Leptin and Thyroid Hormones as Endocrinal Biomarkers of Inflammation in End-Stage Renal Disease and Renal Transplant

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Abstract: Background: Renal functions affect thyroid and adipocytokines as leptin in many ways. Low free triiodothyronine (fT3) and free thyroxine (fT4) are frequent alteration in patients with end-stage renal disease (ESRD). This derangement has been recently linked to inflammation in haemodialysis patients. Whether this association holds true in relation to other inflammation markers in hemodialysis patients and who undergoing kidney transplantation has been under our study. Methods: We investigated the relationship between low-grade inflammation [C-reactive protein (CRP) and serum albumin levels] and free triiodothyronine (fT3) in a cohort of 30 patients from different centers of hemodialysis: Faysal Kidney Dialysis Unit and Health Insurance Dialysis Units: [10 were under hemodialysis (HD group); 10 were with succeeded kidney transplant (ST group); and 10 with failed kidney transplant (FT group)] and all investigations and BMI were done for all patients, no inter-current illnesses was found] and a group of 10 healthy subjects. Thyroid hormones were measured using enhanced chemiluminescnce technique; serum leptin was measured using enzyme-linked immunosorbent assays (ELISA); CRP and the other routine chemistry tests were done using the chemistry automation. Results: HD group had significant lower fT3 levels (2.3±21 pg/ml) than ST group (2.89±29 pg/ml); $P<0.01$, while had no significant difference in fT3 levels compared with FT group (2.34±21 pg/ml); $P>0.05$. The healthy subjects showed highly significant difference in fT3 levels (3.34±29 pg/ml) than in all HD, ST and FT groups; ($P<0.01$). In HD group, free T3 levels were inversely related to serum creatinine, cholesterol (R=-0.645; $P<0.05$ and R= -0.715; $P<0.01$ respectively) while were directly related to diastolic blood pressure (R=0.342; $P<0.05$). In FT group, serum leptin showed a direct correlation with CRP and serum creatinine (R= 0.725; $P<0.01$ and R=0.758; $P<0.01$ respectively) and an inverse correlation with hemoglobin (R=-0.747; $P<0.01$) while fT4 showed a direct significant correlation with serum albumin (R=0.651; $P<0.05$). Conclusion: The relationship between fT3, fT4, CRP and serum albumin suggests the inflammation– malnutrition involved in the low T3, low T4 syndromes in hemodialysis patients. Among patients with ESRD undergoing kidney transplantation, those displaying lower pretransplant serum fT3 and fT4 levels are at higher risk for subsequent graft failure. We need values of serum fT3 and fT4 levels for graft survival in a larger scale suggesting that measurement of pretransplant serum fT3 and fT4 levels might represent a clinically useful parameter to identify patients with increased risk for graft failure. A possible role of adipocytokines may be found in the metabolic disturbances that frequently accompany thyroid dysfunction in chronic renal failure.
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1. Introduction

The kidney normally plays an important role in the metabolism, degradation and excretion of several thyroid hormones (Malyszko et al., 2006). Chronic renal failure (CRF) affects thyroid function in many ways, including low circulating thyroid hormone levels, altered peripheral hormone metabolism, insufficient binding to carrier proteins, possible reduction in tissue hormone content and altered iodide storage in the thyroid gland (Lim, 2001). Thus, patients with renal failure may have various abnormalities of thyroid function; nevertheless, they are typically clinically euthyroid. Thyroid hormones as well as recently discovered secretory products of adipose tissue—adipocytokines—take part in energy metabolism. Leptin is considered to be a fundamental signal of satiety to the brain and has a variety of actions, ranging from interference with sympathetic activity to haematopoiesis and the reproductive system (Soltys et al., 2000). Little studies to date have been reported concerning the possible role of adipocytokines in the metabolic disturbances that frequently accompany thyroid dysfunction in chronic renal failure (Santini et al., 2004). The object of our study was to assess the serum concentration of leptin in relation to thyroid function in patients with CRF maintained on chronic haemodialysis (HD) and in kidney allograft recipients. In this study, we investigated the

relationships between C-reactive protein (CRP), the solidly established marker of the malnutrition-inflammation syndrome (Kaysen 2001, Stenvinkel et al., 2002 & Fernandez-Real et al., 2003) and the metabolically active hormones (free T3 & free T4) in all patients.

In addition, patients with chronic renal failure have signs and symptoms suggestive of thyroid dysfunction (Avasthi et al., 2001); nevertheless, they are typically euthyroid. The clinical impression of euthyroidism is supported by normal serum thyroid stimulating hormone (TSH) in most of these patients. Many of the clinically euthyroid patients with nonthyroidal illness (NTI) have low circulating concentrations of total and absolute free tri-iodothyronine (T3), low or normal concentrations of total thyroxine (T4), elevated concentrations of absolute free T4, and normal or subnormal levels of TSH. However, it was reported that simultaneous elevation of TSH compensates for these low levels. Consequently, patients are usually clinically euthyroid. This has been named "euthyroid sick syndrome" (ESS) which was first described about 4 decades earlier (Abozenah et al., 2008).

Thyroid hormones as well as recently discovered secretory products of adipose tissue -adipocytokines- take part in energy metabolism. Adipose tissue is now known to express and secrete a variety of hormones and cytokines, among them is leptin. Leptin is the 16-kDa protein product of the obesity gene (ob) (Zhang et al., 1994). It is a mediator of metabolism and disease in a variety of organ systems, most notably as an agent of energy stores. Leptin interacts with putative receptors in the hypothalamus decreasing appetite, increasing energy expenditure and regulating body weight (Obermayer-Pietsch et al., 2001). However, its role in renal disease as an inflammatory agent has sparked new interest in the molecule for nephrologists (Briley and Szczech 2006).

In the present study, we prospectively assess the serum concentration of leptin in relation to thyroid function in chronic renal failure (CRF) treated conservatively, in those maintained on chronic haemodialysis (HD) and in kidney allograft recipients.

2. Materials and Methods

Study population

This was an open-label, unblinded evaluation of the pathological differences between four groups of subjects from different centers of kidney diseases: Faysal Kidney Dialysis Unit and Health Insurance Dialysis Units: haemodialysed patients (HD) (n=10), kidney transplant recipients (ST) (n=10), and chronic renal failure (CRF) failed for kidney transplantation (FT) (n=10). Also healthy volunteers (n=10) were recruited from the medical staff. All participants gave informed consent and the study followed the Medical University Ethics Committee rules. Subjects with diabetes, liver disease, or any known infectious disease were excluded. No subjects were taking any medication or herbal remedies known to affect lipid metabolism at time of the analysis.

In all patients, blood was drawn in the morning between 8 and 9 a.m. before the onset of the midweek dialysis session (and heparin administration). Blood was taken without stasis. Samples were aliquotted and stored at -20°C before assay.

Clinical tests

Body weight and height were recorded (Chan et al., 2004); BMI values were calculated. Blood pressure was recorded semiautomatically by use of a Dinamap recorder (Critilzon).

Biochemical analysis

The following parameters were measured: haemoglobin (Hb), haematocrit (Ht), creatinine, cholesterol, triglycerides, albumin and C-reactive protein (CRP) were determined by standard enzymatic methods (interassay CVs < 3%). TSH (Wayne, 1990), Free T3 (FT3) (Wayne, 1999) and free T4 (FT4) (Villanova, 1990) were measured by automated chemiluminescence immunoassay (ACS-180, American Kang Ning Company). The intra assay and interassay coefficient of variation were 2% and 6% respectively, for both FT3 and FT4. Plasma leptin concentration was measured by commercially available DSL Active TM Human Leptin Enzyme-Linked Immunosorbent ELISA kit (Diagnostic Systems Laboratories, USA (Hanigaya et al., 1997). The interassay CV for this method was < 7%.

Statistical analysis

All analyses were performed with SPSS 10.0. Data were reported as means ± standard deviation (SD). Analysis of variance (ANOVA) or Kruskall–Wallis ANOVA (the difference between the mean of two variables was calculated by Mann–Whitney U-test) were used to compare differences between groups, with $P<0.05$ considered statistically significant, when appropriate. Linear regression analysis employed Pearson or Spearman coefficients as appropriate.

3. Results

Biochemical characteristics among the different investigated groups

Biochemical characteristics of the patients with homodialysis (HD), kidney transplant recipients (ST), failed for transplant (FT) and healthy volunteers are presented in Table 1. Body mass index (BMI) was significant among the investigated groups. Significant difference was reported between HD, ST, FT and control regarding SBP, HB, Ht, triglyceride, albumin,

FT3, and leptin. In homodialysed patients, Hb and Ht were significantly lower than in ST and FT groups, on the other hand serum creatinine, cholesterol, triglycerides, C-reactive protein were significantly higher than ST group. For ST patients, significant difference was detected with FT regarding DSP, Hb, Ht, creatinine, triglyceride, C-reactive protein, FT3, Ft4 and leptin. Serum levels of TSH and leptin were significantly higher in HD, ST and Ft as compared the control group.

Table (1): Biochemical characteristics of the investigated groups

Characteristics	Control	HD	ST	FT
Gender	6m, 4f	7m, 3f	7m, 3f	6m, 4f
Age (years)	41.2 ± 5	43 ± 5	39.7 ± 4	43.6 ± 5
BMI (kg/m^2)	24.1 ± 0.2	23.1 ± 0.2*** $^{\#\#}$	24.5 ± 0.2*** $^{\#\#}$	23.7 ± 0.3*** $^{\#\#\,л\,л}$
Systolic BP (mmHg)	115.5 ± 4	140 ± 3.3***	140 ± 4***	140 ± 3.3***
Diastolic BP (mmHg)	77.5 ± 4	74 ± 4.6	72.5 ± 4	77.5 ± 5** $^{л\,л}$
Hb (g/dl)	14.2 ± 1	10 ± 0.9***	13 ± 1** $^{\#\#}$	11 ± 1*** $^{\#\,л\,л}$
Ht (%)	44 ± 3	30.7 ± 3***	40.3 ± 3** $^{\#\#}$	34.8 ± 4*** $^{\#\,л\,л}$
Creatinine (mg/dl)	0.89 ± 0.01	11.8 ± 2.1***	1.35 ± 0.1$^{\#\#}$	6.38 ± 1$^{\#\#\,л\,л}$
Cholesterol (mg/dl)	178 ± 15	213 ± 20***	190 ± 15$^{\#\#}$	201 ± 14***
Triglycerides (mg/dl)	87 ± 21	188 ±12***	131 ±22*** $^{\#\#}$	164 ± 47*** $^{л\,л}$
Albumin (g/L)	4.3 ± 0.4	3.4 ± 0.4***	3.8 ± 0.3*** $^{\#}$	3.7 ± 0.3***
CRP (mg/dl)	4.7 ± 0.4	21.2 ± 6.3***	6.6 ± 0.8$^{\#\#}$	13.2 ± 4.1*** $^{\#\#\,л\,л}$
TSH (μIU/ml)	1.48 ± 0.3	2.6 ± 1.2***	1.6 ± 0.3$^{\#\#}$	2 ± 0.4*
FT3 (pg/ml)	3.4 ± 0.3	2.3 ± 0.2***	3 ± 0.2*** $^{\#\#}$	2.3 ± 0.2*** $^{л\,л}$
FT4 (ng/ml)	1.4 ± 0.2	1 ± 0.1***	1.4 ± 0.2$^{\#\#}$	1 ± 0.1*** $^{л\,л}$
Leptin (ng/ml)	7.2 ± 1.4	24 ± 5***	13 ± 4*** $^{\#\#}$	17 ± 4.5*** $^{\#\#\,л}$

HD; hemodialysis, ST; succeeded kidney transplant, FT; failed transplant, m; male, f; female. Data given are mean ± SD

*P<0.05, **P<0.01, ***P<0.0001 *vs* control, $^{\#}$ P<0.01,
$^{\#\#}$$P$<0.0001 HD *vs* ST, FT, ^{л}P<0.05, $^{л\,л}$ P<0.0001 ST *vs* FT.

Correlation between biochemical parameters in different investigated groups

In HD patients (Table 2), regarding the thyroid hormones, TSH was significantly correlated with age, BMI, creatinine, cholesterol, TG, albumin and CRP, while FT3 was significantly correlated with creatinine and cholesterol; however, FT4 was non-significantly correlated with the biochemical parameters. For serum leptin, only the significant correlation was reported with SBP.

In kidney transplant recipients (ST), neither thyroid hormones nor leptin reported significant correlation with the investigated biochemical variables. For patients failed for kidney transplantation (FT), TSH and FT4 were significantly correlated with DBP (R= 0.731, *P*= 0.016, and R= 0.716, *P*= 0.02, respectively), also FT4 was correlated with albumin (R= 0.652, *P*=0.041). In FT patients, leptin was correlated negatively with Hb (R= -0.748, *P*= 0.013), Ht (R= -0.75, *P*=0.012) and creatinine (R= -0.79, *P*= 0.011) and correlated positively with cholesterol (R= 0.97, *P*=0.034), triglyceride (R= 0.779, *P*= 0.008) and CRP (R= 0.725, *P*= 0.018).

For healthy volunteers, SBP and DBP were correlated (R= 0.67, *P*= 0.033), Hb was positively correlated with Ht (R= 1, *P*< 0.0001) and negatively correlated with cholesterol (R= -0.663, *P*= 0.036). Both triglyceride and Ht were negatively correlated with cholesterol (R= -0.637, *P*= 0.048, and R= 0.661, *P*= 0.037, respectively), moreover, triglyceride was significantly correlated with albumin (R= 0.816, *P*= 0.004). Among the thyroid hormones, only Ft4 showed significant correlation with both triglyceride (R= 0.845, *P*= 0.002) and albumin (R= 0.763, *P*= 0.01). Serum leptin was negatively correlated with Hb (R= -0.81, *P*= 0.005) and Ht (R= -0.808, *P*= 0.005) and positively with cholesterol (R= 0.891, *P*= 0.001).

Levels of CRP, FT3, FT4 and leptin among succeeded (ST) and failed kidney (FT) transplant

Using analysis of variance test, FT3 and FT4 were significantly higher in succeeded kidney transplant

Table (2): Pearson correlation coefficient (*R*) of biochemical variables in HD patients.

	Age	BMI	SBP	DBP	Hb	Ht	Creat.	Choles.	TG	Alb.	CRP	TSH	FT3	FT4	Leptin
Age															
R	_	0.565	0.452	-0.436	-0.434	-0.493	0.622	0.667*	0.298	-0.319	0.447	0.777*	0.279	0.409	0.502
P		0.089	0.189	0.208	0.21	0.148	0.055	0.035	0.404	0.37	0.195	0.008	0.435	0.24	0.139
BMI															
R		_	0.00	0.062	0.663*	0.652*	-0.28	-0.584	-0.585	0.718*	-0.573	0.732*	0.221	0.223	0.42
P			1	0.864	0.037	0.041	0.117	0.076	0.075	0.019	0.083	0.016	0.54	0.517	0.227
SBP															
R			_	0.544	0.293	0.373	-0.354	-0.008	0.371	0.2	0.342	-0.162	0.231	0.558	0.633*
P				0.104	0.412	0.288	0.316	0.982	0.292	0.579	0.332	0.656	0.52	0.094	0.049
DBP															
R				_	-0.151	-0.161	-0.138	-0.212	-0.038	-0.273	-0.011	-0.212	0.336	-0.049	-0.417
P					0.676	0.657	0.704	0.557	0.917	0.446	0.975	0.556	0.343	0.894	0.23
Hb															
R					_	0.976*	-0.765*	-0.351	-0.343	0.906*	0.327	0.623	0.153	0.35	0.497
P						0.0001	0.01	0.319	0.332	0.0001	0.357	0.054	0.674	0.321	0.144
Ht															
R						_	-0.759*	-0.361	-0.298	0.904*	-0.278	-0.628	0.155	0.467	-0.463
P							0.011	0.307	0.404	0.0001	0.437	0.052	0.67	0.173	0.178
Creat.															
R							_	0.78*	0.609	0.732	0.63	0.819*	-0.645*	-0.562	0.64*
P								0.008	0.061	0.016	0.051	0.004	0.044	0.091	0.046
Choles.															
R								_	0.819*	0.445	0.9*	0.884*	-0.716*	0.439	0.457
P									0.004	0.198	0.0001	0.001	0.02	0.204	0.185
TG															
R									_	0.447	0.919*	0.738*	0.61	0.059	0.661
P										0.196	0.0001	0.015	0.061	0.871	0.647
Alb.															
R										_	-0.411	-0.638*	0.358	0.552	-0.562
P											0.238	0.047	0.31	0.098	0.091
CRP															
R											_	0.832*	-0.536	-0.011	0.245
P												0.003	0.111	0.752	0.495
TSH															
R												_	0.53	-0.383	0.548
P													0.115	0.255	0.101
FT3															
R													_	0.585	0.63
P														0.076	0.051
FT4															
R														_	0.616
P															0.058
Leptin															
R															_
P															

(ST) as compared to failed transplant group (FT) (Figures 1 and 2, respectively). However, CRP was higher in FT as compared to ST (*P*< 0.0001) (Figure 3). Leptin showed no significant result among the two groups.

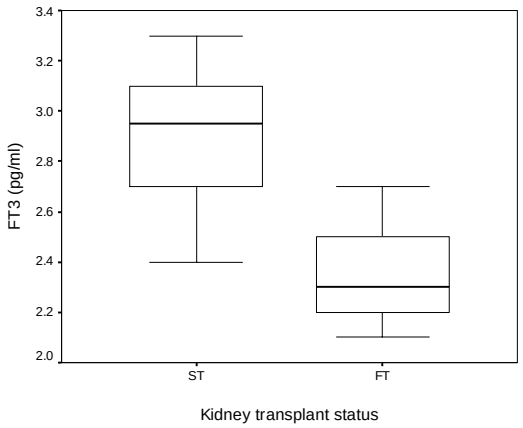


Figure (1): Level of FT3 among the status of kidney transplantation for ST and FT. Significant correlation (F=23.6, *P*<0.0001) was observed between FT3 and the status of kidney transplantation for ST and FT were [mean ± SD was 2.89 ± 0.29 with 95%CI for mean (2.68- 3.1) and median 2.95, and 2.3 ± 0.2 with 95%CI for mean (2.19- 2.48) and median 2.3], respectively.

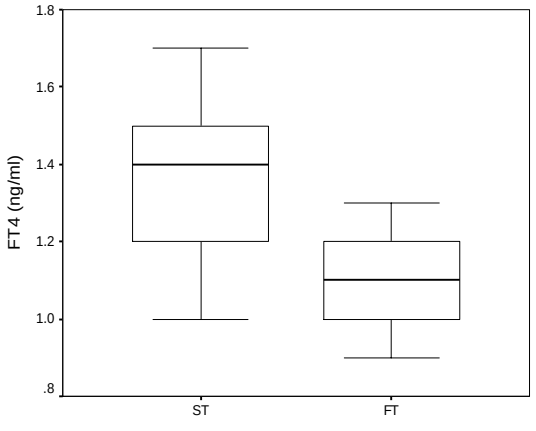


Figure (2): Level of FT4 among the status of kidney transplantation for ST and FT. Significant correlation (F=9.84, *P*=0.006) was observed between FT3 and the status of kidney transplantation for ST and FT were [mean ± SD was 1.4 ± 0.2 with 95%CI for mean (1.19 – 1.55) and median 1.4, and 1 ± 0.1 with 95%CI for mean (0.99- 1.188) and median 1.1], respectively.

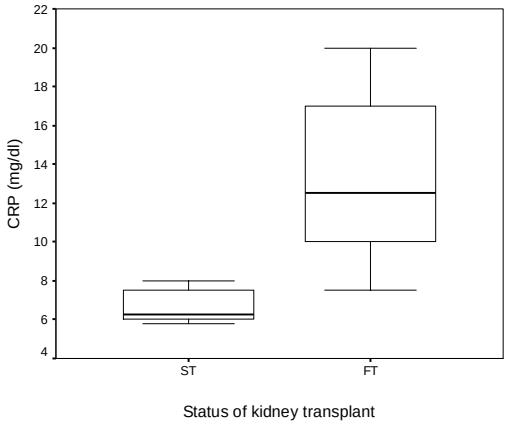
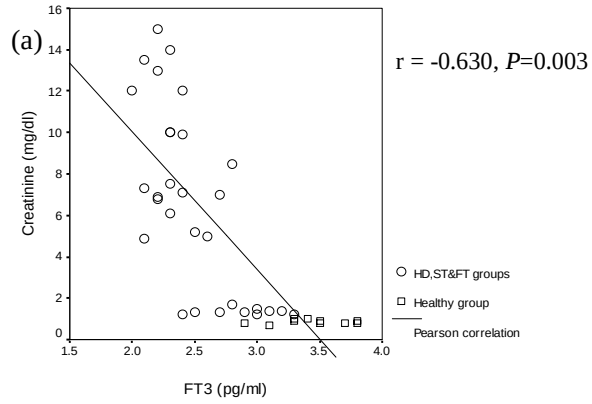


Figure (3): Level of CRP among the status of kidney transplantation for ST and FT. Significant correlation (F=24.5, *P*<0.0001) was observed between CRP and the status of kidney transplantation for ST and FT were [mean ± SD was 6.6 ± 0.8 with 95%CI for mean (6-7.2) and median 6.2, and 13.2 ± 4 with 95%CI for mean (10.3-16.2) and median 16.2], respectively.

Correlation between creatinine and thyroid hormones (FT3 and FT4)

Hemodialysed, ST and FT were collected in one group and compared to healthy ones for the correlation between creatinine and the thyroid hormones (FT3 and FT4). Accordingly, inverse significant correlations were observed between creatinine and FT3 as well as creatinine versus FT4 however a direct correlation was observed between creatinine and leptin , Figures 4 (a, b, and c, respectively).



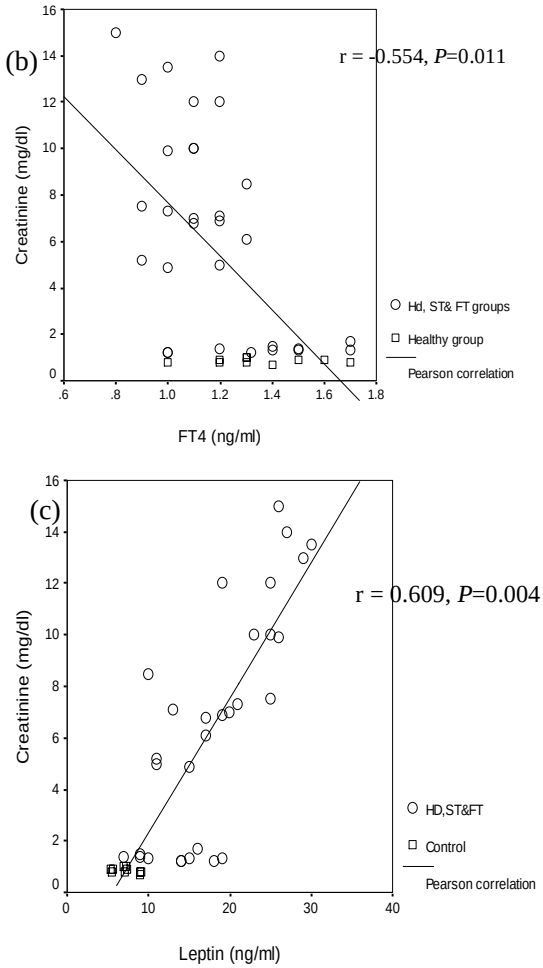


Figure (4): Correlation between creatinine in the healthy group (n=10) and creatinine in the remaining investigated groups (HD=10, KTR=10, and FT=10) regarding (a) FT3, (b) FT4 and (c) leptin.

4. Discussion

Chronic kidney disease (CKD) often progresses from early stage (partial) to end stage (complete) failure. There is no cure for end-stage renal disease (ESRD). The damage done to the kidneys is irreversible. Treatment at the end stage of kidney failure involves replacing the lost functions of the kidneys by dialysis or by a kidney transplant. Patients with end-stage renal failure are candidates for transplantation. A successful transplant frees the patient from dialysis and provides the kidney's other metabolic functions. Patients with severe kidney disease and hypothyroidism need less T4 after renal transplantation (Thomas et al., 2002). Low T3 is a frequent alteration in patients with ESRD. This derangement has been recently linked to inflammation in haemodialysis patients. Approximately one fourth of patients with end stage renal disease (ESRD) display low fT3, thyroid

dysfunction being an emerging problem also in patients with moderate to severe chronic kidney diseases (Lo et al., 2005).

Although no recommendations are available regarding the treatment of mild abnormalities of thyroid hormone levels in patients with CKD not requiring dialysis, these abnormalities could represent a risk factor for cardiovascular disease and might also be implicated in kidney disease progression. The nature and consequences of the link between CKD and low thyroid function are not yet clear. When hypothyroidism becomes more severe, it can cause reduced heart function, which can lead to progressively worsening kidney function. Thus the presence of subclinical hypothyroidism in patients with CKD might be a risk factor for both cardiovascular disease and progressive kidney disease (Stenvinkel et al., 2008). Because of the lack of follow-up data, the study cannot determine whether there is any causal relationship between subclinical hypothyroidism and CKD. Further studies should evaluate if mild elevations of the thyroid hormone are harmful for patients with kidney disease and explore the possibility of treating mild abnormalities of thyroid function with thyroid hormone replacement (Ripoli et al., 2005).

Our results showed the relationship between fT3, CRP and serum albumin suggested that inflammation–malnutrition might be involved in the low T3 syndrome in dialysis patients. Thyroid dysfunction might be implicated in the pathogenic pathway which links micro-inflammation to survival in dialysis patients (Enia et al., 2007). The present survey showed that inflammation is linked to the low-T3 syndrome in case of renal failure patients. Indeed, we observed inverse relationships between fT3 levels and CRP. Also there was a direct relationship between fT3 and serum albumin level, which was a negative acute phase reactant and a nutrition marker as well. Chronic metabolic acidosis (CMA) in normal adults results in complex endocrine and metabolic alterations including growth hormone (GH) insensitivity, hypothyroidism, hyperglucocorticoidism, hypoalbuminaemia and loss of protein stores. Similar alterations occur in chronic renal failure, a prototypical state of CMA. Correcting CMA may improve nutritional and metabolic parameters and thus lower morbidity and mortality (Wiederkehr et al., 2004).

We observed the increased levels of serum leptin in hemodialysis patients. This elevation was not only due to increased production but also from retention of the hormone. Several recent studies (Wolf et al., 2002 & Stamatiadis et al., 2004) have demonstrated that leptin is cleared principally by the kidney. Thus serum leptin concentrations are increased in patients with chronic renal failure and those patients undergoing maintenance dialysis, and it has been speculated that hyperleptinemia may contribute to uremic anorexia and malnutrition. Serum CRP concentrations have also been found to be significantly elevated in hemodialysis patients and reflects chronic inflammation and, as an acute-phase reactant, is a sensitive and independent marker of malnutrition (Christ-Crain et al., 2003).

In conclusion, the relationship between fT3, fT4, CRP and serum albumin suggests that inflammation–malnutrition might be involved in the low T3, low T4 syndromes in hemodialysis patients. The results of this study demonstrate that among patients with ESRD undergoing kidney transplantation, those displaying lower pretransplant serum fT3 and fT4 levels are at higher risk for subsequent graft failure. The demonstration of a predictive value of serum fT3 and fT4 levels for graft survival in a larger scale suggests that measurement of pretransplant serum fT3 and fT4 levels might represent a clinically useful parameter to identify patients with increased risk for graft failure.

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References

1. Malyszko J, Malyszko J, Wolczynski S, Mysliwiec M. Adiponectin, leptin and thyroid hormones in patients with chronic renal failure and on renal replacement therapy: are they related? Nephrol Dial Transplant 2006; 21: 145–152.
2. Lim VS. Thyroid function in patients with chronic renal failure. Am J Kidney Dis 2001; 38[Suppl 1] : S80 –S84.
3. Soltys BJ, Kang D, Gupta RS. Localization of P32 protein (gC1q-R) in mitochondria and at specific extramitochondrial locations in normal tissues. Histochem Cell Biol 2000; 114: 245–255.
4. Santini F, Marsili A, Mammoli C et al. Serum concentrations of adiponectin and leptin in patients with thyroid dysfunctions. J Endocrinol Invest; 2004; 27: RC5–RC7.
5. Kaysen GA. The microinflammatory state in uremia: Causes and potential consequences. J Am Soc Nephrol 2001;12 : 1549 –1557.
6. Stenvinkel P, Barany P, Heimburger O, Pecoits-Filho R, Lindholm B. Mortality, malnutrition, and atherosclerosis in ESRD: What is the role of interleukin-6? Kidney Int Suppl 2002; 80 : 103 –108.
7. Fernandez-Real JM, Lopez-Bermejo A, Casamitjana R, Ricart W. Novel interactions of adiponectin with the endocrine system and inflammatory parameters. J Clin Endocrinol Metab 2003; 88: 2714–2718.
8. Avasthi G, Malhotra S, Narang APS, SenguptaS. Study of thyroid function in patients of chronic renal

failure Indian J Nephrol 2001; 11: 165-169.
9. Abozenah H, Shoeb S, Sabry A, Hesham Ismail H. Relation between thyroid hormone concentration and serum levels of interleukin-6 and interleukin-10 in patients with nonthyroidal illness including chronic kidney disease. IJKD 2008; 2:16-23.
10. Zhang Y, Proenca R, Maffei M, Barone M, Friedman JM (1994): Positional cloning of the mouse obese and its human homologue. Nature 1994; 372: 425–432.
11. Obermayer-Pietsch BM, Frühauf GF, Lipp RW, Sendlhofer G, Pieber TR. Dissociation of leptin and body weight in hyperthyroid patients after radioiodine treatment. January 2001;25: 115-120.
12. Briley LP, Szczech LA Leptin and renal disease Semin Dial. 2006; 19: 54-9.
13. Chan DC, Watts GF, Sussekov AV, Barrett PH, Yang Z, Hua J, et al. Adipose tissue compartments and insulin resistance in overweight- obese Caucasian men. Diabetes Res Clin Pract 2004; 63: 77–85.
14. Wayne, PA. National Committee for Clinical Laboratory Standards. Procedures for handling and processing of blood specimens. A proved Guidelines ; NCCLS publication 1990; H18-A.
15. Wayne PA. National Committee for Clinical Laboratory Standards. Procedures for the handling and processing of blood specimens; second edition; a proved guidelines 1999; NCCLS Document H18-A2; 40p.
16. Villanova, PA. National Committee for Clinical Laboratory Standards. Procedures for handling and processing of blood specimens. A proved Guidelines ; NCCLS publication 1990; H18-A.
17. Hanigaya A, Nagashima K, Nako Y, et al. Relationship between concentration of serum leptin and fetal growth. J Clin. Endoc. And Metab; 1997; 28:3281
18. Thomas MC, Mathew TH, Russ GR. Changes in thyroxin requirements in patients with hypothyroidism undergoing renal transplantation. Am J Kidney Dis 2002; 39: 354-357.
19. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int 2005; 67 : 1047 –1052.
20. Stenvinkel P, Carrero J, Axelsson J, Lindholm B, Heimburger O, Massy Z . Emerging Biomarkers for Evaluating Cardiovascular Risk in the Chronic Kidney Disease Patient: How Do New Pieces Fit into the Uremic Puzzle? Clin. J. Am. Soc. Nephrol., 2008; 3: 505 – 521.
21. Ripoli A, Pingitore A, Favilli B, et al. Does subclinical hypothyroidism affect cardiac pump performance? Evidence from a magnetic resonance imaging study. J Am Coll Cardiol. 2005; 45:439.
22. Enia G, Panuccio V, Cutrupi S, Pizzini P, Tripepi G, Mallamaci F, Zoccali C. Subclinical hypothyroidism is linked to micro-inflammation and predicts death in continuous ambulatory peritoneal dialysis. Nephrology Dialysis Transplantation 2007 22:538-544.
23. Wiederkehr MR, Kalogiros J, Krapf R. Correction of metabolic acidosis improves thyroid and growth hormone axes in haemodialysis patients. Nephrol Dial Transplant 2004; 19:1190–1197.
24. Wolf G, Chen S, Han DC, Ziyadeh FN. Leptin and renal disease. Am J. Kidney Dis 2002; 39:1-11.
25. Stamatiadis DN, Chan JL, Cogswell R, Stefanopoulou HC, Bullen J, Katsilambros N. et al. Elevated leptin fragments in renal failure correlate with BMI and hematopoiesis and are normalized by hemodialysis. Clin. Endocrinol (Oxf) 2004;60:434-41.
26. Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, Muller B. Elevated C-reactive protein and homocysteine values: Cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosis 2003, 166:379 –386.

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