Research Article

The role of Leptin and Insulin like Growth factor -1 in patients with end stage renal disease under haemodialysis (pre & post dialysis)

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Abstract

Aims: The present study is conducted to evaluate the level of Leptin, Insulin like growth factor -1 (IGF-1) and Albumin (Alb) in heamodialyzed patients pre- and post-dialysis compared with healthy control.

Patients and Method: A study was made on 25 dialyzed patients attending the dialysis unit in AL-Yarmook teaching hospital from the period between May and August 2009 (male only) with age range (25-55) years, and their duration time with dialysis was more than one year. Serum Leptin, IGF-1 was measured by ELISA method, Albumin level was measured by kit.

Results: The mean serum Leptin level was significantly lower in post-dialysis patients when compared with pre-dialysis, but still higher than healthy control. While insulin like growth factor-1 was higher in post-dialysis than pre-dialysis but the difference was not significant, and both of them were significantly lower than healthy control.

Conclusions: The present study shows that Leptin level has been proved to be elevated in patients with pre- dialysis, due to renal failure that may be impairs either its synthesis or clearance. We have also demonstrated an increase in the level of IGF-1 in post-dialysis when compared with pre-dialysis, but the level still lower than healthy control, thus early decrease in serum IGF-1 may allow early detection of malnutrition in haemodialyzed patients.

Keywords: Leptin, Insulin like growth factor-1 (IGF-1), Albumin, Haemodialysis, Correlation of pre- and post-dialysis

INTRODUCTION

Dialysis is a process for removing waste and excess water from the blood, and is used primarily to provide an artificial replacement for lost kidney function in people with renal failure. Dialysis may be used for those with an acute disturbance in kidney function, or progressive but chronically worsening kidney function.[1, 2]

Protein and calorie (energy) malnutrition is common in patients with end-stage renal disease and is a powerful predictor of morbidity and mortality in this population. Clinicians, using hypoalbuminemia as their principal nutritional marker, have recognized for many years that their malnourished dialysis patients had a poor prognosis, and serum albumin appeared to be the most significant marker of mortality in patients with renal failure.[3] Malnutrition in haemodialysis patients has been

attributed to three main mechanisms: insufficient feeding, abnormal nutrient metabolism and nutrient losses due to dialysis procedures.[4] Appetite regulation can be regarded as a series of feedback loops governing satiation (the process which stops ingestion at the end of a meal), satiety (the process which provides background inhibition of feeding urges) and feeding (which occurs in the absence of satiety).

One potential relationship between malnutrition and inflammation in patients with end-stage renal disease is appetite suppression triggered by the inflammatory response. The link between inflammation and anorexia may be through the hormone Leptin.[5]

Leptin is a 16-KDa protein identified as the product of the obese gene; it is a hormone that is secreted by adipocytes, provides signals from the peripheral tissues to the central nervous system to inhibit appetite and increase energy expenditure,[6] and increase overall sympathetic nerve activity,[7] facilitate glucose utilization and improve insulin sensitivity.[8]

It has shown that Leptin function as a positive acute phase protein in experimental animals, being positively regulated at the mRNA level by the cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1).[9, 10] Since serum Leptin levels are markedly increased in patients with chronic renal failure, activation of the inflammatory response in this patients population may be responsible, in part, for increased Leptin levels.[11]

IGF-1 is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults. It consists of 70 amino acids in a single chain with three intermolecular disulfide bridges; IGF-1 has a molecular weight of 7649 Daltons.[12]

It was shown that the bioactivity of this hormone is reduced in uremic sera, several mechanisms have been identified, these include: Increased plasma concentrations of two classes of compounds: sufficiently small to be haemodialyzed or too large for effective removal by haemodialysis, impaired phosphorylation of tyrosine kinase in the β – subunit of the IGF-1 receptors in skeletal muscle of rats with CRF.[13, 14]

This study was conducted to shown if the changes of serum Leptin, IGF-1, and Albumin levels are correlated in pre- and post-haemodialysis patients as compared with healthy control.

PATIENTS AND METHODS

A study was made on 25 haemodialyzed patients (pre- and post- dialysis) from dialysis unit in AL-Yarmook Teaching Hospital for the period between May and August 2009 (Male only) with age range 25-55 years and their duration time with dialysis was more than one year, using the polyflux capillary dialyzer/Gambro, Dialysatoreu Gmbh (D-72379 Hechingen/Germany).

Twenty (20) healthy control male individuals' sex and age matched with the patients were selected.

Serum Leptin, Insulin like growth factor (IGF-1) were measured by ELISA technique. Albumin was measured by a kit.

Statistical analysis: Results were expressed as mean± SD (standard deviation) for data showing a normal distribution. Comparisons were performed by Mann-Whitney U test, whenever the P value was lower than 0.05 it is considered as significant.

RESULTS

We found that the mean age of patients was (47.4±11.3) years, and their weight is (66.6 ± 9.9) Kg.

Using ELISA technique, serum Leptin, IGF-1, and Albumin level were estimated in ESRD patients who undergo haemodialysis (pre- and post-dialysis) and healthy control.

The results of serum Leptin showed a decrease level in post-dialysis when compared with pre-dialysis, but it is not significant (11.83± 17.99 , 9.36 ±14.35 respectively) with P-value > 0.05 .

Concerning the correlation of serum Leptin level (pre- and post-dialysis) with healthy control, there are significant increases in haemodialyzed patients (pre- and post- 11.83± 17.99, 9.36±14.35 and 2.76±1.7 respectively) with P-value < 0.05. While the level of IGF-1 in sera of haemodialyzed patients showed interesting significant decrease level in post-dialysis (56.32 ± 21.22) comparing with pre-dialysis (58.25 ± 28.19), with P-value <0.05.

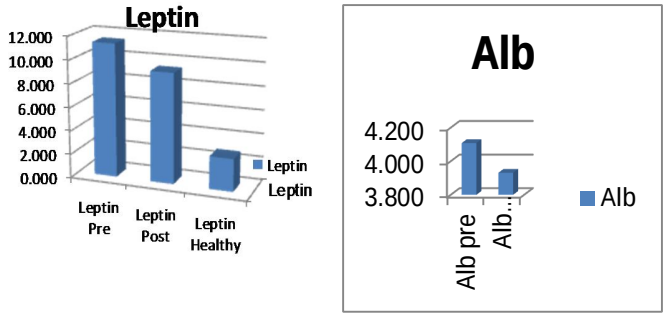
Furthermore the same results when compared IGF-1 level in pre-dialysis (58.25 ± 29.19) with healthy control (182.6± 70.33) with P- value < 0.05, and when we compared post-dialysis (56.32 ± 21.22) with healthy control (182.6 ± 70.3), P-value< 0.05.

No significant correlation between the level of Albumin in pre- and post-dialysis (4.11±1.41, 3.93±1.66 respectively) P- value > 0.05.

These results are shown in table1 and figure 1.

Table 1: The levels of serum Leptin, IGF-1, and albumin in pre-, post-dialysis with healthy control.

	Pre-Dialysis	Post-Dialysis	Healthy Control	P-value
N	25	25	20	
Mean Leptin (ng/L)±SD	11.83± 17.99	9.36± 14.35		0.662
	11.83± 17.99		2.76± 1.7	0.034
		9.36± 14.35	2.76± 1.7	0.048
Mean IGF-1 (µg/L) ±SD	58± 28.19	56.32± 21.22		0.003
	58± 28.19		182.6± 70.33	0.001
		56.32± 21.22	182.6± 70.33	0.001
Mean Albumin (mg/L)±SD	4.11± 1.41	3.93± 1.66		0.687



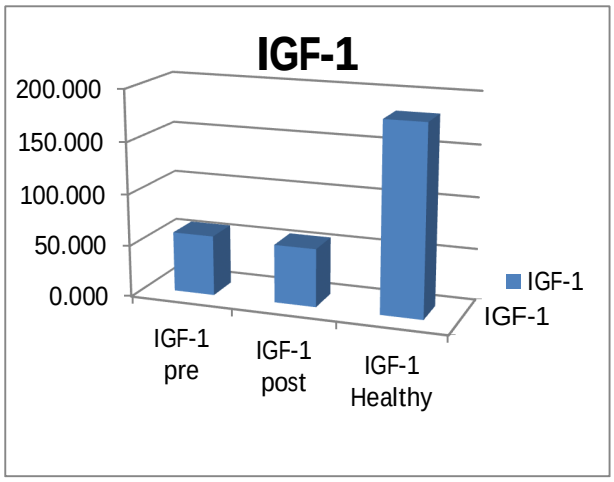


Figure 1. The levels of serum Leptin, IGF-1, and albumin in pre-, post-dialysis with healthy control.

DISCUSSION

Malnutrition is a common feature in end-stage renal disease,[15] anorexia has been commonly reported in these patients, who often fail to increase their food intake. Furthermore, this spontaneous reduction in food intake may appear before end-stage renal disease.[16]

Leptin has been proved to be elevated in patients with pre-dialysis; due to renal failure its synthesis or clearance may be impaired, although the kidney is responsible for about 80% of Leptin clearance in healthy adults.[17-19] The results of this study are in agreement with these studies.

The molecular weight of circulating Leptin is~ 16KDa, so this hormone theoretically should be able to pass the glomerular membrane completely. However, the extraction fraction of ~ 6 is substantially less than the filtration fraction of the normal kidney; therefore renal removal of Leptin cannot be explained only by simple glomerular filtration. Either the peptide is completely filtered and largely reabsorbed by proximal tubular cells, or glomerular filtration of this hormone is hindered as a result of its negative electric load. Because normally no Leptin is found in the urine, the former explanation seems to be the more likely one, provided that Leptin is not metabolized in the tubules. In some studies an inverse relationship has been found between glomerular filtration rate and plasma Leptin concentrations, substantial rises in Leptin occur only when glomerular filtration rate falls below very low levels. Thus, even when its function is severely impaired, the kidney may still play a role in leptin clearance.[20]

This study observed that serum Leptin was insignificantly decreased in post-dialysis as compared with pre-dialysis. This result is in agreement with the results of others.[21, 22] More studies revealed that the major cause of the elevated Leptin levels in renal failure is reduced renal clearance,[23] but other factors such as hyperinsulinemia[24] and inflammation[25] have been implicated in augmenting leptin secretion in renal failure.

A study have been done by Wright[26] found that the dialysis membrane may affect the plasma Leptin level because of its surface adsorption characteristics ,thus researchers studying Leptin biology in haemodialysis patients should be aware that the choice of low-flux dialysis membrane might exert a small effect on their results.

The reduction of serum IGF-1 concentration of this study is in agreement with other studies.[27-31]

The reduction in circulating concentration of IGF-1 observed in some patients could be attributed to one of three major etiologies: low circulating concentrations of growth hormone(GH),liver failure, and protein-calorie deprivation.[27] GH deficiency is unlikely because GH increases in patients with CRF;[28] however, an inhibitory effect of dietary protein calorie deprivation on the binding of GH to the liver may lead to decreased synthesis of IGF-1.[29] The decrease in IGF-1,observed in some heamodialyzed paients,is likely to reflect catabolism.[30]

Acute intercurrent illnesses, such as infections, preceding the measurement of IGF-I could also have contributed to the catabolic status of some patients, serum IGF-I concentrations decrease well before any change in other biochemical or anthropometric indices of malnutrition can be detected,[31, 32] so it is way predict early malnutrition.

In conclusion, the present study shows that Leptin level has been proved to be elevated in patients with pre-dialysis, due to renal failure that may be impairs either its synthesis or clearance. We have also demonstrated an increase in the level of IGF-1 in post-dialysis when compared with pre- dialysis, but the level still lower than healthy control, thus early decrease in serum IGF-1 may allow early detection of malnutrition in haemodialyzed patients.

REFERENCES

1. Pendse S, Singh A, Zawada E.lnitition of dialysis .In: Handbook of Dialysis.4th ed .New York.NY;2008-14-21.
2. Atlas of Disease of the kidney, volume 5, Principles of Dialysis: Diffusion, Convection, and Dialysis Machines (PDF).http//www.kidneyatlas.org/book5/adk501.ccc.QXD.pdf .Retrieved 2011-09-02.
3. Hakim RM, Levin N. Malnutrition in hemodialysis patients. ***Am J Kidney Dis*** 1993; 21:125-37.
4. N. Cano Marsella. Francia. Hemodialysis, inflammation and malnutrition. ***NEFROLOGÍA*** 2001; 21: 437-42.
5. Chazot C, Laurent G, Charra B, Blanc C, VoVan C, Jean G, et al. Malnutrition in long-term haemodialysis survivors. ***Nephrol Dial Transplant*** 2001; 16:61-9.
6. Stenvinkel P. Leptin–a new hormone of definite interest for the nephrologists. ***Nephrol Dial Transplant*** 1998; 13:1099-101.
7. Patel SB, Ream GP, Spear RM, Freeman RH, Villarreal D. Leptin: linking obesity, the metabolic syndrome, and cardiovascular disease. ***Curr Hypertens Rep*** 2008; 10:131-7.
8. Boden G, Chen X, Kolaczynski JW, Polansky M. Effects of prolonged hyperinsulinemia on serum leptin in normal human subjects. ***J Clin Invest*** 1997; 100:1107-13.
9. Sharma K, Considine RV, Michel B, Dunn SR, Weisberg LS, Kurnik BR, et al. Plasma leptin is partly cleared by the kidney and is elevated in hemodialysis patients. ***Kidney Int*** 1997; 51:1980 -5.
10. Grunfeld C, Zhao C, Fuller J, Pollack A, Moser A, Friedman J, et al. Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. ***J Clin Invest*** 1996; 97:2152-7.
11. Kirchgessner TG, Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Tumor necrosis factor–alpha contributes to obesity-related hyperlipidemia by regulating leptin release from adipocytes. ***J Clin Invest*** 1997; 100:2777-82.
12. Sarraf P, Frederich RC, Turner EM, Ma G, Jaskowiak NT, Rivet DJ 3rd, et al. Multiple cytokines and acute inflammation raise mouse leptin levels: Potential role in inflammatory anorexia. ***J Exp Med*** 1997; 185:171-5.
13. Phillips LS, Fusco AC, Unterman TG, del Greco F. Somatomedin inhibitor in uremia. ***J Clin Endocrinol Metab*** 1984; 59:764-72.
14. Ding H, Gao X-L, Hirschberg R, Vadgama JV, Kopple JD. Impaired actions of insulin-like growth factor 1 on protein synthesis and degradation in skeletal muscle of rats with chronic renal failure. Evidence for a postreceptor defect. ***J Clin Invest*** 1996; 97:1064-75.
15. KOpple JD. McCollum Award Lecture, 1996: Protein-energy malnutrition in maintenance dialysis patients. ***Am J Clin Nutr*** 1997; 65: 1544-57.
16. MAroni B, BUrkart J, BUrrowes J, COckram D, DRabik M, DWyer J, et al. Baseline nutritional characteristics of the HEMO study participants: Interim report. (abstract) ***J Am Soc Nephrol*** 1996; 7:1456,
17. STenvinkel P, Heimbürger, O, Lönnqvist F. Serum leptin concentrations correlate to plasma insulin concentrations independent of body fat content in chronic renal failure. ***Nephrol Dial Transplant*** 1997; 12:1321-5.
18. Merabet E, Dagogo-Jack S, Coyne DW, Klein S, Santiago JV, Hmiel SP, et al. Increased plasma leptin concentration in end-stage renal disease. ***J Clin Endocrinol Metab*** 1997; **82**:847-50.
19. Meyer C, Robson D, Rackovsky N, Nadkarni V, Gerich J. Role of the kidney in human leptin metabolism. ***Am J Physiol*** 1997; **273**:E903-7.
20. A.J. Fogteloo, A.E.Meinders, H.Pijl, A.A. Kroon, M. Frolich, P.W. De Leeuw-. Renal clearance of endogenous leptin in hypertensive humans with or

without renal artery stenosis. Submitted 17 October 2000,accepted in final form 28 March 2001.

21. Don BR, Rosales LM, Levine NW, Mitch W, Kaysen GA. Leptin is a negative acute phase protein in chronic hemodialysis patients. ***Kidney Int*** 2001; 59:1114-20.
22. Horoz M, Aslan M, Koylu AO, Bolukbas C, Bolukbas FF, Selek S, et al. The relationship between leptin level and oxidative status parameters in hemodialysis patients. ***Artif Organs*** 2009; 33:81-5.
23. Sharma K, Considine RV, Michael B, Dunn SR, Weisberg LS, Kurnik BR, et al. Plasma leptin is partly cleared by the kidney and is elevated in hemodialysis patients. ***Kidney Int*** 1997; 51:1980-5.
24. Stenvinkel P, Heimbürger O, Lönnqvist F. Serum leptin concentrations correlate to plasma insulin concentrations independent of body fat content in chronic renal failure. ***Nephrol Dial Transplant*** 1997; 12:1321-5.
25. Schwartz MW, Baskin DG, Bukowski TR, Kuijper JL, Foster D, Lasser G, et al. Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice. ***Diabetes*** 1996; 45:531-5.
26. Wright MJ, Woodrow G, Young G, Brownjohn AM, Turney JH. Biocompatible dialysis membranes do not reduce plasma leptin levels. ***Nephrol Dial Transplant*** *2000; 15:925-6.*
27. Van Wyk JJ, Underwood LE. The somatomedins and their actions.In: Litwack 0, ed. Biochemical actions of hormones. NewYork: Academic Press, Inc, l978;5:lOl-48.
28. Lim VS, Kathpalia SC, Henriguez C. Endocrine abnormalities associated with chronic renal failure. ***Med Gin North Am*** l978; 62:1341-4.
29. Maes M, Underwood LE, Ketalscegers JM. Low serum somatomedin-C in protein deficiency; relationship with changes in liver somatogenic and lactogenic binding sites. ***Mol Cell Endocrinol*** 1984; 37:301-9.
30. Valerie Jacob, Jayne E Le Carpentier, Stephen Salzano Valerie Naylor, Graham Wild, Cohn B Brown, and A Meguid ELNahas. IGF-1, a marker of under nutrition in hemodialysis patients. Downloaded from www.ajcn.org by guest on June 5, 2012.
31. Biachi R, Mariani G, Toni MG, Carmassi F. The metabolism of human serum albumin in renal failure on conservative and dialysis therapy***. Am J Gin Nutr*** 1978; 31:1615-26.
32. Alvestrand A. Nutritional requirements of hemodialysis patients. In: Mitch WE, Klahr 5, eds. Nutrition and the kidney. Boston:Little, Brown and Company Publishers, 1988:180-97.