

Association of Serum Leptin and Coronary Artery Calcification in end Stage Renal Disease Patients on Dialysis

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ABSTRACT

Background: Patients with End Stage Renal Disease (ESRD) on dialysis have 2 to 5-fold more coronary artery calcification (CAC) than age-matched individuals. Leptin receptors are expressed in atherosclerotic lesions, and leptin signaling has been implicated in the promotion of vascular calcification. In this study, we evaluated the role of Serum Leptin in coronary artery calcification in ESRD patients on dialysis. **Methods:** This study was done on 50 CKD-ESRD patients on maintenance dialysis and 20 normal subjects. Plasma leptin was measured in all CKD-ESRD patients and normal control by DRG Leptin ELISA Kit. Blood samples were obtained for analysis of leptin prior to dialysis. All patients with ESRD and normal subjects were subjected to Multi Row Spiral Computed Tomography (MSCT) for detection of coronary artery calcification scoring (CACS). **Results:** The mean serum leptin value in ESRD subjects was 8.91 ± 1.42 ng/ml. The mean serum leptin value in normal subjects was 3.14 ± 0.61 ng/ml. This difference in serum leptin value between ESRD on dialysis and normal subjects was statistically significant ($Z=2.91$, $p < 0.05$). The mean CACS in 50 patients with ESRD was 91.4 ± 32.7 Agatston units. The mean CACS in normal subjects was 7.75 ± 6.5 Agatston units. Difference in prevalence of CACS between ESRD patients on dialysis and normal subjects was statistical significant. In ESRD patients on dialysis with CACS in range 0-10, 11-100 and 101-400 Agatston units, the mean serum leptin values were 3.1 ± 0 ng/ml, 6.2 ± 3.4 ng/ml, 14.3 ± 3.5 ng/ml respectively. So it was evident that with increase in CACS, the serum leptin values also increased. The difference in the serum leptin concentration between the group with CACS in the range of (0-10), (11-100), (101-400) Agatston units were statistically significant. [$z=5.16$, $p < 0.05$), ($z= 7.8$, $p < 0.05$) respectively]. **Conclusion:** CAC is amplified in renal patients and it progresses rapidly with advancement of the disease. Our study results suggest a positive co relation with Serum leptin and CAC in ESRD patients. In ESRD patient's serum leptin is elevated as compared to normal subjects. Hence, we conclude that controlling serum leptin will reduce CAC burden.

Keywords: Atherosclerosis, Dialysis, End Stage Renal Disease.

INTRODUCTION

The American Heart Association recently stated that individuals with Chronic Kidney Disease (CKD) should be included in the highest risk group for cardiovascular disease and therefore should receive aggressive preventive measures to reduce the prevalence and severity of cardiovascular disease.^[1,2] Patients with End Stage Renal Disease (ESRD) on dialysis have 2 to 5 fold more coronary artery calcification than age-matched individuals with angiographically proven coronary artery disease. In addition to increased traditional risk factors, CKD patients also have a number of non-traditional cardiovascular risk factors that may play a prominent

role in the pathogenesis of arterial calcification, including duration of dialysis and disorders of mineral metabolism.

Recently, interest has been focused on the roles of hyperphosphatemia, elevated levels of the calcium and phosphorus product, hyperparathyroidism and obesity in the development of cardiovascular disease in ESRD. The clustering of central obesity with insulin resistance, dyslipidemia, and chronic inflammation may account for part of the proatherosclerotic effects of adiposity.^[3,4] Obesity is associated with a marked increase in circulating leptin concentrations. Leptin receptors are expressed in atherosclerotic lesions, and leptin signaling has been implicated in the promotion of vascular calcifications, thrombosis and atherosclerosis in mice models, suggesting a role for leptin in atherosclerosis in vivo. Peripheral actions of leptin that may promote atherosclerosis include endothelial activation and migration,^[5,6] smooth muscle cell

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proliferation and calcification,^[7] and activation of monocytes and adaptive immune responses.^[8,9]

MATERIALS AND METHODS

Study design

This study was done on 50 CKD-ESRD Patients on maintenance dialysis and 20 normal subjects conducted at Mission of Mercy Hospital attending the dialysis unit from April 2017 to November 2017. Mean Age of the patients in study group was 51.3 + 10.8 yrs. The mean duration of dialysis in months was 21.75 + 11.71 months. 40 (M 25, F 15) patients were on haemodialysis and 10 patients were on peritoneal dialysis.

The mean BMI in this study group was 22.43 + 4.75 kg/m² Minimum BMI was 32.6 kg/m.^[2]

Inclusion & exclusion criteria

Inclusion Criteria for the study group was patient with ESRD on dialysis for more than 3 months while exclusion Criteria was patients with active infection, inflammation and patients unwilling to participate in study.

Methods

Plasma leptin was measured in all CKD-ESRD patients and normal controls by DRG Leptin Elisa Kit. Blood samples were obtained for analysis of leptin prior to dialysis. All patients with ESRD and normal subject were subjected Multi Row Spiral Computed Tomography (MSCT) for detection of coronary artery calcification scoring (CACS). The biochemical abnormalities and the extent of coronary calcification were recorded.

Statistical analysis

Statistical data was analyzed by non parametric tests like Chi (x²) test using alpha error of 5% and parametric tests used were Z test and a p value of <0.05 was considered as significant. Correlation was calculated using t-square test between MSCT Score and serum Leptin concentration.

RESULTS

Details of the patients were recorded in prepared proforma using questionnaire method and a detailed history was taken and patient examined thoroughly. The results of the data of the patient values were analyzed. Serum leptin values were increased in 48 (96%) out of 50 patients with ESRD on dialysis.

Serum leptin value

The mean serum leptin value in ESRD subjects was 8.91 + 1.42 ng/ml. The minimum value was 3.10 ng/ml and maximum was 18.90 ng/ml in our study.

The mean serum leptin value in normal subjects was 3.14 + 0.61 ng/ml.

This difference in serum leptin value between ESRD on dialysis and normal was statistically significant (Z=2.91, p <0.05) [Figure 1].

Coronary Artery Calcification scoring

Coronary Artery Calcification was studied in 50 patients with ESRD on dialysis and in 20 normal subjects. The maximum CACS was 204.0 while the minimum case was 8 Agatston units. The mean CACS in normal subjects was 7.75 + 6.5 Agatston units.

The difference in the prevalence of CACS between the ESRD patients on dialysis and normal subjects was statistically significant (Z=14.3, P < 0.05).

Serum Leptin and Coronary Artery Calcification scoring in the ESRD on dialysis

In ESRD patients on dialysis with CACS in the range 0-10, 11-100 and 101-400 Agatston units, the mean serum leptin values were 3.1 + 0 ng/ml, 6.2 + 3.4 ng/ml, 14.3 + 3.5 ng/ml respectively.

Table 1: Serum Leptin and Coronary Artery Calcification in the ESRD on dialysis

Leptin values	CACS	95% CI
0-4.9 (n=13)	32.3 ± 14.1 (a)	4.7 – 59.9
5-9.9 (n=22)	59.0 ± 19.1 (b)	21.6 – 96.4
10-14.9 (n=7)	139.6 ± 21.6 (c)	96.7 – 182.5
15-19.9 (n=8)	186.9 ± 10.5 (d)	166.3 – 207.5

From the above table it is evident that with increase in serum leptin values in ESRD patients on dialysis the mean CACS increases which is statistically significant [a vs b, Z=4.7 (p < 0.05); b vs c, Z=8.7 (P <0.05) and c vs d, Z=5.2 (P<0.05)].

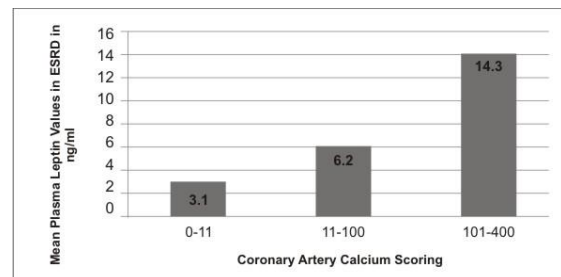


Figure 1: Bar diagram sharing Serum Leptin and Coronary Artery Calcification in ESRD on dialysis.

Table 2: Correlation between Serum Leptin and CACS in ESRD (Pearson correlation)

	LEPTIN	CACS
Pearson Correlation	1	.816**
Sig. (2-tailed)		.000
N	50	50
Pearson Correlation	.816**	1
Sig. (2-tailed)	.000	
N	50	50

** Correlation is significant at the 0.01 level (2-tailed).

A positive correlation was found between plasma leptin and coronary artery calcification [Table 2]

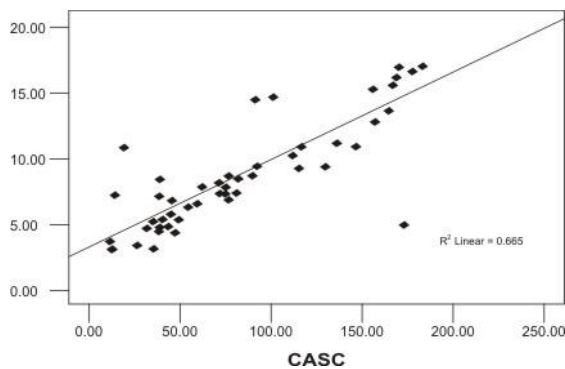


Figure 2: Correlation between serum Leptin and CAC in ESRD

DISCUSSION

Cardiovascular disease accounts for more than 50% of deaths among ESRD patients. Patients with ESRD have more Coronary Artery Calcification (CAC) than age matched individuals with angiographically proven coronary artery disease. CKD patients have a number of nontraditional risk factors that may play a prominent role in the pathogenesis of CAC along with traditional risk factors. Leptin along with other adipokines are thought to modulate coronary artery calcification. Serum leptin displays a strong association with cardiovascular risk factors including insulin resistance, metabolic syndrome and inflammatory markers. Peripheral actions of leptin that may promote vascular calcification are endothelial activation and migration, smooth muscle cell proliferation and calcification, activation of monocytes and adaptive immune response. Leptin receptors are expressed in atherosclerotic lesions and leptin signaling has been implicated in the promotion of both thrombotic and vascular calcification in mice model.^[10-12]

This study was a cross sectional study conducted on 50 patients with ESRD on dialysis and 20 normal subjects. Our study was conducted to find out the association of serum leptin values with coronary artery calcification in ESRD patients on dialysis. Our study showed that in ESRD patients on dialysis serum leptin values were significantly higher than normal subjects ($z = 14.1$, $p < 0.05$). This observation is in concordance with the study by Michael Landt et al,^[13] where serum leptin was increased in ESRD compared to mean values obtained in normal subjects and this finding was statistically significant. In the present study, CAC scoring was studied in 50 ESRD patient on dialysis and 20 normal subjects. The difference in CACS between ESRD patients and normal subjects was statistically significant ($z = 14.3$, $p < 0.05$). This is in confirmatory with the studies done by Stumpor et al,^[14] and Meijanian et al,^[15] who showed that there is excess CAC in CKD patients compared to general population. Their study

had an incidence of CAC of 53.8% and 96% respectively in the ESRD population whereas in our study the prevalence was 96%.

In this study it was evident that with increase in serum leptin values (0-4.9, 5-9, 10-14.9, 15-19.9) in ESRD patients on dialysis the mean CACS increases (32.3 + 14.1, 59.0 + 19.1, 139.6 + 21.6 and 186.9 + 10.5 respectively) which is statistically significant [$Z = 4.7$ ($p < 0.05$); $Z = 8.7$ ($P < 0.05$) and $Z = 5.2$ ($P < 0.05$)] [Table 1]. A positive correlation was found between plasma leptin and coronary artery calcification [Table 2].

This finding is in concordance with the study done by Stomper et al,^[14] who showed that CACS scoring correlated with serum leptin ($R = 0.3$, $p < 0.05$) Ciccone et al,^[16] showed that CAC correlated positively with log leptin concentration in a cross sectional study. This finding is similar to the study by Parhami F et al,^[17] who showed that serum leptin enhances the calcification of vascular cell and coronary arteries. Ridker PM et al,^[18] also showed that serum leptin was positively associated with CAC.

CONCLUSION

Coronary artery calcification is associated with increased cardiovascular mortality and morbidity and so utmost care to be taken to modify most of the traditional and nontraditional factors responsible for CAC. CAC is amplified in renal patients and it progresses rapidly. Our study suggests positive association with serum leptin and CAC in ESRD patients. In ESRD patients, serum leptin is elevated compared to normal subjects. O from our study it is evident that by controlling serum leptin, will reduce coronary artery calcification burden.

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