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RESEARCH ARTICLE

Serum Insulin and Leptin Levels in Chronic Renal Failure Patients Using Radiometric Techniques

Amal A. El-Mahdy[1], Eithar K. El-Adham[1*], A. M. El-Waseef[2], , M. A. Mosleh[1]

1. Radioisotopes Department, Nuclear Research Center, Atomic Energy Authority, Egypt.
2. Division of Biochemistry, Chemistry Department, Faculty of science, Mansoura University, Mansoura, 35516, Egypt.

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Corresponding Author

Eithar K. El-Adham

Abstract

As a very real and growing problem, chronic kidney disease is characterized by progressive deterioration of kidney function which develops eventually into a terminal stage of chronic kidney failure. The present study aimed at investigating the variations which may occur in some biochemical parameters in chronic kidney failure patients under haemodialysis (three times / week) compared to healthy volunteers in the same age range. The results revealed highly significant increase in serum urea, creatinine, triglyceride, insulin and leptin in patients compared to the controls. The increase of insulin levels in patients before dialysis points to the development of insulin resistance and liability to diabetes. Also the significant increases in serum leptin in patients is associated with deteriorated kidney function and decreased renal clearance of leptin

Introduction

Renal failure formerly called renal insufficiency is a situation in which the kidneys fail to function adequately. It is divided into acute and chronic forms a number of other diseases or health problems may cause either form of renal failure to occur (Klahr and Miller 1998). The kidneys filter waste products and toxins from the blood and maintain water balance in the body. To function normally the kidneys require high-volume delivery of blood to be filtered, adequate tissue function and unobstructed outflow tracts for urine and filtered blood. Problems in any of these three areas can cause sudden onset kidney failure, acute renal failure (Lameire et al., 2005). Chronic renal disease is a progressive loss in renal function over a period of months or years. It is defined as either kidney damage or decreased kidney function (decreased GFR of less than 60 ml/min/1.73 m2), for three months or more (Levey et al., 2005).

Chronic kidney disease (CKD) is a very real and growing problem as indicated by demographic trends. The total number of treated patients has markedly increased during the last 30 years, with an incidence that is increasing rapidly. CKD is characterized by progressive deterioration of kidney function, leading to a terminal stage of chronic renal failure (CRF). CRF has traditionally been categorized as mild, moderate, or severe. Other poorly defined terms like uremia and end-stage renal disease (ESRD) have commonly been applied (Snyder and Pendergraph, 2005).

Insulin hormone is an important regulator of energy homeostasis. It stimulates glucose, free fatty acid and amino acid uptake by tissues and tissue anabolism (Joshi et al., 2007). The kidney plays a central role in the metabolism of insulin in normal subjects. Approximately one third of the body's insulin is removed by the kidney. Many studies have shown that the sensitivity to the action of insulin with respect to carbohydrate metabolism is

markedly impaired in patients with end-stage renal failure who are undergoing conservative or dialytic treatment. Therefore, insulin resistance and the compensatory hyperinsulinemia might contribute to the development of cardiovascular complications in ESRD patients (Kobayashi et al., 2005).

Leptin is a protein hormone produced by adipocytes (Zhang et al., 1994). Its basic known function is its central hypothalamic action leading to reduction of food intake and augmentation of energy expenditure and thus to reduction of body weight (Kim et al., 2010). Besides mediating energy homeostasis, body weight, appetite, fat stores or glucose metabolism and the action of insulin, leptin also interacts with the hypothalamic-pituitary-adrenal axis and influences sexual maturation, thereby playing a key role in reproduction and development. It may have a role in cardiovascular and renal functions, and it affects bone formation, liver function, stimulates haematopoiesis and phagocytic activity of macrophages (Blüher and Mantzoros, 2009). As a small peptide hormone, leptin is principally cleared by the kidney. Several studies have investigated the relationship between leptin concentration and body fat content in chronic renal failure patients (Kayardi et al., 2006). The present study was planned to measure serum leptin and insulin levels in chronic renal failure patients.

SUBJECTS AND METHODS

Samples

This study included 15 male patients suffering from CRF and undergoing regular haemodialysis (3 times/ week) with age range 45-55 years and 15 healthy volunteers with matched age range. The patients were selected from the Haemodialysis Unit of the Medical Center of Integrated Sugar Company, El-Hawamdia, and Giza, Egypt. The patients were examined before (B) and after (A) dialysis.

Any patient with diabetes mellitus or congestive heart failure was excluded from the present study. Venous blood samples were collected from all subjects and placed in plain tubes then the serum samples were separated by cooling centrifugation at 3000 rpm using HENZ Jametzki cooling centrifuge (Germany) and preserved at -20°C till analysis. The study protocol was approved by the Institutional Review Committee and conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Biochemical Analysis

Serum creatinine was measured by a kinetic method according to Bowers and Wong, 1980. Serum urea was measured by Berthelot enzymatic colorimetric method of Burtis and Ashwood, 1999. Cholesterol was measured by the method of Ellefson and Caraway, 1976 and Triglycerides were measured by the method of Mgowan et al. 1987. Using radioimmunoassay (RIA), insulin was determined according to the method described by Bates, 1983, while leptin was determined according to the method described by Zhang et al., 1994.

Statistical Analysis

Data were analyzed using the computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. The statistical significance of the mean values between groups was performed using student´s t-test. Correlation between two parameters was determined by Pearson's correlation coefficient (r). The results were expressed as Mean±SD and values of $P < 0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

RESULTS

Table 1 shows a highly significant increase in the mean value of serum urea, creatinine and triglycerides concentrations in the CRF (B, A) patients compared to their levels in the controls, and no difference in the mean value of serum cholesterol concentration between CRF (B, A) patients and controls.

On the other hand, highly significant elevations in the mean serum insulin and leptin levels in the patients group (B) compared to their levels in the controls were found (Table 2). There were positive correlations in CRF-B patients

group between serum insulin and leptin levels (r = 0.299, P = 0.018, Fig. 1), serum leptin level and cholesterol concentration (r = 0.366, P = 0.008, Fig. 2), and serum leptin level and triglycerides concentration (r = 0.412, P = 0.005, Fig. 3).

Table 1: Serum urea, creatinine, cholesterol and triglycerides concentrations in controls and chronic renal failure (CRF) subjects

Parameter	Control Mean±SD	CRF-B Mean±SD	CRF-A Mean±SD	P-value
S. urea (mg/dL)	25.53±4.52[ab]	269.53±58.64[b]	62.33±8.73[a]	< 0.001*
S. creatinine (mg/dL)	0.91±0.18[ab]	8.65±2.83[b]	4.25±0.93[a]	< 0.001*
S. cholesterol (mg/dL)	159.33±18.89	173.67±17.12	138.80±19.88	NS
S. triglycerides (mg/dL)	82.20±19.23[ab]	182.67±35.42[b]	124.87±35.73[a]	< 0.001*

*Significant value (P < 0.05). P < 0.001 is considered highly significant. P > 0.05 is considered non-significant (NS). Chronic renal failure (CRF). Before dialysis (B). After dialysis (A). [b]Significant value between control group and CRF-B group. [a]Significant value between control group and CRF-A group.

Table 2: Serum insulin and leptin levels in controls and chronic renal failure (CRF) subjects

Parameter	Control Mean±SD	CRF-B Mean±SD	CRF-A Mean±SD	P-value
S. insulin (µIU/mL)	16.18±3.64[b]	29.57±5.22[b]	19.53±4.78	< 0.001*
S. leptin (ng/mL)	6.50±1.90[b]	24.63±7.42[b]	10.95±4.80	< 0.001*

*Significant value (P < 0.05). P < 0.001 is considered highly significant. Chronic renal failure (CRF). Before dialysis (B). After dialysis (A). [b]Significant value between control group and CRF-B group.

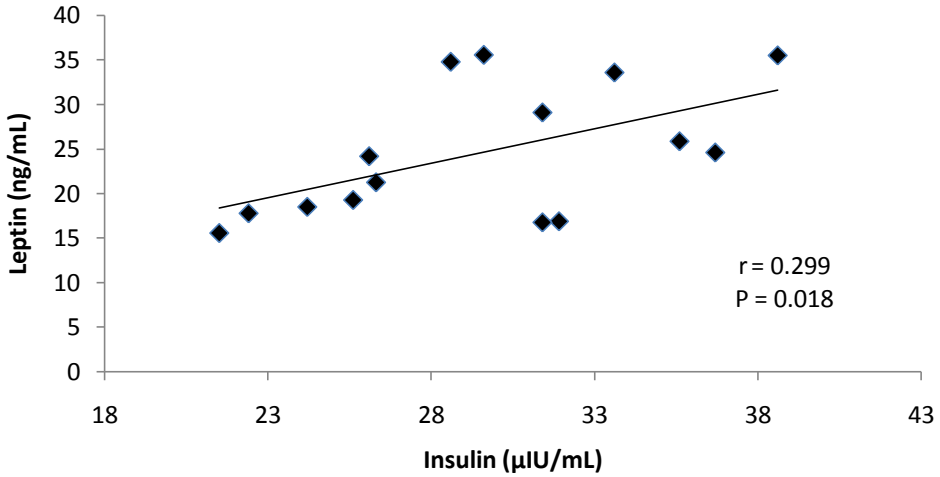

Figure 1: Correlation between serum insulin and leptin levels in chronic renal failure-before dialysis (CRF-B) patients.

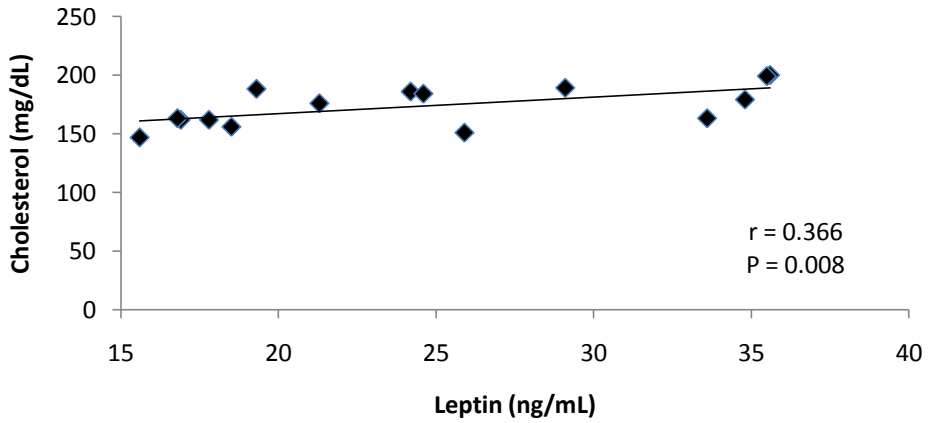

Figure 2: Correlation between serum leptin and cholesterol levels in chronic renal failure-before dialysis (CRF-B) patients.

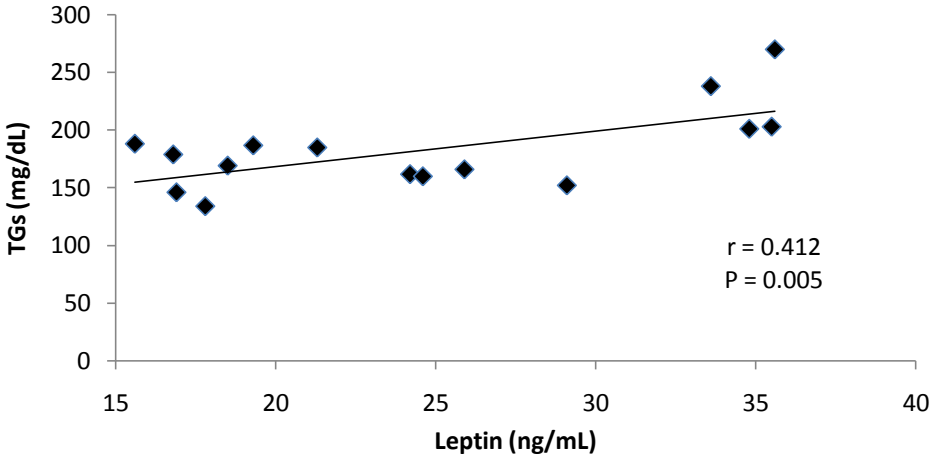

Figure 3: Correlation between serum leptin and triglyceride levels in chronic renal failure-before dialysis (CRF-B) patients.

DISCUSSION

Renal failure disease is characterized by progressive increase in blood urea nitrogen causing uremia and electrolyte imbalance. This disease includes acute renal failure i.e: a sudden loss of renal function that may results from accidental injury, excessive blood loss, poisoning or medication. It may be progressed over a period of years to chronic renal failure (CRF) (serum creatinine concentration >3.0 mg/dL) (Albright, 2001). The results of the present study showed highly significant increase in the mean values of both serum urea and creatinine concentrations in CRF (before and after dialysis) patients compared to the corresponding levels in the controls (Table 1). These results are in agreement with the results of Brenner and Rectors, 2000 and Dziedzic et al., 2008 who observed that in the course of renal failure; patients may be asymptomatic with excess serum creatinine and blood urea nitrogen. The rise of serum creatinine level due to the initial decrease in creatinine filtration by glomeruli is matched by enhanced creatinine secretion by the cells of proximal tubules. In addition, a relatively large rise in serum creatinine concentration reflects a relatively small decrease in GFR in patients with pre-existing chronic renal insufficiency (Brenner and Rectors, 2000). Levey et al., 2005 reported 30-40% reduction in enzymatic activity of the urea cycle in chronic kidney disease patients with a down-regulation of ureagenesis and accumulation of nitrogenous substances including middle molecule toxins.

Hyperlipidemia has been incriminated as a risk factor of atherosclerotic vascular disease in dialysed patients (de Gómez Dumm et al., 2001). Lipids are essential component of biological membranes, free molecules and metabolic

regulators that control cellular function and homeostasis. In the present results for chronic renal failure patients-before dialysis, there was a non-significant increase in serum cholesterol concentration while serum triglycerides concentration was significantly increased compared to the corresponding control levels. These results agree with the results of de Gómez Dumm et al. 2001, Weiner et al. 2004, Kastarinen et al. 2009, and Tsimihodimos et al. 2011 who reported that hyperlipidemia had been incriminated as a risk factor of atherosclerotic vascular disease in dialysed CRF patients. These authors reported that plasma triglycerides, but not cholesterol, are increased in most patients with advanced renal failure. On the other hand Trevisan et al. 2006 and Sumathi et al. 2010 reported increased cholesterol and triglyceride levels in dialysed patients. After dialysis, the result obtained revealed that, CRF patients exhibited a non-significant decrease in serum cholesterol concentration compared to the controls (Table 1). Although the pathophysiological mechanisms for the relationship between lipid levels and progression of renal disease are well not understood, there are data that oxidative stress and insulin resistance may mediate lipid-induced renal damage (Abrass, 2004). The diminished clearance of triglycerides, which can lead to hypertriglyceridemia, stems both from an alteration in the composition of circulating triglycerides and perhaps from reduction in the activity of lipoprotein lipase and hepatic triglyceride lipase which are involved in triglyceride removal (Trevisan et al. 2006; Sumathi et al. 2010; Vaziri, 2006).

The kidneys play a central role in the metabolism of insulin in normal subjects and in renal failure; the kidneys cannot metabolize insulin thereby increasing the risk of hypoglycemia or hyperinsulinemia (Kobayashi et al., 2005). The present results showed a highly significant increase in the mean serum insulin level in CRF patients before dialysis compared to the corresponding level of the controls (Table 2). This result agrees with the results of Satirapoj et al. 2005, Becker et al. 2005, Mark et al. 2008, and Pham et al. 2011 who observed hyperinsulinemia in patients with renal failure, suggesting that abnormal glucose pathaological conditions. These investigators reported high insulin resistance in CKD and attributed this to high prevalence of obesity which is a known risk factor for metabolic abnormalities. The association between chronic kidney diseases (CKD) and insulin resistance in non-diabetic patients is well recognized. Insulin resistances prevalent in end-stage renal disease(ESRD) patients, as well as patients with moderate to advanced CKD. Insulin secretion abnormalities may also be present leading to glucose intolerance. The etiology of the insulin abnormalities may involve uremic toxins from protein catabolism, vitamin D deficiency, metabolic acidosis, anemia, poor physical fitness and cachexia. Glucose and insulin abnormalities in non-diabetic CKD patients are implicated in the pathogenesis of hyperlipidemia and may represent important risk factors for accelerated atherosclarosis in these patients (Mak. 2008)

Leptin is a protein hormone predominantly produced by adipocytes. It is encoded by the ob gene and is involved in the maintenance of a stable body fat mass. It decreases food intake by decreasing NPY (neuropeptide Y, one of the most potent stimulators of food intake) mRNA and increasing α-MSH (alpha-melanocyte-stimulating hormone, an inhibitor of food intake) (Więcek et al., 2002). In the course of chronic kidney insufficiency, due to renal impairment, different endogenous small and middle size compounds (called uremic toxins e.g. leptin) are retained in the body. Leptin is partly cleared by the kidney and has been reported to increase in CRF (Bossola et al., 2004; Briley and Szczech, 2006). In the present study, a highly significant increase in serum leptin level was found in patients CRF-before dialysis, the result support the previous results of Dziedzic et al. 2008, Więcek et al. 2002, Obineche et al. 2002, Stamatiadis et al. 2004, and Shankar et al. 2012 which confirmed that leptin is mainly eliminated via the kidneys. Significantly high leptin levels in renal failure patients were reported by Krizova et al., 2003 who attributed this to the lower clearance of leptin by the kidney and increased insulin and proinflammatory cytokine stimulation of leptin synthesis. The etiology of reduced appetite and malnutrition in patients with CRF is very complex and hyperleptinemia is one of its possible causes (Tellingen et al., 2004). It seems that increased leptin concentration is responsible for anorexia, progression of malnutrition and may play an important role in disturbance in insulin action, sodium management, hematopoesis and bone formation (Briley and Szczech 2006). This increase of serum leptin levels in CRF patients might be due to prolongation of the half-life of leptin due to decreased degradation by the kidney (Brenner and Rector, 2000; Bossola et al., 2004). Furthermore, chronic inflammation plays an important role in the elevation of plasma leptin concentration as confirmed by the association between pro-inflammatory cytokines and leptin synthesis in adipocytes (Kato et al., 2001; Tellingen et al., 2004; Comlekci et al., 2003). Also, an inverse correlation between leptin level and glomerular filtrations rate has been demonstrated in patients with various degrees of renal failure (Tellingen et al., 2004). Uremia is one of the most important features of renal disease; it is associated with increase in several hormones such as glucocorticoids, insulin and growth hormone that was found to increase leptin levels leading to hyperleptinaemia. The important role of the kidney in leptin metabolism was further understood by the fact that leptin levels were normalized after successful transplantation (Bossola et al., 2004; Garibotto et al., 2000). The present study showed that, there was a positive correlation between serum insulin and leptin levels ($r = 0.299$, $P = 0.018$, Fig. 1). This consistent with the results of Obeniche et al. 2002

and EL-Mougi et al. 2006 who found a positive significant correlation between serum leptin and insulin concentrations in CRF-B patients. Leptin promotes atherosclerosis, thrombosis and vascular smooth muscle cell proliferation and migration. In addition, clinical studies have demonstrated a significant correlation between leptin levels and hypertension, hyperlipidemia, perturbed fibrinolysis and chronic inflammation (Diez et al. 2011). Patients with CRF are at increased risk of cardiovascular disease that has been linked to hyperleptinaemia (Kastarinen et al., 2009). In this study, there were positive correlations between serum leptin level and cholesterol concentration ($r = 0.366$, $P = 0.008$, Fig. 2), and serum leptin level and triglycerides concentration ($r = 0.412$, $P = 0.005$, Fig. 3) in CRF-B patients group. These results were in agreement with studies done by Taskapan et al. 2007 and Nasri et al. 2006 who reported that serum leptin levels were positively correlated with serum triglycerides and total cholesterol levels in dialysed patients.

It is not surprising that a link between leptin and insulin should exit in the regulation of energy homeostasis (Margetic et al., 2002). French and Castiglione (2002), reported that leptin receptors are expressed in the islets, suggesting that leptin might influence insulin secretion through a direct action on these cells. On the other hand, insulin appears to act directly at the level of the adipocyte by increasing leptin secretion and expression, perhaps due to increased glucose transport and metabolism (Bastard et al., 2006)

CONCLUSION

On the light of the foregoing information, it can be concluded that, the significant increase in leptin levels in CRF patients is associated with deteriorated kidney function and decreased renal clearance of leptin. Also, the increase in serum insulin levels in patients with CRF-before dialysis points to the development of insulin resistance and liability to diabetes. These results highlight the importance of leptin as determinant of dyslipidemia in dialysed CRF patients.

COMPETING INTERESTS

The authors declare that there is no conflict of interest to this manuscript.

REFERENCES

Abrass C.K. Cellular lipid metabolism and the role of lipids in progressive renal disease.Am. J. Nepherol., 2004;24:46-53

Albright RC. Acute renal failure: A practical update. Mayo Clin Proc 2001;76:67-74.

Bastard, J.P., Maachi,M., Lagathu, C., Kim, M.J., Caron, M., Vidal, H., Jacqueline, C. and Bruno, F. Recent advances in the relationship between obesity, inflammation and insulin resistance. Eur. Cytokine Netw.,2006. 17:4-12

Bates, H.M. Insulinoma and pheochromocytoma. Lab Management 1983;21:11-12.

Becker B., Kronenberg F., Kielstein J.T, et al. Renal insulin resistance syndrome, adiponectin and cardiovascular events in patients with kidney disease: The mild and moderate kidney disease study. J Am Soc Nephrol 2005;16:1091-1098.

Blüher S,and Mantzoros C.S. Leptin in humans: Lessons from translational research. Am J. Clin. Nutr. 2009; 89:991-997.

Bossola M, Muscaritoli M, Valenza V, et al. Annorexia and serum leptin levels in hemodialysis patients. Nephron Clin Pract 2004;97:76-82.

Bowers L.D. and Wong E.T. Kinetic serum creatinine assays: A critical evaluation and review. Clin Chem 1980;26:555-561.

Brenner BM, Rector FC. The kidney. 6th ed Saunders, Philadelphia: PA 2000;pp: 1202-1210.

Briley L.P., Szczech L.A. Leptin and renal disease. Semin Dial 2006;19:54-59.

Burtis CA, Ashwood ER. Tietz Textbook of Clinical Chemistry. 3rd ed. 1999 AACC.

Comlekci A, Akpinar H, Yesil S, et al. Serum leptin levels in patients with liver cirrhosis and chronic viral hepatitis. Scand J Gastroenterol 2003;38:779-786.

de Gómez Dumm NT, Giammona AM, Touceda LA, et al. Lipid abnormalities in chronic renal failure patients undergoing hemodialysis. Medicina 2001;61:142-146.

Diez JJ, Bossola M, Fernández-Reyes MJ, di Stasio E, Tazza L, Luciani G, et al. Relationship between leptin and all-cause and cardiovascular mortality in chronic hemodialysis patients. Nefrologia 2011;31:206-212.

Dziedzic M, Duma D, Burska A, et al. Evaluation of the liver function and leptin concentration in hemodialysed patients. Annales 2008;21:72.

Ellefson RD, Caraway WT. 1976. Fundamentals of Clinical Chemistry. 6th ed Tietz, N.W 1976; P 506.

EL-Mougi HM, EL-Yazeed SA, Yousry ZA, Fattah AA. Serum leptin in patients with chronic renal failure on different modes of management. Egyptian J Hospital Medicine 2006;25:610-619.

French, S. and Castiglione, K. Recent advances in the physiology of eating. Proceedings of the Nutrition Society. 2002. 61:489-96

Garibotto G, Barreca A, Sofia A, et al. Effects of growth hormone on leptin metabolism and energy expenditure in hemodialysis patients with protein-calorie malnutrition. J Am Soc Nephrol 2000;11:2106-2113.

Joshi, SR, Parikh RM, Das AK. Insulin-history, biochemistry, physiology, and pharmacology. JAPI. 2007;55:19-25.

Kastarinen H, Kesaneimi YA, Ukkola O. Leptin and lipid metabolism in chronic kidney failure. Scand J Clin Invest 2009;69:401-408.

Kato A, Odamaki M, Maruyama Y, et al. Association between circulating leptin and soluble receptors for tumor necrosis factor-alpha in hemodialysis patients. Clin Nephrol 2001;56:370-377.

Kayardi M, Icagasioglu S, Yilmaz A, et al. Serum leptin levels and malnutrition in patients with chronic renal failure. Saudi Med J 2006;27:477-481.

Kim H, Choi G, Jeo J, et al. Leptin and ghrelin in Korean systemic lupus erythromatosus. Lupus 2010;19:170-174.

Klahr, S. and Miller, S. Acute oliguria. N. Engl. J. Med., 1998, 338 (10):671-5.

Kobayashi S, Maesato K, Moriya H, et al. Insulin resistance in patients with chronic kidney disease. Am J Kidney Dis 2005;45:275-280.

Krízová J, Sulková S, Bednárová V, et al. Soluble leptin receptor levels in patients with chronic renal failure. Physiol Res 2003;52:347-351.

Lameire, N., Van Biesen, W. and Vanholder, R. Acute renal failure. Lancet, 2005;365(9457):417-30

Lerma EV, Nissenson, AR. Nephrology secrets. 3rd ed. Philadelphia: Elsevier Mosby; 2012.

Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: A position statement from kidney disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089-2100.

Mak RH. Insulin and its role in chronic kidney disease. Pediatr Nephrol 2008;23:355-362.

Margetic, S., Gazzola, C., Pegg, G. and Hill, R. Leptin: A review of its peripheral actions and interactions. Int. J. Obs.Relat. Metab. Disord. 2002. 26(11):1407-33

Mgowan MW, Artiss JD, Stadbergh DR, et al. A peroxidase-coupled method for colorimetric determination of serum triglycerides. Clin Chem 1987; 29:538-552.

Nasri H, Shirani S, Baradaran A. Lipids in association with leptin in maintenance hemodialysis patients. J Med Sci 2006;6:173-179.

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.

Pham H, Utzschneider KM, Boer IH. Measurement of insulin resistance in chronic kidney disease. Curr Opin Nephrol Hypertens 2011;20:640-646.

Satirapoj B, Supasyndh O, Boonyavarakul A, et al. The correlation of insulin resistance and renal function in non-diabetic chronic kidney disease patients. J Med Assoc Thai 2005;88:97-104.

Shankar A, Syamala S, Xiao J et al. Relationship between plasma leptin level and chronic kidney disease. Int J Nephrol 2012, Article ID 269532, 6 pages.

Snyder S, Pendergraph B. Detection and evaluation of chronic kidney disease. Am Fam Physician 2005;72:1723-1732.

Stamatiadis DN, Chan JL, Cogswell R, et al. Elevated leptin fragments in renal failure correlate with BMI and haematopoiesis and are normalized by haemodialysis. Clin Endocrinol 2004;60:434-441.

Sumathi ME, Manjunath MT, Jayapraka MD, et al. Study of lipid profile and oxidative stress in chronic renal failure. Biomedical Research 2010;21:451-456.

Taskapan MC, Taskapan H, Sahin I, Keskin L, Atmaca H, Ozyalin F. Serum leptin, resistin, and lipid levels in patients with end stage renal failure with regard to dialysis modality. Ren Fail 2007;29:147-154

Tellingen A, Grooteman MP, Schoorl M, et al. Enhanced long-term reduction of plasma leptin concentrations by super-flux polysulfone dialysers. Nephrol Dial Transplant 2004;19:1198-1203.

Trevisan R, Dodesini AR, Lepore G. Lipids and renal disease. J Am Soc Nephrol 2006;17:145-147.

Tsimihodimos V, Mitrogianni Z, Elisaf M. Dyslipidemia associated with chronic kidney disease. Open Cardiovasc Med J 2011; 5:41-48.

Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanism and potential consequences. Am J Physiol Renal physiol 2006;290:262-272.

Weiner DE, Sarnak MJ. Managing dyslipidemia in chronic kidney disease. J Gen Intern Med 2004;19:1045-1052.

Więcek A, Kokot F, Chudek J, et al. The adipose tissue- a novel endocrine organ of interest to the nephrologist. Nephrol Dial Transplant 2002;17:191-195.

Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the obese gene and its human homologue. Nature 1994;372:425-432.