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Thyroid Dysfunction in patients with Nephrotic Syndrome

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Abstract:

Background: Nephrotic syndrome is a nonspecific kidney disorder characterised by Proteinuria, hypoalbuminaemia, oedema & hyperlipidemia. In nephrotic syndrome there is marked increased in the glomerular permeability to macromolecules.

Aims: To asses thyroid status in patient with nephrotic syndrome; To measure FT3, FT4 and TSH in patient with nephrotic syndrome and Level of proteinuria with Thyroid hormone level.

Methods: After fulfilling inclusion and exclusion criteria 50 diagnosed cases of idiopathic NS admitted in Nephrology unit of Rajshahi Medical College Hospital were included in this study. Thyroid status was evaluated in all the patients. In patients with NS mean (± SD) of FT4, FT3 and TSH were 39.34 (±29.49), 1.05 (±0.83) and 11.34 (±18.15) respectively. Significant positive correlation was found between serum albumin and serum FT4 ($r = +0.733$, $p < 0.001$) and also with total FT3 ($r = +0.762$, $p < 0.001$). But no correlation was found between serum albumin and serum TSH ($r = -0.670$, $p<0.001$) in patients with NS. So, it was found that nephrotic range proteinuria is associated with thyroid hormone loss in urine and this can lead to significant reduction in serum FT4, FT3 and significant increase in serum TSH. Patients with NS can develop subclinical hypothyroidism or even overt hypothyroidism. **Conclusion:** Thyroid hormones are necessary for the growth and development of kidney. On the contrary different form of kidney diseases are associated with various types of thyroid dysfunctions. This association between renal disease and thyroid dysfunction has been known for years. In patients with nephrotic syndrome (NS) large amount of protein is lost in urine along with thyroid hormones and hormone binding proteins. This hormone loss may lead to low FT4, FT3 and sometimes high TSH level

Key Words: Nephrotic syndrome, Proteinuria, thyroid dysfunction.

Introduction

The interactions between kidney and thyroid functions are known for years. Thyroid hormones are necessary for growth and development of kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, decline in of kidney function is accompanied by changes in the synthesis, secretion, metabolism and elimination of thyroid hormone. Kidney disease such as glomerular or tubular disease, nephrotic syndrome, acute kidney injury, CKD and dialysis are known to causes different forms of thyroid dysfunction (Iglesias P & DIez JJ, 2009).

Nephrotic syndrome refers to a secondary phenomenon that occurs when substantial amount of protein are lost in the urine. It is characterized by overt proterinuria- usually >3.5 g/ 24 hours, hypoalbuminemia (< 30g/l), oedema, and generalized fluid retension. Intravascular volume depletion with hypotension or expansion with hypertension may occur. The consequences of nephrotic syndrome are hypoalbuminemia with avid sodium retention, hypercholesterolemia, hyercoagulability and infection (Goddard J, Turner AN & Stewart LH, 2010. p481). In India the

annual incidence of nephrotic syndrome in children was found ranging from 2-7 per 100,000 and prevalence from 12-16 per 100,000 (Bagga A & Mantan M, 2005). A national population-based cross-sectional survey in Australia have shown the prevalence of proteinuria in adult is 2.4% (Steven J et al, 2003). Although a minimum annual incidence of nephrotic syndrome is 9.0 cases per million adult population (Sharpstone P, Ogg CS & Cameron JS, 1969), it is difficult to establish prevalence of nephrotic syndrome in adult because the condition is usually a result of an underlying disease.

In patient with nephrotic syndrome urinary losses of albumin are not fully compensated by the increased hepatic productions with hypoalbuminemia as a consequence. In patients with proteinuria many other proteins besides albumin are lost in the urine. Among these are hormones and hormone binding proteins (Gilles R et al, 2008). Several studies have documented urinary loss of thyroid hormones and thyroxin binding globulin (TBG) in patient with proteinuria (Feinstein EI et al. 1982, Iglesias Pet al. 2009, Junglee NA et al. 2006, Kaptein EM et al. 1982 & Kaptein EM et al. 1991). Urinary losses of binding proteins such as thyroxin binding globulin (TBG), thransthyrrectin or prealbumin, albumin and thyroid hormone bound to them result in a reduction in serum total thryroxin (T4) and sometimes in total T3 levels. These changes are related both to degree of proteinuria and to serum albumin levels (Feinstein EI et al, 1982 & Iglesias P et al, 2009). 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 (Gilles R et al, 2008). So nephrotic syndrome was known to be associated with changes in serum thyroid hormone levels, ie- thyroxin (T4), T3 and TSH for many years (Iglesias P et al, 2009, Junglee NA et al. 2006, Kaptein EM et al. 1982, Kaptein EM et al. 1991& Feinstein EI et al.1982).

Clinical relevance of this observation of thyroid dysfunction in patients with nephrotic syndrome is yet to be defined. So far we know such type of observation is lacking in our country. The purpose of the present study is to evaluate thyroid hormone status in patients with nephrotic syndrome in a tertiary care hospital.

Materials and Method:

This cross-sectional Observational study was conducted on patients attending in in inpatient and outpatient Department of Rajshahi Medical College Hospital, Rajshahi from April, 2023 to October 2023. A total of 50 patients were selected through purposive sampling. Inclusion criteria: a) Diagnosed patients of Nephrotic syndrome b) Both male & female c) Age more than 18 years d) Participants and / or legally accepted guardians who gave consent and willing to comply with study procedure. Exclusion criteria: a) Secondary nephrotic syndrome. b) Significant renal failure (Serum creatinine > 3 mg / dl). c) Known cases of thyroid disease. d) Systemic illness known to cause thyroid dysfunction eg.-MI, Heart Failure, Chronic liver diseases, Chronic Kidney diseases, Malignancy, Sepsis, Inflammatory condition. General Objective: To assess thyroid status in patient with nephrotic syndrome. Specific Objectives: a) To measure FT_3, FT_4 and TSH in patient with nephrotic syndrome. b) Level of proteinuria with Thyroid hormone level c) To see socio-demographic data of study population All the data's were checked and edited after collection. Then the data were entered into computer and statistical analyses of the results were obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-22) with the help of statistician. The results were presented in tables and figures. In each group, calculation for the continuous variables [mean, standard deviation, no of observations], frequency are calculated in percentage (%). Statistical significance was set at $p<0.05$ and confidence interval was set at 95% level.

Results:

This study shows majority of the patients 27(54.0%) were in the age group 31-40 years followed by 12(24.0%) 20-30 years. The mean age was 32.2±8.5 years.

Age in years	Frequency	Percentage (%)
20-30	12	24.0
31-40	27	54.0
41-50	3	6.0
> 50 yrs	8	16.0
Total	50	100.0
Mean±SD	32.2±8.5	

Table 1: Age distribution of the study patients (n=50)

Out of 50 nephrotic syndrome patients 46.0% were male and 54% were female. The male: female ratio were 1:1.2

Sex	Frequency	Percentage (%)
Male	23	46.0
Female	27	54.0
Total	50	100.0
Male: female ratio	1:1.2	

Table 2: Sex distribution of the patients (n=50)

Out of 50 nephrotic syndrome patients 40.0% were normal weight, 12% patients were overweight and 32.0% patients were obese and 16% patients were under weight

BMI (kg/m^2)	Frequency	Percentage (%)
Under weight (<18.5)	5	16.0
Normal (18.5-23)	20	40.0
Overweight (23-25)	6	12.0
Obese (>25)	16	32.0
Total	50	100.0
Mean±SD	22.98±2.89	

Table 3: BMI distribution of the patients (n=50)

Out of 50 cases, 10.0% were service holder, 12% business, 16.0% student, 18.0% were farmer and 44.0% patients were housewife.

Occupation	Frequency	Percentage (%)
Service	5	10.0
Business	6	12.0
Laborer	8	16.0
Farmer	9	18.0
Housewife	22	44.0
Total	50	100.0

Table 4: Occupational distribution of the study subjects (n=50)

Most patients had UTP between 3.5-10 gm/ 24 hours 45(90.0%) with a mean of 5.96±2.88 gm/24 hours

Urinary findings	Frequency	Percentage (%)	Mean±SD
Urinary output (ml)			
<500	3	6.0	
500-1000	26	52.0	992.0±685
1000-2000	14	28.0	
>2000	7	14.0	
Urinary albumin			
++	6	12.0	
+++	21	42.0	
++++	23	46.0	
Urinary RBC			
Nill	14	28.0	
<5	15	30.0	
5-10	7	14.0	8.2±2.6
10-15	3	6.0	
15-20	1	2.0	
<20	10	20.0	
Urinary WBC			
Nill	8	16.0	
<5	6	12.0	
5-10	14	28.0	
10-15	9	18.0	11.6±3.12
15-20	6	12.0	
<20	7	14.0	
Urinary Cast			
Nil	25	50.0	
+	11	22.0	
++	9	18.0	
+++	5	10.0	
UTP (gm/24 hours)			
<5	23	46.0	
5-10	22	44.0	5.96±2.88
>10	5	10.0	

Table 6: Biochemical findings in patients with nephrotic syndrome (n=50)

Low serum FT4 was found in 36(72.0%) of patients and low FT3 was found in 35(70%) of patient with NS. Mean (± SD) TSH was 11.34 (±18.15) in patients with NS. Most of the patient (60%) had elevated TSH among them 25(50%) were between 5-20 mIU/L (sub clinical hypothyroidism) and 5 (10%) were above 20 mIU/L.

Thyroid hormone levels	Frequency	Percentage (%)
FT4 (nmol/L)		
High (>173)	0	0.0%
Normal (54-173)	14	28.0%
Low (>54)	36	72.0%
Mean±SD 39.34±29.49		
FT3 (nmol/L)		
High (>3.54)	0	0.0%
Normal (1.23-3.54)	15	30.0%
Low (<1.23)	35	70.0%
Mean±SD 1.05±0.83		

TSH (mlu/L)		
High (>20)	5	10.0%
Subclinical (5-20)	25	50.0%
Normal (<5)	20	40.0%
Low(<0.4)	0	0.0%
Mean±SD 11.34±18.15		

Table 7: Distribution of the NS patients by thyroid hormone levels (n=50)

Table 8 shows ccorrelation between serum albumin and FT4, FT3 and TSH level in nephrotic syndrome patients. Here significant positive correlation between serum albumin with FT4 and FT3 but significant negative correlation with TSH.

Parameters		**Pearson correlation test**	
		r	p
Serum albumin (g/dL)	FT4	+ 0.733*	<0.001
	FT3	+ 0.762*	<0.001
	TSH	- 0.670*	<0.001

***Significant**

Table 8: Correlation between serum albumin and Total T4, T3 and TSH in study patients (n=50)

Pearson's correlation coefficient (r) test was performed to compare relationship between serum albumin and FT4, FT3 and TSH. The test of significance was calculated and p value < 0.05 was accepted as level of significance.

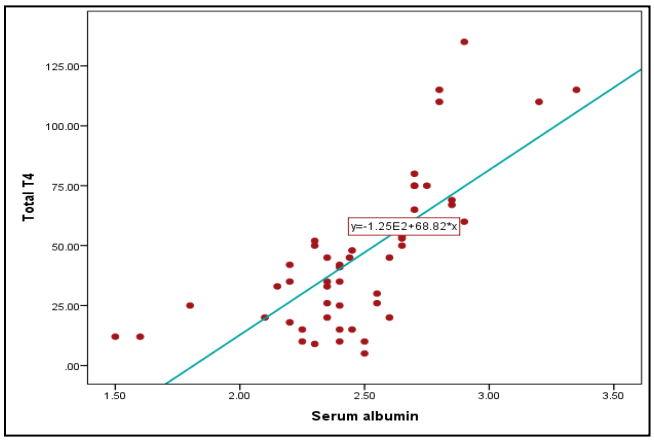

Fig. 1: Scatter diagram showing correlation between serum albumin with total T4

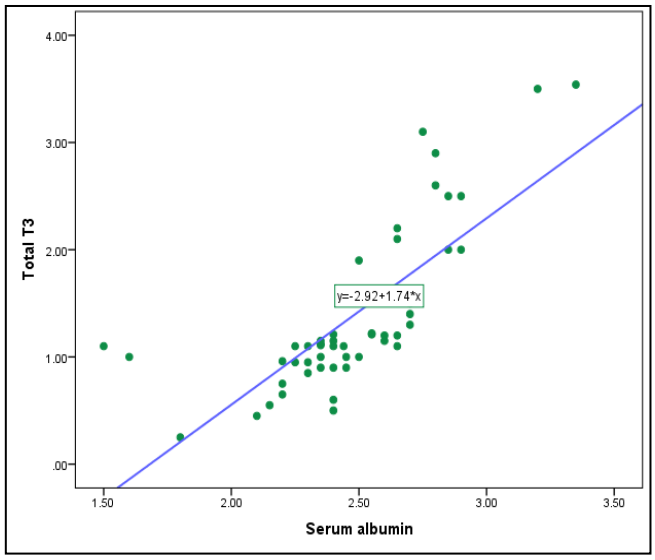

Fig. 2: Scatter diagram showing correlation between serum albumin with total T3

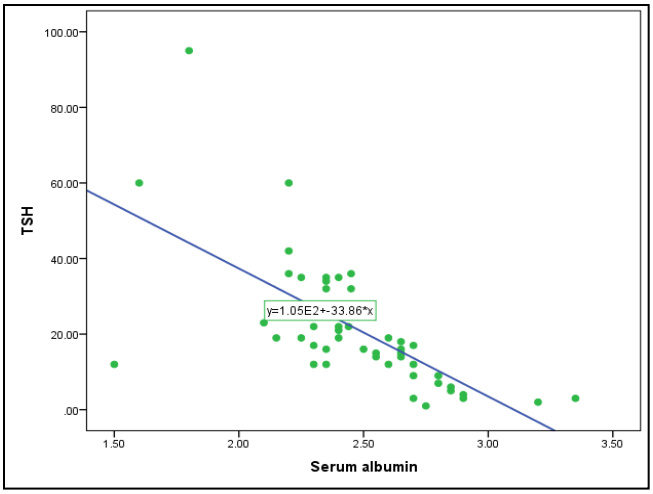

Fig. 3: Scatter diagram showing correlation between serum albumin with TSH

Discussion:

Age of NS varies in different part of the world. In our study highest frequency was observed in age group 31-40 years in patients with NS. The mean age was 32.2±8.5 years. Similar pattern of age distribution was observed by Afrasiabi et al. (1979) and Okpechi et al. (2010). But higher age was noted in patients with NS in Netherlands (mean= 52 years) and Turkey (mean= 47 years) as described by Gilles et al. (2008) and Oguz et al. (2009). Lower age group was found to be affected in other parts of the world as well as in other studies in Bangladesh (Anon 1989, Tarik et al. 2007 and Habib et al. 2012). Although age distribution of patients in our study may not represent the actual pattern of age distribution in patients with NS in Rajshahi Medical College Hospital. Because we have taken purposively collected small number of sample after exclusion of certain patient i.e. secondary NS & Significant renal failure. Male-female ratio in our study was 1:1.17. Similar sex ratio was observed by Habib et al. (2012) in patients of same institute and in Africa by Okpechi et al. (2010). Male predominance was observed by Tarik et al. (2007) and also in children by Chowdhury et al. (2010) and Shah et al. (2013). Female predominance also observed in california USA (Afrasiabi et al. 1979).

We had included patient of NS with UTP > 3.5 gm/ 24 hours. In children higher urinary protein was observed (Chowdhury et al. 2010 and Ito et al. 1994) as compared to adults (Oguz et al. 2009 & Afrasiabi et al. 1979) which were more or less similar to our study. Relatively more hypoalbuminemia was also noted among children (Ito et al. 1994, Ahmed et al. 2011 & Chowdhury et al. 2010) than adults (Oguz et al. 2009, Afrasiabi et al. 1979 & Gilles et al. 2008).

Serum albumin in most of our patient was also relatively higher than that found in children. High serum cholesterol was found in all patients in this study. And this finding is invariable as reported by other studies both in adults and children. Proteinuria is associated with urinary excretion of thyroid hormones and thyroxine binding globulin (TBG). Which is a universal finding (Ito et al. 1994, Fonseca et al. 1991, Afrasiabi et al. 1979 & Gavin et al. 1978). Ito et al. (1994) observed that mean serum T4 & T3 to be significantly lower and TSH to be significantly high in children with NS as compared to healthy subjects. After this study we have agreed upon the above findings but some degree of difference in observation was noted in other studies. i.e. Afrasiabi and colleagues (1979) found only T3 to be significantly lower, at Nijmegen, the Netherlands Gilles et al. (2008) found only TSH to be significantly higher and only lower T4 was noted by Feinstein and others (1982). Unlike others a significantly 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. In this study significant positive correlation of serum T4 and T3 with serum albumin was seen. Similar correlation was observed by Ito et al. (1994) and Afrasiabi et al. (1979). Similar correlation and also a negative correlation between serum albumin and TSH were described by Gilles et al. (2008). Some author did not find any correlation of serum albumin with TSH as does our study. Overt hypothyroidism associated with NS should always be treated. Because overt hypothyroidism is associated with cardiovascular morbidity and mortality. But whether of not subclinical hypothyroidism associated with NS be treated with L-thyroxine remains unclear. Sahni et al. (2014) prospectively studied 35 children with NS who also had subclinical hypothyroidism (mean TSH= 8.93±3.15 µIU/ml) during nephrosis. They found that this thyroid dysfunction resolves after remission of NS (mean TSH= 5.77±0.65 µIU/ml). So Sahni and colleagues concluded that subclinical hypothyroidism state in NS is temporary and improves with remission. So, no treatment is needed. On the contrary a trial of low dose L-thyroxine in 59 patient with primary NS and thyroid dysfunction done by Anon (2010) shown that small doses of L-thyroxine can influence remission of NS, in terms of shortening the course and improving the cure rate.

Moreover, studies have described that thyroxine replacement can slow the decline in renal function in CKD patient with subclinical hypothyroidism. Shin et al. (2013) was studied 113 patient with stage 2-4 CKD and subclinical hypothyroidism and found statistically significant impact of thyroid hormone on the decline in eGFR. They found that the decline in eGFR were significantly attenuated by L-thyroxine supplement in both stage 2 and stage 3-4 CKD patients. It was also observed that thyroid hormone replacement therapy had delayed reaching CKD stage 5 within 10 years in 81.1% of CKD patients with subclinical hypothyroidism. In addition to Kreisman et al. (1999) and others Connor & Taylor (2008) reported two cases of reversible renal impairment secondary to hypothyroidism. Patients were found to have hypothyroidism and reduced GFR. Other causes of renal impairment were excluded and renal biopsy showed no feature of GN. Replacement with L-thyroxine brought about complete recovery of renal function. Behind this, three mechanisms were suggested- (1) reduction of GFR due to low cardiac output and renal blood flow, (2) Thyroxine may mediate tubular secretion of creatinine and (3) Hypothyroidism may increase creatinine release from muscle. A similar case was reported by Asim and Esnawi (2010). So hypothyroidism can cause renal impairment in the absence of glomerular disease. L-thyroxine replacement can reverse the renal impairment in patients without glomerular disease. Thyroxine can also slow the progression of CKD and delay the onset of ESRD in patient with stage 2-4 CKD with subclinical hypothyroidism. Therefore, Shin et al. (2013) concluded that thyroid hormone treatment should be considered in patients with renal impairment and subclinicalhypothyroidism.

Clear benefit of thyroxine replacement was observed in case of patients with CKD whereas controversial results were found in case of ARF (Acker et al. 2000).

Considering the effect of L-thyroixine on progression of CKD observed by several researchers we can say that, L-thyroxine replacement may be of benefit in patients with NS and subclinical hypothyroidism who also have renal impairment. But larger randomized controlled trial will be necessary to recommend L-thyroxine replacement in this patient group without renal impairment.

Conclusion:

Thyroid hormones are necessary for the growth and development of kidney. On the contrary different form of kidney diseases are associated with various types of thyroid dysfunctions. This association between renal disease and thyroid dysfunction has been known for years. In patients with nephrotic syndrome (NS) large amount of protein is lost in urine along with thyroid hormones and hormone binding proteins. This hormone loss may lead to low FT4, FT3 and sometimes high TSH level. NS was found to be associated with subclinical and overt hypothyroidism. We have systematically evaluated patients with NS to see the frequency and pattern of thyroid dysfunctions in patients with NS. 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 inserum FT4, FT3 and significant increase in serum TSH. Patients with NS can develop subclinical hypothyroidism or even overt hypothyroidism. Apparently it is related to the degree of proteinuria and also to the thyroid reserve of the patient as not all patients with reduced serum FT4 and FT3 has raised TSH level. It was found that L-thyroxine replacement can improve outcome in patients with subclinical hypothyroidism and renal impairment. But despite tremendous influence of thyroid hormone over renal function its role in NS remains unclear.

Limitation:

It is a small scale cross sectional study. So to decide whether or not we screen all the patient with NS a large scale study should be done. Other limitations of our study are patient and healthy individuals are not screened for auto-immune thyroid disease (ie. Anti-TPO antibody) and fT4 & fT3 were not measured.

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