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Original Article

Thyroid Dysfunction In Patient With Nephrotic Syndrome

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Abstract

A large amount of protein is lost in urine along with thyroid hormones and hormone binding proteins in nephrotic syndrome (NS). This hormone loss may lead to low T4, T3 and sometimes high TSH level and often to be associated with subclinical or overt hypothyroidism. This study was done to assess thyroid dysfunction in patients with NS and to correlate thyroid hormones with albumin level of those subjects. Forty diagnosed patients of idiopathic NS and same number of age matched healthy control were selected in this study. Thyroid status was evaluated in all the subjects. In patients with NS mean (± SD) of T4, T3 and TSH were 39.34 (±29.49), 1.05 (±0.83) and 11.34 (±18.15) respectively. Mean (±SD) of T4, T3 and TSH in healthy control were 83.34 (±27.23), 2.04 (±0.70) and 2.73 (±1.79) respectively. Mean serum total T4 and T3 of patients with NS were found to be significantly lower (t= -6.935, df= 78, p<0.001 and t = -5.750, df = 78, p<0.001 respectively) and mean TSH was found to be significantly higher (t= 2.984, df = 78, p<0.01) in patients with NS as compared to healthy control. Sub clinical hypothyroidism was observed in 20 (50%) and overt hypothyroidism in 4 (10%) of patients. Significant positive correlation was found between serum albumin and serum total T4 (r = 0.818, p <0.001) and also with total T3 level (r = 0.903, p <0.001). But no correlation was found between serum albumin and serum TSH (r = - 0. 292, p>0.05) in patients with NS. So, nephrotic range proteinuria may be associated with loss of thyroid hormone in urine and can lead to subclinical or even overt hypothyroidism.

Key words: Nephrotic syndrome, proteinuria, thyroid dysfunction.

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Introduction

NS is a common renal disease. Proteinuria is a hallmark of NS. Thyroid disease may be associated with different forms of glomerulonephritis (GN) and membranous glomerulopathy is frequently associated with hypothyroidism. Other forms of GN such as IgA nephropathy, mesangiocapillary or membranoproliferative and minimal change disease (MCD) also has been reported to be associated with Thyroid dysfunction[1,2,3]. Moreover, autoimmune thyroid disease has occasionally been reported in patients with GN.

In patients with proteinuria, albumin and other proteins (ie. hormones and hormone binding proteins) are lost in the urine[4]. Several studies have documented urinary loss of thyroid hormones and thyroxine binding globulin (TBG) in patient with proteinuria[1,5,6,7]. Urinary losses of binding proteins such as thyroxine binding globulin (TBG), thransthyretin or prealbumin, albumin result in a reduction in serum total thyroxine (T4) and

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sometimes in total T3 levels. These changes are related both to degree of proteinuria and to serum albumin levels[1,5]. In patient with nephrotic syndrome losses of thyroid hormones may also lead to low free thyroid hormone levels unless production is increased under the influence of thyroid stimulating hormone (TSH)[1]. As a consequence, proteinuria in NS may promote the development of primary hypothyroidism in patients with low thyroid reserve[1]. TSH also metabolized and excreted by kidney. Study had shown that the excretion of TSH can be influenced by renal disease (NS, CKD and tubular disease)[8]. But this renal excretion of TSH appears to be clinically insignificant because of its short half life (60 minutes) and much higher reserve of pituitary gland[8].

Material and Methods

This Cross sectional comparative study was carried out in nephrology unit of Rajshahi medical college hospital and Nuclear medicine center, Rajshahi, from January, 2013 to December, 2014. NS was diagnosed on the basis of generalized edema, proteinuria (>3.5 g / 24 hours), hypoalbuminemia (serum albumin <3g / l) and hypercholesterolemia. Forty patients with idiopathic Nephrotic Syndrome were purposively selected from Nephrology department and forty age matched healthy subjects were included as control. Patients with secondary Nephrotic Syndrome, significant renal failure (serum creatinine > 3 mg / dl), known cases of thyroid disease and acute illness known to cause thyroid dysfunction were excluded from this study. Data was analyzed with SPSS software program version-16.0.

Results

Among forty patients of NS, 18 were male and 22 were female. Mean (±SD) age of patients and control subjects were 32±11 and 38±11. Mean (±SD) BMI of patients and control subjects were 22.9±3.9 and 21.2±2.9 respectively. All the patients had hypoalbuminemia (Serum albumin <3.5 gm/dl). Serum albumin was between 2-3 mg/dl in most of the patients (36, 90%). Mean (±SD) of serum albumin was 2.38 ± 0.31 (Table 1). Low serum T4 was found in 29 (72.5%) of patients and low T3 was found in 28 (70%) of patient with NS. Whereas among healthy control low T4 was found in only 3 (7.5%) and low T3 was found in only 2 (5%) patients. Mean (± SD) TSH was 11.34 (±18.15) in patients with NS and 2.73 (± 1.79) mIU/L in healthy control. Most of the patient (60%) had elevated TSH level and among them 20 (50%) were between 5-20 mIU/L (sub clinical hypothyroidism) and 4 (10%) were above 20 mIU/L. Among the healthy individuals TSH were elevated in only 3 (7.5%) subjects and were between 5-20 mIU/L. Serum total T4 and T3 were significantly lower ($t= -6.935$, $df= 78$, $p<0.001$ & $t= -5.750$, $df= 78$, $p<0.001$ respectively) and serum TSH was significantly higher ($t= 2.984$, $df= 78$, $p<0.01$) in patients with NS as compared to healthy subjects (Table 2). A significant positive correlation was found between serum albumin with serum total T4 ($r= 0.874$, $p<0.001$) (Figure 1A) and also with total T3 ($r= 0.901$, $p<0.001$) (Figure 1B). No correlation was found between serum albumin and serum TSH ($r= - 0. 292$, $p>0.05$) (Figure 1C).

Discussion

Proteinuria is associated with urinary excretion of thyroid hormones and thyroxine binding globulin (TBG) which is a universal finding.[9,10,11] It showed that serum T4 & T3 to be significantly lower and TSH to be significantly higher in NS as compared to healthy subjects. But some different observations were noted in other studies[4,5,9] i.e. found only T3 to be significantly low, found only TSH to be significantly higher and only lower T4 was noted. Unlike others, a significant higher proportion of subclinical hypothyroidism in 20 (50%) patients and overt hypothyroidism in 4 (10%) patients was observed in our study. Among them 10 (25%) had TSH >10. Occurrence of subclinical and overt hypothyroidism was also described by Gilles et al. (2008) but at much lower frequency. A significant positive correlation of serum total T4 and total T3 with serum albumin was seen. Similar correlation also was observed in some studies[9,10]. Similar correlation and also a negative correlation between serum albumin and TSH were described by Gilles et al[4]. However,

some authors did not find any correlation of serum albumin with TSH as does our study.

Overt hypothyroidism is associated with cardiovascular morbidity and mortality and should always be treated. But whether or not subclinical hypothyroidism associated with NS be treated with L-thyroxine remains unclear. Some studies showed that this thyroid dysfunction resolves after remission of NS[12]. So they concluded that subclinical hypothyroid state in NS is temporary and improves with remission. So, no treatment is needed.

Conclusion

We have systematically evaluated patients with NS to observe the frequency and pattern of thyroid dysfunctions. Considering the result of this study and observations done by other researchers it can be concluded that nephrotic range proteinuria is associated with thyroid hormone loss in urine and this can lead to significant reduction in serum T4, T3 and significant increase in serum TSH level.

Recommendation

High index of suspicion is required to identify hypothyroidism in patients with NS and should be screened for thyroid status if proteinuria is heavy and prolonged. A large RCT can be performed to see whether thyroid hormone replacement has any influence on NS.

Limitations Of Study

It is a small scale cross sectional study. Study patient and healthy subjects are not screened for auto-immune thyroid disease (ie. Anti-TPO antibody) and free T4 & free T3 were not measured in this study.

Table I: Baseline characteristics of patient with NS and healthy control.

Baseline characteristics		Patient (N=40)		Control (N=40)	
		N (%)	Mean ±SD	N (%)	Mean ± SD
Age (yrs)		--	32±11	--	38±11
Sex	Male	18 (45)		18 (45)	
	Female	22 (55)		22 (55)	
BMI	Under weight (<18.5)	6 (15)	22.99± 3.98	3 (7.5)	21.2± 2.9
	Normal (18.5-23)	16 (40)		26 (65)	
	Overweight (23-25)	5 (12.5)		5 (12.5)	
	Obese (>25)	13 (32.5)		6 (15)	
Serum Albumin (gm/dl)			2.38± 0.31		
Serum creatinine (mg/dl)			1.37± 0.55		

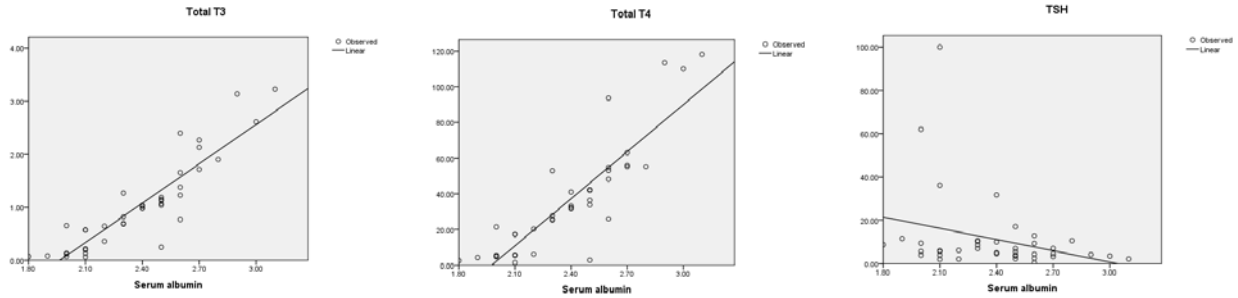
NB: BMI = Body Mass Index (Goddard J, Turner AN & Stewart LH, 2010).

Table II: Comparison of serum T4, T3 and TSH between patients with NS and healthy control.

Thyroid hormone levels (nmol/L)		Patient (N=40)		Control (N=40)		
		N (%)	Mean ± SD	N (%)	Mean ± SD	t (p)
Total T4	High (>173)	0 (0.0)	39.34 ± 29.49	0 (0.0)	83.34 ± 27.23	-6.935 (<0.001)
	Normal (54-173)	11 (27.5)		37(92.5)		
	Low (<54)	29 (72.5)		3 (7.5)		
Total T3	High (>3.54	0 (0.0)	1.05 ± 0.83	0 (0.0)	2.04 ± 0.70	-5.750 (<0.001)
	Normal (1.23-3.54)	12 (30)		38 (95)		
	Low (<1.23)	28 (70)		2 (5)		
TSH	High (>20)	4 (10)	11.34 ± 18.15	0 (0.0)	2.73 ± 1.79	2.984 (<0.01)
	Subclinical (5-20)	20 (50)		3 (7.5)		
	Normal (<5)	16 (40)		37 (92.5)		
	Low (<0.4)	0 (0.0)		0 (0.0)		

NB: TSH = Thyroid stimulating hormone.

Figure 1: Correlation between serum albumin and serum total T4 (A) (r = 0.818, p <0.001), total T3 (B) (r =0.903, p <0.001) and total TSH (C) (r = - 0.292, p>0.05) in patients with NS.



A B C

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