

SICK EUTHYROID SYNDROME IN CHRONIC KIDNEY DISEASE

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ABSTRACT: BACKGROUND: Sick euthyroid syndrome is an undermined entity seen in many chronic illness. CKD is one of the forerunners in terms of magnitude in the list of chronic illnesses. Also there is evidence of abnormal thyroid metabolism at several levels in uremia. Hence the need to evaluate thyroid function in CKD patients exists, as revealed by recent studies. **AIMS:** To study thyroid function test in patients of chronic renal failure. Also, to study the correlation between thyroid function test and severity of renal failure, defined by creatinine clearance. **MATERIALS & METHODS:** In a cross sectional observational case control study, 50 patients of chronic renal failure either on conservative management or on maintenance haemodialysis and 50 normal healthy subjects as control were enrolled. Creatinine clearance was calculated by Cockcroft – Gault Equation. Thyroid function tests were done by C.L.I.A (Chemiluminescence Immunoassay). **RESULTS:** Of the 50 patients (M:F – 58:42%), with a mean age 40.58 ± 12.65 years, 28 (56%) were on conservative management, 22 (44%) were on hemodialysis for a minimum period of three months. All patients were clinically euthyroid. Thyroid function tests were normal (all parameters within normal range) in 13 (26%) patients. However 37 (74%) out of 50 patients of CKD had deranged thyroid function test (sick euthyroid syndrome). Mean Total T3 in patients of CKD and controls were 71.52 ± 27.88 ng/dl and 95.34 ± 16.31 ng/dl respectively ($p < 0.005$). Mean Free T3 in patients of CKD and controls were 2.19 ± 0.70 pg/ml and 3.23 ± 0.79 pg/ml respectively ($p < 0.005$). Mean Total T4 in patients of CKD and controls were 6.03 ± 1.60 µg/dl and 6.88 ± 1.06 µg/dl respectively ($p < 0.005$). Mean Free T4 in patients of CKD and controls were 1.18 ± 0.55 ng/ml and 1.29 ± 0.24 ng/dl respectively (no statistically significant difference). Mean TSH in patients of CKD and controls were 2.90 ± 1.39 vs. 2.81 ± 0.99 µIU/ml respectively (no statistically significant difference). On applying correlation statistics, no statistically significant correlation was found between creatinine clearance and thyroid function test (r NS). Similarly, no statistically significant correlation was found between blood urea, serum creatinine, and various thyroid function test. **CONCLUSION:** Our study indicated low Total T3, Free T3 and Total T4 levels in 74% CKD patients as compared to controls. However, Free T4 and TSH level were found to be comparable to controls. Deranged thyroid function in patients of CKD could be due to sick euthyroid syndrome. No statistically significant correlation was found between thyroid function test and severity of renal failure.

KEYWORDS: Thyroid, Sick euthyroid Syndrome, Chronic Kidney Disease

INTRODUCTION: Chronic kidney disease is fast emerging as an important chronic illness of great morbidity and mortality. In past two decades, with the advent of renal replacement therapy like hemodialysis and renal transplantation, it has been possible to increase the longevity of CKD patients. With longevity arise the problems of various organs involvements and insight in their genesis. Endocrinopathies is one of them and one of the most debated topics in renal disease. Can cold intolerance, fatigue, anorexia be attributed to thyroid dysfunction or they are just part of spectrum of term "Uremia"; as kidney plays a significant role in thyroid hormone metabolism by

conversion of T4 to T3 and excretion of inorganic iodides. Do the toxic substances of uremia affect thyroid gland? Does duration of uremia affect the dysfunction? Is thyroid dysfunction related to disease severity? Answer to all these question hold keys to newer diagnostic strategies, better planning and management with the aim to reduce morbidity and mortality in these patients. Various authors like Ramirez G(1976)¹, Lim VS(1977)², Kaptein EM(1983)³, Mehta HJ(1991)⁴, Kayima JK(1992)⁵, Reinhardt W(1997)⁶, Zoccali C(2005)⁷, Honda H(2006)⁸ have tried to solve this puzzle from various angles and have postulated abnormalities at various level in hypothalamo-pituitary-thyroid axis, aberrant binding of thyroid hormone with serum binding protein and peripheral metabolism of thyroid hormone and iodides. They have also studied the effect of various modes of dialysis on thyroid functions. Recent studies have found relationship between free T3 and inflammation markers (IL-6 and C-reactive protein) and markers of endothelial activation (intercellular adhesion molecule-1 [ICAM-1] and vascular cellular adhesion molecule-1 [VCAM-1])⁹. Low circulating free T3 is frequently observed in inflammatory illnesses, and the same association exists in patients with CKD and in ESRD¹⁰.

MATERIALS AND METHODS: This cross sectional observational case control study, was conducted at Teerthanker Mahaveer Medical College, Moradabad, UP with the approval of the ethical committee during a one year period from May 2012 to April 2013. 50 patients of chronic renal failure and 50 normal healthy subjects as control. Patients were either on conservative management (group 1) or on haemodialysis (group 2) for minimum 3 months duration.

Inclusion criteria: Patients who were clinically diagnosed as chronic renal failure with derangements in kidney function test (blood urea, serum creatinine, creatinine clearance) and were found to have small shrunken kidney with increased echogenicity and loss of corticomedullary differentiation on ultrasonography were included in the study.

Exclusion criteria: Acute renal failure, Known thyroid disease, Diabetes mellitus, Acquired immune deficiency syndrome, Pregnancy, patients on Drugs: antithyroid drugs, anti epileptics, propranolol, amiodarone, steroids, oral contraceptive pills, lithium.

50 patients, according to inclusion and exclusion criteria and 50 normal subjects were included in the study. All these patients were subjected to detailed history (symptoms, past illnesses, treatments - Oliguria/ anuria, Anorexia, Vomiting/nausea, Constipation/ diarrhea, Wt gain/loss, oedema, Fatigue/weakness, Myalgia, Breathlessness, Tingling / numbness, Cold intolerance, Bleeding tendency, Neuro-psychiatric symptoms, Menstrual complaints) and a thorough general and systemic exam. All routine investigations along with Renal functions, Creatinine clearance by Cockcroft-Gault method, Renal ultrasound and Thyroid function tests (Total & free T3, Total & free T4, TSH) was done. Thyroid function tests were done by C.L.I.A (Chemiluminescence Immunoassay). The data thus collected was analyzed using statistical software SPSS.v15 using student "t" test, one way analysis of variance (ANOVA), percentage, proportion, and correlation statistics.

RESULTS: Out of 50 patients of CKD, 29 (58%) were male and 21 (42%) were female. Similarly, out of 50 controls, 29 (58%) were male and 21 (42%) were female. The mean age of patients and control were 40.58 ± 12.65 years and 41.76 ± 13.67 years respectively. Age range of study patients was 19 years to 64 years. Maximum (52%) patients were in age group 31 – 50 years. Mean duration of symptoms was 8.77 ± 4.56 months. Of the 50 patients of CKD, 30 (60%) presented with oliguria, 10

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(20%) presented with anuria. Signs of fluid overload like oedema, rales were seen in 15 (30%) patients. Generalized weakness and fatigue was seen in majority i.e 47 (94%) patients. Asterixis were seen in 35 (70%), pericardial rub was seen in 10 (20%) patients. 30 patients (60%) also had persistent vomiting as presenting complaint. Out of 50 patients, 28 (56%) were in group 1 (conservative management), 22 (44%) were in group 2 (hemodialysis). Mean blood urea in patients and controls were $166.78 \pm 77.21\text{mg}\%$ and $18.19 \pm 4.22\text{mg}\%$ respectively ($p < 0.005$). Mean serum creatinine in patients and controls were $9.57 \pm 5.51\text{mg}\%$ and $0.67 \pm 0.16\text{mg}\%$ respectively ($p < 0.005$). All patients were clinically euthyroid, none having any symptoms or signs of either hypothyroidism or hyperthyroidism. Thyroid function tests were normal (all parameter within normal range) in 13 (26%) patients. However 37 (74%) out of 50 patients of CKD had deranged thyroid function test. The mean Total T3 in patients of CKD and controls were 71.52 ± 27.88 vs. $95.34 \pm 16.31\text{ng/dl}$ respectively ($p < 0.005$). 27 (54%) patients of CKD had Total T3 value less than normal range ($< 60\text{ng/dl}$) whereas none of the control had Total T3 value less than normal range. Mean Total T4 in patients of CKD and controls were 6.03 ± 1.60 vs. $6.88 \pm 1.06\mu\text{g/dl}$ respectively ($p < 0.005$). 13 (26%) of the CKD patients as compared to none in the control group had serum T4 concentration below normal range. Mean Free T3 in patients of CKD and controls were 2.19 ± 0.70 vs. $3.23 \pm 0.79\text{pg/ml}$ respectively ($p < 0.005$). 10 (20%) of the CKD patients as compared to none in the control group had serum Free T3 concentration below normal range. The mean Free T4 in patients of CKD and controls were 1.18 ± 0.55 vs. $1.29 \pm 0.24\text{ng/dl}$ respectively (p NS, no statistically significant difference). Mean TSH in patients of CKD and controls were 2.90 ± 1.39 vs. $2.81 \pm 0.99\mu\text{IU/ml}$ respectively (p NS, no statistically significant difference). Thus, there was statistically significant decrease in Total T3, Total T4 and Free T3 in patients of CKD as compared to controls. However Free T4 and TSH in two groups were comparable.

Parameter	Control (n=50)	Patients (n=50)	Group 1 (n=28)	Group 2 (n=22)
TT3 (N 60-200ng/dl)	95.34 ± 16.31	71.52 ± 27.88	74.05 ± 24.45	62.41 ± 17.85
TT4 (N 4.5-2 $\mu\text{g/dl}$)	6.88 ± 1.06	6.03 ± 1.60	6.09 ± 1.76	5.98 ± 1.48
FT3 (N 1.7-4.2pg/ml)	3.23 ± 0.79	2.19 ± 0.70	2.19 ± 0.86	2.70 ± 0.56
FT4 (N 0.7-1.8ng/dl)	1.29 ± 0.24	1.18 ± 0.55	1.21 ± 0.71	1.25 ± 0.20
TSH (N 0.3 - 5.5 $\mu\text{IU/ml}$)	2.81 ± 0.99	2.90 ± 1.39	2.89 ± 1.58	3.32 ± 0.13

TABLE 1: Thyroid function test in controls and in patients

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Parameter	Controls (n=50)	Creatinine clearance (ml/minute)		
		< 8ml (n=16)	8 - 15ml (n=23)	> 15ml (n=11)
TT3 (N 60-200ng/dl)	95.34 ± 16.31	78.33 ± 26.14	70.61 ± 20.55	76.15 ± 30.32
TT4 (N 4.5-2µg/dl)	6.88 ± 1.06	4.77 ± 1.57	6.72 ± 1.56	6.06 ± 1.82
FT3 (N 1.7-4.2pg/ml)	3.23 ± 0.79	1.73 ± 0.80	2.29 ± 0.67	2.37±1.04
FT4 (N 0.7-1.8ng/dl)	1.29 ± 0.24	0.96 ± 0.44	1.58 ± 0.82	0.85 ± 0.40
TSH (N 0.35.5µIU/ml)	2.81 ± 0.99	2.22 ±1.68	2.48 ±1.16	3.93 ± 1.69

TABLE 2: Thyroid function test and severity of renal failure (by creatinine clearance)

There was no statistically significant difference in Total T3, Total T4, Free T3 and Free T4 values between the groups as per creatinine clearance (p NS). However there was a direct correlation between TSH and creatinine clearance, value of TSH decreased as creatinine clearance decreased (P < 0.05). On applying correlation statistics, no statistically significant correlation was found between blood urea, serum creatinine, creatinine clearance and thyroid function tests i.e.; Total T3, Total T4, Free T3, Free T4 and TSH (r - NS).

DISCUSSION: Any severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease, making these measurements potentially misleading. The major cause of these hormonal changes is the release of cytokines. The most common hormone pattern in sick euthyroid syndrome is a decrease in total and unbound T₃ levels (low T₃ syndrome) with normal levels of T₄ and TSH. The magnitude of the fall in T₃ may correlate with the severity of the illness. T₄ conversion to T₃ via peripheral deiodination is impaired. Fluctuation in TSH levels also creates challenges in the interpretation of thyroid function in sick patients. The underlying mechanism may be mediated by cytokines including IL-12 and IL-18¹¹. As kidney plays a significant role in thyroid hormone metabolism by conversion of T₄ to T₃ and excretion of inorganic iodides, thyroid function has been evaluated by many investigators in patients with CKD. Levels of Total T₃ and Free T₃ suffer reduction in CKD, which is thought to be due to impairment in deiodination of T₄, secondarily to decrease activity of de-iodinase enzymes. As kidneys are important organ of excretion of iodide, accumulation of inorganic iodides may lead to decreased uptake by thyroid glands due to Wolf-Chaikoff effect and may cause hypothyroidism¹². A multitude of defects at all levels of hypothalamic - pituitary - thyroid - peripheral axis does seem to exist in uremia¹³, which include impaired release of TSH in response to TRH (thyrotrophic releasing hormone), impaired thyroid hormone secretion in response to TSH. Cytokines particularly IL-1, IL-6, TNF - α and interferon β are thought to affect the hypothalamus, pituitary and other tissues, inhibiting production of TRH, TSH, thyroglobulin, T₃, TBG and also thought to decrease the activity of type I deiodinase and to decrease the binding capacity of T₃ nuclear receptor⁸. In our study, 37 (74%) out of 50 patients of CKD had deranged thyroid function test (sick euthyroid syndrome). Total T₄, Total T₃, Free T₃ values were found lower in CKD patients as compare to controls. However, Free T₄ and TSH values in patients and controls were comparable. Also, no statistically significant correlation was found between serum Total T₃, Total T₄, Free T₃, Free T₄ and TSH values and

creatinine clearance (r NS) i.e., there was no statistically significant correlation between thyroid function test and severity of renal failure. "Low T3 syndrome" was the common type in our study. 27 (54%) patients of CKD had Total T3 value less than normal range (< 60ng/dl) and 10 (20%) patients had low free T3 levels. Mean TSH in these patients of were comparable to controls suggesting an impaired feedback mechanism and/or abnormality TSH secretion. Total T4 concentration was found to be low or low normal. 13 (26%) of the CKD patients as compared to none in the control group had serum T4 concentration below normal range. However, Free T4 was within normal limit. This could be attributed to lowering of thyroxin binding globulin concentration as well as inhibitors of thyroid hormone binding to thyroid binding proteins^{12,13}. These binding inhibitors are associated with non-esterified fatty acid (NEFA) fraction in the serum^{14,15}. rT3 level could not be measured in our study.

CONCLUSION: Deranged thyroid function in patients of CKD could be due to sick euthyroid syndrome. Most common hormonal pattern was low total T3, low total T4 and low free T3 in decreasing frequency.

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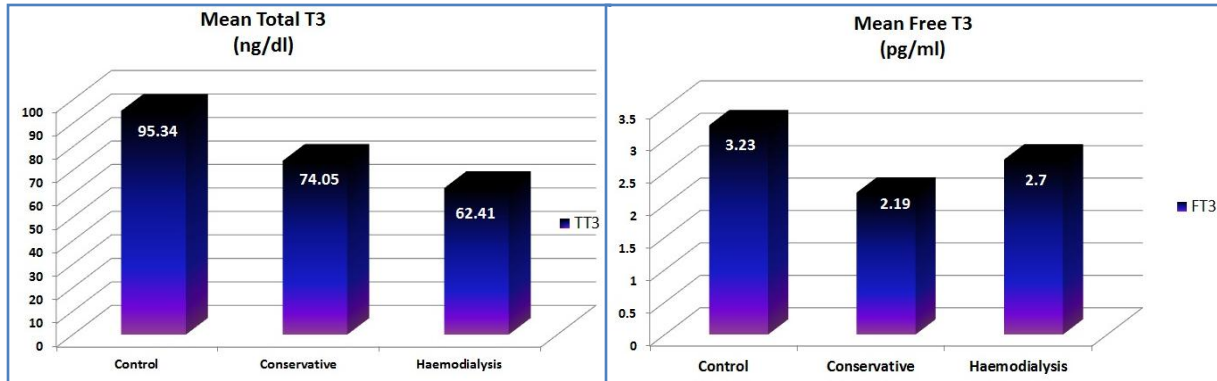


Chart 1

Chart 2

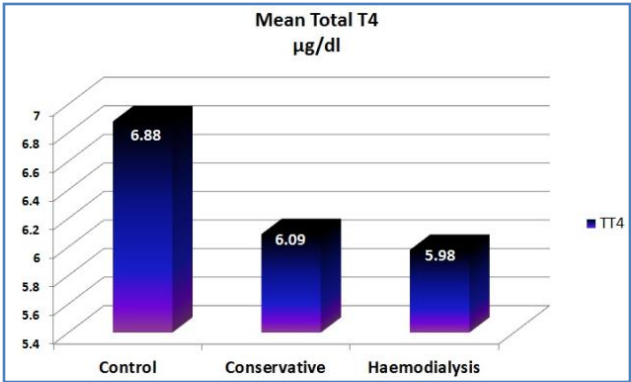
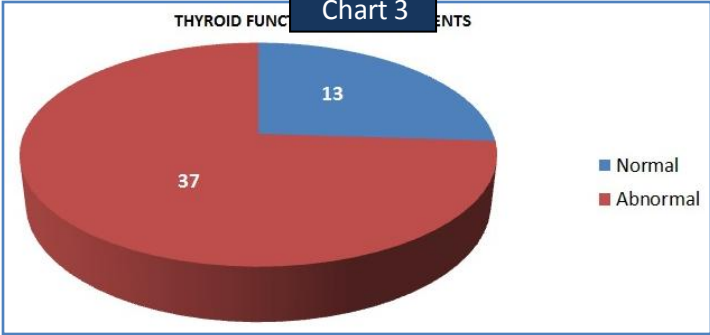
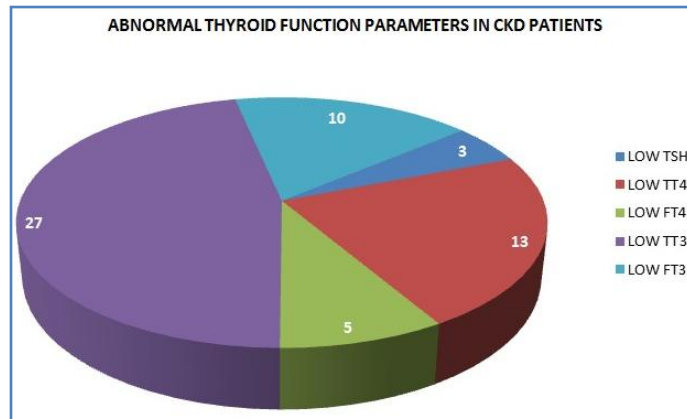


Chart 3



Pie 1



Pie 2

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