Asymptomatic Thyroid dysfunction in patients of chronic renal failure

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(Received 17 /6 /2013 , Accepted 31 / 7 / 2013)

الخلاصة

خمسون مريضا مصابا بعجز الكلية المزمن اجريت لهم تحاليل وظائف الغدة الدرقية وتمم مقارنتها مع مجموعة من المرضى الغير مصابين بعجز الكلية من حيث العمر والجنس وقد وجد 20%من مرضى عجز الكلية يعانون فشل (ضعف) في وظائف الغدة الدرقية. كل المرضى الغير مصابين بعجز الكلية هم من الناحية الكيميائية (طبيعي) في وظائف الغدة الدرقية وكان متوسط قراءة بلاسما (t3 ,t4) اقل وكان متوسط قراءة (tsh) اعلى بالمقارنة مع المجموعة الطبيعية نستنتج من هذا فشل وظائف الغدة الدرقية من الناحية السريرية والكيميائية عند مرضى الفشل الكلوي .

Abstract

Fifty patients with chronic renal insufficiency underwent clinical evaluation & studies of thyroid function the results were compared with age & sex-matched controls. (20%) of patients had biochemical hypothyroidism with low serum T3, T4, & high serum TSH. All the members of the control group were biochemically euthyroid. The mean values of serum T3, T4 were significantly lower & mean serum TSH was significantly higher as compared to controls. There was no correlation of thyroid functions with decrease in renal function. To conclude thyroid dysfunction occurs both clinically & biochemically in patients with chronic renal insufficiency.

Introduction

Patients with chronic renal failure often have signs & symptoms suggestive of thyroid dysfunction. These findings include dry skin, sallow complexion, low temperature, cold intolerance, decreased basal metabolic rate, lethargy, fatigue, edema & hyporeflexia. (1).Serum triiodothyronine (T3) levels were consistently found to be low without any regard to treatment of CRF (1). Serum total & free thyroxin (T4) concentrations have been reported as low, normal or high. Serum thyroid Stimulating hormone (TSH) levels were found to be normal in most patients of CRF even in those whose CRF is complicated by low T3 concentration. The incidence of goiter has also been variably reported in literature (2, 3, and 4).

Thyroid hormone play an important role in growth, development, and physiology of the kidney (5, 6). On the other hand, children with congenital hypothyroidism have an increased prevalence of congenital renal anomalies. These findings support an important role of TH during early embryogenesis (7, 8). The kidney also plays a role on the regulation of metabolism and elimination of Thyroid hormone and is an important target organ for Thyroid hormone actions (9). The decrease in the activity of Thyroid hormone is accompanied by an inability to excrete an oral water overload (10). This effect is not due to an incomplete suppression of vasopressin production, or a decrease in the reabsorptive ability in the dilutor segment of the kidney tubule, but rather to a reduction in the glomerular filtration rate (GFR) (11,12,13). T3 is also involved in sulfate homeostasis through the regulation of kidney sodium-sulfate cotrasporter, NaS(i)-1, a protein entailed in the control of serum sulfate levels (14). Finally, different studies in animals

have shown That TH act on the regulation of kidney dopaminergic system (15).

Effects of thyroid dysfunction on the kidney

Thyroid dysfunction causes significant changes in kidney function (Table 1). Both hypothyroidism and hyperthyroidism affect renal blood flow, GFR, tubular function, electrolytes homeostasis, electrolyte pump functions, and kidney structure (9, 16).

Table 1 Effects of thyroid dysfunction on the kidney.

Hypothyroidism	Thyrotoxicosis
Increased serum creatinine	Decreased serum creatinine
Decreased glomerular filtration	Increased glomerular filtration
Decreased renal plasma flow	Increased renal plasma flow
Decreased sodium reabsorption	Increased tubular reabsorption
Decreased renal ability to dilute urine	Resistance to rhEPO action?

Kidney disease associated to thyroid dysfunction

The different types of kidney diseases can be associated with various disorders of thyroid function (17).

Glomerular disease

Thyroid dysfunction has been reported to be associated with IgA glomerulonephritis (18, 19), mesangiocapillary or membranoproliferative glomerulonephritis (20), and minimal change glomerulonephritis (21).

Tubular disease

Isolated cases of hyperthyroidism have been reported in association with tubulointerstitial nephritis and uveitis, a self-limited syndrome of unknown etiology that responds to glucocorticoids (22).

Acute kidney injury

Acute kidney injury (AKI) is associated with abnormalities in thyroid function tests similar to those found in euthyroid sick syndrome (ESS). Contrary to the usual form of the ESS, patients with AKI may not exhibit an elevation or reverse (r)T3 levels (4).

Chronic kidney disease

CKD affects both hypothalamus–pituitary–thyroid axis and TH peripheral metabolism (23). Uremia influences the function and size of the thyroid (24). Uraemic patients have an increased thyroid volume compared with subjects with normal renal function and a higher prevalence of goiter, mainly in women (24). Also, thyroid nodules and thyroid carcinoma are more common in uraemic patients than in the general population (24). Serum TSH concentrations are usually normal or elevated in CKD, but its response to its releasing hormone (TRH) is generally low (25). In fact, the prevalence of primary hypothyroidism, mainly in the subclinical form, increases as GFR decreases (26).

Material and methods

This cross sectional study carried in AL-Merjan teaching hospital in dialysis unit exclusion criteria include

1. Known case of goiter.
2. Known case of any thyroid dysfunction.
3. Any patient use amiodarone, thyroxine.
4. Known case of thyroid surgery.

Fifty Chronic renal failure (CRF) patients (21 men and 29 women) with mean age of 43 ± 6 years were selected for this study. Twenty age matched healthy volunteers (8 men and 12women) were taken as control. The blood sample collected from these subjects was ceritrifuged and the serum was used for the estimation of urea, creatinine, protein, and albumin, T3, T4 and TSH. The thyroid status of all subjects was estimated by radioimmunoassay Serum concentrations of urea, creatinine, total protein and albumin were estimated by using commercial kits

Statistical analysis

The data between control and test groups was compared using unpaired student's t test. Correlation was determined by Pearson's correlation coefficient. The level of significance used was P value less than 0.05.

Results

The data for the chronic renal failure (CRF) patients and healthy subjects are shown in Table I. There was no significant difference between the two groups with respect to age and gender. Serum creatinine and urea levels were significantly increased in CRF patients compared to control subjects. Serum T3, T4, total protein and albumin levels of CRF patients were significantly decreased compared to control subjects.

Table I: Mean and standard deviation of serum biochemical parameters in controls (n = 20) and chronic renal failure (n = 50).

	Controls	CRF
Age (in years)	45.50±6.39	43.70±6.04
Urea (mg/dl)	31.60±5.40	94.80±62.91*
Creatinine (mg/dl)	0.67±0.10	3.58±2.61*
Total Protein (g/dl)	6.15±0.43	5.40±0.96*
Albumin (g/dl)	4.02±0.28	3.11±0.57*

*P<0.05

t3 * group Crosstab

			group		Total
			crf	control	
t3	.00	Count	0	0	0
		% within t3	0.0%	100.0%	100.0%
		% within group	0.0%	0%	0%
	normal	Count	34	19	53
		% within t3	64.2%	35.8%	100.0%
		% within group	68.0%	90.5%	74.6%
	low	Count	12	0	12
		% within t3	100.0%	0.0%	100.0%
		% within group	24.0%	0.0%	16.9%
	high	Count	4	1	5
		% within t3	80.0%	20.0%	100.0%
		% within group	8.0%	4.8%	7.0%
Total		Count	50	20	70
		% within t3	70.4%	29.6%	100.0%
		% within group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	8.642[a]	3	.034
Likelihood Ratio	12.055	3	.007
Linear-by-Linear Association	5.455	1	.020
N of Valid Cases	71		

a. 5 cells (62.5%) have expected count less than 5. The minimum expected count is .30.

t4 * group

Crosstab

			group		Total
			crf	control	
t4	.00	Count	0	0	0
		% within t4	0.0%	100.0%	100.0%
		% within group	0.0%	0%	0%
	normal	Count	34	19	53
		% within t4	64.2%	35.8%	100.0%
		% within group	68.0%	90.5%	74.6%
	low	Count	10	0	10
		% within t4	100.0%	0.0%	100.0%
		% within group	20.0%	0.0%	14.1%
	high	Count	6	1	7
		% within t4	85.7%	14.3%	100.0%
		% within group	12.0%	4.8%	9.9%
Total		Count	50	20	70
		% within t4	70.4%	29.6%	100.0%
		% within group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	8.368[a]	3	.039
Likelihood Ratio	11.317	3	.010
Linear-by-Linear Association	6.072	1	.014
N of Valid Cases	71		

a. 5 cells (62.5%) have expected count less than 5. The minimum expected count is .30.

TSH * group

Crosstab

			group		Total
			crf	control	
tsh	.00	Count	0	0	0
		% within tsh	0.0%	100.0%	100.0%
		% within group	0.0%	0%	0%
	normal	Count	28	18	46
		% within tsh	60.9%	39.1%	100.0%
		% within group	56.0%	85.7%	64.8%
	low	Count	10	1	11
		% within tsh	90.9%	9.1%	100.0%
		% within group	20.0%	4.8%	15.5%
	high	Count	12	1	13
		% within tsh	92.3%	7.7%	100.0%
		% within group	24.0%	4.8%	18.3%
Total		Count	50	20	70
		% within tsh	70.4%	29.6%	100.0%
		% within group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	9.602[a]	3	.022
Likelihood Ratio	10.897	3	.012
Linear-by-Linear Association	7.577	1	.006
N of Valid Cases	71		

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is .30.

Discussion

Serum T3 concentration was less than the normal range in 12 of the 50 patients with chronic renal failure (24%). The mean serum T3 concentration of 60.3 ± 25.06 nm/l in patients with chronic renal failure group was significantly (P<0.03) lower than that in control subjects (133 ± 25.36 nm/l). These results confirm earlier observations of several authors (27, 28, 29, 32) that in about one third to one half of cases of chronic renal failure serum T3 are below the normal range.

Serum T4 concentration was diminished below the normal range in 10 patients (20%) with chronic renal failure in the present study. The mean differed significantly (P<0.03) for chronic renal failure (40.08 ± 10.20 nm/l) and for control subjects (70.99 ± 10.02 nm/l) (30, 31, 32). Low total T4 values in chronic renal failure patients may be primarily related to impaired T4 binding to serum carrier proteins. It has been reported that many inhibitors of T4 binding to serum carrier proteins are present in CRF patients and thus contributing to the decreased levels of T4 in CRF (30). The decreased total T3 levels can also be attributed to the increase in excretion of bound and free T4 in urine of chronic renal failure as reported in other previous study (34). Serum mean TSH concentrations were within the normal range in chronic renal failure and did not differ from that found in the controls. Reduced serum TSH levels have not been reported to date in euthyroid chronic renal failure patients. In conclusion T3 and T4 levels were significantly reduced.

Serum TSH was elevated above the normal level in 12 patients (24%) for with chronic renal failure in the present study. The mean differed significantly (P<0.02) for chronic renal failure (7.08 ± 1.20 u/ml) and for control subjects (3.5 ± 1.02 u/ml)

Our results are comparable with Joseph et al (28, 33) who studied 127 patients of CRF, who had low T3, T4, and fT4 but had high TSH levels suggesting maintenance of pituitary-thyroid axis.

This study has several limitations that should be noted. First, because this study is cross-sectional, the present analysis is limited in its ability to establish causal or temporal relationships between subclinical thyroid dysfunction and kidney disease. Second, the definition of kidney function was based on estimated GFR rather than on more precise measurement of kidney function, such as iothalamate clearance. Third, nonthyroidal (*e.g.*, low T3 syndrome, which is typically seen in some ill patients, including those with end-stage renal disease) and thyroidal causes of this abnormlaty were not identified. Finally, because our analysis depended on automated databases to establish the presence of subclinical thyroid dysfunction and kidney disease. Moreover, thyroid function tests could be requested when there was a (clinical) suspicion of altered thyroid function, thus tending to inflate the magnitude of the estimate of the relation. However, in this study we excluded all patients with low or high FT4 levels, who are those likely to have clinical symptoms of hypothyroidism or hyperthyroidism, respectively.

Conclusion

Subclinical primary hypothyroidism is more common in persons with CKD not requiring chronic dialysis compared with those with normal kidney function in a large sample of unselected outpatient adults. Future clinical and experimental studies should explore potential causal mechanisms linking subclinical primary hypothyroidism and CKD. The possible adverse effects of subclinical hypothyroidism on cardiovascular risk associated with CKD are presently unknown. Whether adult patients with CKD should be routinely screened for subclinical primary hypothyroidism requires further investigation

References

1. Yashpal et al. Thyroid function in uraemia. Ind J Nephrol (New Series) 1991; 1:2, vol.1, No.2, April-June, 1991.
2. Ramirez G. O'Neil WM, Jubiz W. Bloomer HA. Thyroid dysfunction in uraemia. Evidence with thyroid and hypophyseal abnormalities. Ann Int Med 1976; 84:672
3. Lim VS, Fang VS, Refetoff S. Katz Al. T3 hypothyroidism in uraemia. Impaired T4 to T3 conversion. No. 636. Abstracts of 6th International Congress of Nephrology,1975
4. Kaptein EM, Quion-Verde H, Chooljian CJ, Tang WW, Friedman PE, Rodriquez HJ & Massry SG. The thyroid in end stage renal disease. Medicine 1988 67 187–197.
5. Gattineni J, Sas D, Dagan A, Dwarakanath V & Baum MG. Effect of thyroid hormone on the postnatal renal expression of NHE8. American Journal of Physiology. Renal Physiology 2008 294 F198–F204.
6. Katyare SS, Modi HR, Patel SP & Patel MA. Thyroid hormone induced alterations in membrane structure-function relationships: studies on kinetic properties of rat kidney microsomal Na(C), K (C)-ATPase and lipid/phospholipid profiles. Journal of Membrane Biology 2007 219 71–81.
7. Vargas F, Moreno JM, Rodrı´guez-Go´mez I, Wangensteen R, Osuna A, Alvarez-Guerra M & Garcı´a-Estan˜ J. Vascular and renal function in experimental thyroid disorders. European Journal of Endocrinology 2006 154 197–212.
8. Kumar J, Gordillo R, Kaskel FJ, Druschel CM & Woroniecki RP. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. Journal of Pediatrics 2009 154 263–266.
9. Den Hollander JG, Wulkan RW, Mantel MJ & Berghout A. Correlation between severity of thyroid dysfunction and renal function. Clinical Endocrinology 2005 62 423–427.
10. Liu XM, Bai Y & Guo ZS. Study on urinary function and metabolism of water and electrolytes in primary hypothyroidism. Zhonghua Nei Ke Za Zhi 1990 29 299–302.
11. Emmanouel DS, Lindheimer MD & Katz AI. Mechanism of impaired water excretion in the hypothyroid rat. Journal of Clinical Investigation 1974 54 926–93.
12. Lin HH & Tang MJ. Thyroid hormone upregulates Na, K-ATPase alpha and beta mRNA in primary cultures of proximal tubule cells. Life Sciences 1997 60 375–382.
13. Segarra AB, Ramı´rez M, Banegas I, Hermoso F, Vargas F, Vives F,Alba F, de Gasparo M & Prieto I. Influence of thyroid disorders on kidney angiotensinase activity. Hormone and Metabolic Research2006 38 48–52.
14. Dawson PA & Markovich D. Regulation of the mouse Nas1 promoter by vitamin D and thyroid hormone. Pflugers Archiv: European Journal of Physiology 2002 444 353–359.
15. Del Compare JA, Aguirre JA, Ibarra FR, Barontini M & Armando I. Effects of thyroid hormone on the renal dopaminergic system. Endocrine 2001 15 297–303.
16. Villabona C, Sahun M, Roca M, Mora J, Go´mez N, Go´mez JM, Puchal R & Soler J. Blood volumes and renal function in overt and subclinical primary hypothyroidism. American Journal of the Medical Sciences 1999 318 277–280.
17. Gurkan S, Dikman S & Saland MJ. A case of autoimmune thyroiditis and membranoproliferative glomerulonephritis.Pediatric Nephrology 2009 24 193–197.
18. Enrı´quez R, Sirvent AE, Amoro´s F, Andrada E, Cabezuelo JB & Reyes A. IgA

nephropathy and autoimmune thyroiditis. Clinical Nephrology 2002 57 406–407.
19. Ikeda K, Maruyama Y, Yokoyama M, Kato N, Yamanoto H, Kaguchi Y, Nakayama M, Shimada T, Tojo K, Kawamura T & Hosoya T. Association of Graves' disease with Evans' syndrome in a patient with IgA nephropathy. Internal Medicine 2001 40 1004–1010.
20. Dizdar O, Kahraman S, Genc¸toy G, Ertoy D,Arici M,Altun B,YasavulU&TurganC.Membranoproliferativegl omerulonephritisassociated with type 1 diabetes mellitus and Hashimoto's thyroiditis. Nephrology,Dialysis, Transplantation 200419988–989.
21. Tanwani LK, Lohano V, Broadstone VL & Mokshagundam SP. Minimal change nephropathy and Graves' disease: report of a case and review of the literature. Endocrine Practice 2002 8 40–43.
22. Ebihara I, Hirayama K, Usui J, Seki M, Higuchi F, Oteki T, Kobayashi M & Yamagata K. Tubulointerstitial nephritis and uveitis syndrome associated with hyperthyroidism. Clinical and Experimental Nephrology 2006 10 216–221.
23. Singh PA, Bobby Z, Selvaraj N & Vinayagamoorthi R. An evaluation of thyroid hormone status and oxidative stress in undialyzed chronic renal failure patients. Indian Journal of Physiology and Pharmacology 2006 50 279–284.
24. Kutlay S, Atli T, Koseogullari O, Nergizoglu G, Duman N & Gullu S. Thyroid disorders in hemodialysis patients in an iodinedeficient community. Artificial Organs 2005 29 329–332.
25. Witzke O, Wiemann J, Patschan D, Wu K, Philipp T Saller B et al. Differential T4 degradation pathways in young patients with preterminal and terminal renal failure. Hormone and Metabolic Research 2007 39 355–358.
26. Lo JC, Chertow GM, Go AS & Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney International 2005 67 1047–1052.
27. Ramirez G, O'Neill W Jr, Jubiz W, Bloomer HA. Thyroid dysfunction in uremia: evidence for thyroid and hypophyseal abnormalities. *Ann Int Med* 1976; 84: 672–725.
28. G Avasthi, S Malhotra, APS Narang, S Sengupta. Study of thyroid function in patients of chronic renal failure. Indian J Nephrol 2001; 11: 165-169.
29. Paqualini T. Zantieifer D, Balzaretti H. Granillo E, Patricia FD, Ramierz ZJ, Ruiz S. Gutman R. Ferraris J. Evidence of hypothalamus pitutitaary thyroid abnormalitieas in children with end stage renal disease. J Paed 1991; 118:873-78.
30. Huang TS, Boado RJ, Chopra IJ, Solomon DH, Teco GNC. The effect of free radicals on hepatic 5'-monodeiodination of thyroxine and 3, 3', 5'- triiodothyronine. Eiidocrinology 1987; 121: 498– 503.
31. Hardy MJ, Ragbeer SS, Nascimnto L. Pituitary-Thyroid function in chronic renal failure assesed by a highly sensitve thyrotropin assay. J Clin Endo Met Lab 1988; 66:233-36.
32. Arif S Malik. Evaluation of Thyroid Function in Patients with Chronic Kidney Disease. IRAQI J MED SCI, 2011; VOL.9 (2)
33. Joseph LJ, Desai KB, Mehta HJ, Mehta MN, Almedia AF et al. Measuremettmt of serum thyrotropin levels using senstive immunoradiometric assays in patients with chronic renal failure. Alterations suggesting intact pituitary thyroid axis. Thyroidology 1993; 5:35-39.
34. Pagliacci MC, Pelicei G, Grigani F et al. Thyroid function tests in patients undergoing maintenance peritoneal dialysis. Nephron 1987; 46: 225–230.