p 0.0002).

6. Mean serum leptin levels were increased in the CKD patients. Serum leptin level in CKD cases was 23.35 ± 12.97 ng/ml, compared to controls 9.19 ± 9.31 ng/ml.

7. Like adiponectin; Leptin levels are found to rise progressively with decreasing GFR. serum leptin is found to be increased irrespective of age groups and gender. However, a significant positive correlation of serum Leptin and BMI was found.

8. Leptin: adiponectin ratio is found to be significantly associated with CKD in our study. The leptin adiponectin ratio found to be 1.36 ± 1.14 , 1.87 ± 0.75 , 2.4 ± 0.96 in CKD stage 3, 4,5 respectively, suggesting the ratio increased as the severity of CKD progressed.

9. Both systolic and diastolic blood pressure was found to be significantly increased in patients with CKD compared to control groups. (p value<.0001)

10. Variables like B. Urea, Body Weight, Hb (gm/dl), S. calcium, S. phosphorus, serum creatinine(mg/dl) had significant correlation with CIMT in CKD patients.

11. There is direct relationship between serum leptin levels and BMI in both CKD and control group of patients(p<0.0001). Definite correlation was found between Leptin/adiponectin ratio and BMI in CKD patients.

12. The correlation of serum leptin and leptin: adiponectin ratio with average CIMT was found to be stronger (correlation coefficient was 0.733 and 0.669 respectively; p<.0001).) compared to correlation of adiponectin with average CIMT (correlation coefficient 0.49; p<.0001).

13. Multivariate regression analysis showed serum Leptin, serum adiponectin, Leptin/adiponectin ratio all three are well predictors of CIMT in predialysis CKD patients; leptin having the highest level of correlation.

There were some limitations in this study. The study was a hospital based one; Also, the sample size of the study group was small and therefore the findings may not generally be applicable to the overall population. To assess the clinical value of leptin, adiponectin levels or their ratio as a potential surrogate marker of cardiovascular risk in or therapeutic target in CKD, end point-driven studies are needed to be done. Whether measures to reduce adipokines like leptin, adiponectin can potentially reduce cardiovascular events in chronic kidney diseases patients, is needed to be evaluated by quality randomized control trials, which can help CKD patients at risk of cardiovascular morbidity and mortality.

REFERENCES

- 1. Jia T, Carrero JJ, Lindholm B, Stenvinkel P. The complex role of adiponectin in chronic kidney disease. Biochemie. 2012;94(10):2150-2156.
- 2. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative metaanalysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3(7):514-517.
- Zoccali C. Endothelial dysfunction in CKD: a new player in town?. Nephrol Dial Transplant 2008; 23:783-785.
- Abdallah E, Waked E, Nabil M, El-Bendary O. Adiponectin and cardiovascular outcomes among hemodialysis patients. Kidney Blood Press Res. 2012;35(4):247–253.

- Iwashima Y, Horio T, Kumada M, Suzuki Y, Kihara S, Rakugi H et al. Adiponectin and Renal Function, and Implication as a Risk of Cardiovascular Disease. Am J Cardiol. 2006;98(12):1603–8.
- Hayashi M, Shibata R, Takahashi H, Ishii H, Aoyama T, Kasuga H et al. Association of adiponectin with carotid arteriosclerosis in predialysis chronic kidney disease. Am J Nephrol. 2011;34(3):249–255. Arteriosclerosis in predialysis chronic kidney disease. Am J nephrol 2011;34:249-255
- Gardener H, Sjoberg C, Crisby M, Goldberg R, Mendez A, Wright CB et al. Adiponectin and carotid intima-media thickness in the northern Manhattan study. Stroke. 2012;43(4):1123–1125
- B. Gasbarrino K, Gorgui J, Nauche B, Cote R, Daskalopoulou SS. Circulating adiponectin and carotid intima-media thickness: A systematic review and meta-analysis. Metabolism. 2016;65(7):968–986.
- Scholze A, Rattensperger D, Zidek W, Tepel M. Low serum leptin predicts mortality in patients with chronic kidney disease stage 5. Obesity. 2007;15(6):1617–1622.
- Kalantar ZK, Kuwae N, Wu DY. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. Am J Clin Nutr. 2006;83: 202–210
- 11. Norata GD, Raselli S, Grigore L, Garlaschelli K, Dozio E, Magni P et al. Leptin:adiponectin ratio is an independent predictor of intima media thickness of the common carotid artery. Stroke. 2007;38(10):2844–2848
- Satoh N, Naruse M, Usui T, Tagami T, Suganami T, Yamada K, et al. Leptin-to-adiponectin ratio as a potential atherogenic index in obese type 2 diabetic patients. Diabetes Care 2004; 27:248
- Mak RH, Cheung W, Cone RD, Marks DL. Leptin and inflammation-associated cachexia in chronic kidney disease. Kidney International. 2006;69:794–799
- 14. Shankar A , Syamala S, Xiao J, Muntner P. "Relationship between Plasma Leptin Level and Chronic Kidney Disease,". International Journal of Nephrology.2012:34-40