ISSN (Print): 2663-9491 ISSN (Online): 2789-6897

Original Article

Assessment of Thyroid Function in Patients with Variable Degree of Proteinuria

DOI: https://dx.doi.org

Abu Sayed Mohammad Morshed [1], SM Imrul Anwar, [2] Md Shahadat Hossain, [3] Mohammad Ehasun Uddin Khan, [4] Istiaque Musharraf, [5] Abu Noim Md Abdul Hai, [6] Mahabubur Rahman, [7] Md Ashraf Uddin Chowdhury [8]

Received: 30 OCT 2021
Accepted: 06 NOV 2021
Published: 11 NOV 2021

Published by:
Sheikh Sayera Khatun Medical College Gopalganj, Bangladesh

How to cite this article:
Morshed ASM, Anwar SI, Hossain MS, Khan MEU, Musharraf I, Hai ANMA, Rahman M, Chowdhury MAU. Assessment of Thyroid Function in Patients with Variable Degree of Proteinuria . The Insight [Internet]. 2021 Nov. 11 [cited 2021 Nov. 11];4(01). Available from: https://bdjournals.org/index.php/insight/article/view/98

ABSTRACT

Introduction: *Patients with proteinuria may suffer from substantial losses of thyroxine-binding globulin that may affect the thyroid status. Proteinuric patients with thyroid dysfunction need to be identified for appropriate measure to reduce morbidity and mortality.* ***Methods:*** *All protein uric patients other than those with diabetes mellitus, lupus nephritis, pre-diagnosed thyroid disease and patients with transient proteinuria were our study subjects. Then quantification of protein by 24 hours' urinary total protein (UTP) was done in every subject. Patients having proteinuria less than 1 gm/24 hrs/1.73 m² of body surface area (BSA) were excluded. From 140 study subjects finally 94 were selected by inclusion and exclusion criteria. They were further divided into non-nephrotic (42 patients) and nephrotic (52 patients) group. Twenty-nine healthy age and sex matched controls were taken. Thyroid hormone parameters, Serum albumin and lipid profile were done in each subject.* ***Results:*** *The mean age of the control group was 31±9 years, that of non-nephrotic group was 35±14 years and in the nephrotic group was 36±16 years. The mean urinary total protein in control group was 0.07±0.04 gm/24 hrs, in non-nephrotic group 1.58±0.82 gm/24 hrs and in nephrotic group it was 8.28±3.37 gm/24 hrs. The mean thyroid stimulating hormone (TSH) was found 2.02±1.26 mIU/L in control group, 3.57±2.04 mIU/L in non-nephrotic group and 5.65±3.95 mIU/L in nephrotic group. The mean*

1. *Assistant Professor, Nephrology, Shaheed Tajuddin Ahmad Medical College, Gazipur, Bangladesh*
2. *Assistant Professor, Nephrology, National Institute of Kidney Diseases and Urology (NIKDU), Dhaka,*
3. *Assistant Professor, Nephrology & Dialysis, Central Police Hospital, Rajarbag, Dhaka, Bangladesh*
4. *Assistant Professor, Nephrology, Dhaka Medical College, Dhaka, Bangladesh*
5. *Medical Officer, Nephrology, National Institute of Kidney diseases and Urology (NIKDU), Dhaka*
6. *Assistant Professor, Nephrology, Shaheed Tajuddin Ahmad Medical College, Gazipur*
7. *Assistant Professor, Neurology, Sheikh Sayera Khatun Medical College, Gopalgonj, Bangladesh*
8. *Assistant Professor, Cardiology, Sheikh Sayera Khatun Medical College, Gopalgonj, Bangladesh*

free triidothyronine (FT_3) in control group was 4.20±0.42pmol/L, in non– nephrotic group 3.81±1.00 pmol/L and in nephrotic group 3.63±0.95 pmol/L. The mean free thyroxine (FT_4) value was 13.97±2.76 pmol/L, 14.16±5.23 pmoL/L, 13.03±3.45pmol/L in control, non-nephrotic and nephrotic group respectively. ***Conclusion:*** *Thyroid dysfunction especially subclinical hypothyroidism and low T_3 were more common in proteinuric patients.*

Keywords: Proteinuria, Nephrotic syndrome, Subclinical hypothyroidism, thyroid function, Low T_3 syndrome.

The Insight 2021; 4(1): 22:28

INTRODUCTION

Proteinuria is a hallmark of renal diseases. Severe proteinuria occurs in the nephrotic syndrome, which is characterized by proteinuria, hypoalbuminaemia, oedema and hyperlipidaemia[1]. In patients with proteinuria many other proteins besides albumin, are lost in the urine. Among these are hormones and hormone-binding proteins. Several studies have documented urinary loss of thyroid hormones and thyroxin-binding globulin (TBG) in patients with proteinuria [2], [3], [4], [5].

Thyroid stimulating hormone (TSH) levels were found to be high in nephrotic syndrome and the increase in TSH correlates well with the degree of proteinuria. This leads to the possibility that significant amounts of thyroid hormones are also lost in proteinuric states resulting in a total body negative balance. In situations of long standing heavy proteinuria, it results in clinically significant hypothyroidism [6].

Loss of thyroid hormones may lead to low free thyroid hormone levels unless production is increased under the influence of TSH. Furthermore, loss of albumin and TBG may reduce the binding capacity for thyroid hormones, resulting in a decrease in total triiodothyronine (T3) and thyroxin (T4) concentrations [1].

Untreated subclinical hypothyroidism may be associated with a modest increase in the risk of coronary artery disease [7]. American guidelines recommend that treatment should be considered if the TSH is elevated but below 10 mIU/l in people with symptoms of hypothyroidism, detectable antibodies against thyroid peroxidase, a history of heart disease or are at an increased risk for heart disease[8]. The frequency of low T3 syndrome increases with the severity of the disease [9]. The low T_3 syndrome is now considered to be responsible for increased mortality and morbidity both in patients with chronic kidney disease (CKD) and the non-uremic population [10], [14].

The aim of this study is to evaluate the thyroid functions in patients with proteinuria and to establish a correlation, if any between thyroid dysfunction and severity of proteinuria.

METHODS & MATERIALS

This is a cross sectional study and was carried out in the department of nephrology of Dhaka Medical College Hospital, Dhaka, from January 2016 to December 2016. Study populations were patients having proteinuria from the outpatient and inpatient department of nephrology unit. Sampling method was convenience sampling. It was followed as per inclusion and exclusion criteria. Inclusion criteria were any patients with proteinuria. Exclusion criteria were patients with fever, urinary infection, congestive cardiac failure, thyroid disease, diabetes mellitus, lupus nephritis, renal impairment, any malignancy and patients taking steroid, oestrogen containing products, amiodarone or lithium carbonate.

Twenty-four hours UTP was measured in all individuals. Among them the study

subjects were included as per minimum lower cut off of UTP value of 1 gm/24 hrs/1.73 m². Every patient was thoroughly assessed with detailed history taking and physical examination. Then as per exclusion criteria finally study subjects were selected.

On the basis of 24 hour UTP study subjects were further divided into two groups: nephrotic and non-nephrotic group. Nephrotic range proteinuria was defined as proteinuria above 3.5 gram/day/1.73 m² of body surface area. Non nephrotic range proteinuria was proteinuria below 3.5 gram/day/1.73 m² of body surface area [14, 15]. Normotensive, nonproteinuric, healthy volunteers from patients' attendants, hospital staffs and other community members were taken as controls. They were also evaluated by detailed history taking and physical examination. An informed written consent both from the patients and the controls were taken. Thyroid hormone parameters, albumin, lipid profile and UTP of both patients and controls were taken.

Clinical and biochemical finding of the groups (Non-nephrotic and nephrotic) were compared. Thyroid dysfunction was defined as an aberration of thyroid hormone level from normal reference value. Normal reference value of thyroid hormone level: Serum free tri-iodothyrinine (FT_3) -2.62-5.70 pmol/. Serum free thyroxine (FT_4) -9.14-23.81 pmol/L. Thyroid stimulating hormone (TSH) -0.47-5.01mlU/L[16].

RESULTS

In this study, 94 patients (42 non-nephrotic and 52 nephrotic) with proteinuria and 29 control were included. Thyroid hormone parameters (TSH, FT3, and FT4), serum albumin and lipid profile were done in each subjects. Three groups (Control, Non-nephrotic and Nephrotic) were compared for different characteristics.

Table l: Baseline characteristics of three groups

Parameters	Control (n=29)	Non-Nephrotic (n=42)	Nephrotic (n=52)	p value
Male (number)	20	18	29	-
Female (number)	9	24	23	-
Age(years) (Mean±SD)	31 ± 9	35 ±14	36 ± 16	-
BP-Systolic (mmHg)	117±9	136±12	139±14	0.82
BP-Diastolic (mmHg)	74±12	86±11	87±10	0.74
BMI (Kg/m²)	22.70±1.53	22.77±1.91	22.73±1.74	0.92
BSA (m²)	1.68±.11	1.68±.12	1.67±.09	0.94
UTP(gm/24 hrs) (Mean±SD)	0.07±0.04	1.86±0.59	8.28±3.37	0.00
S Creatinine (mg/dl)	0.78±.17	0.89±.19	0.93±0.19	0.22
TSH(miu/L)	2.02±1.26	3.53±2.04	5.65±3.95	0.00
FT3(pmol/L)	4.2±.42	3.82±1	3.63±.95	0.36
FT4(pmol/L)	13.97±2.76	14.16±5.23	13.03±3.45	0.23
S.Albumin (gm/l)	43.28±4.92	31.1±7.65	24.49±7.03	0.00
Lipid Profile				
T.C(mg/dl)	217.72±36.4	211.81±65.92	301.1±142.08	0.00
HDL(mg/dl)	43.86±9.20	41.19±12.97	48.85±18.63	0.02
LDL(mg/dl)	144.62±27.85	131.78±43.43	205.77±114.91	0.00

TG(mg/dl)	173.69±55.89	208.93±78.91	236.6±128.7	0.21

P value reached from independent t test comparing between non-nephrotic and nephrotic group. BP-Blood Pressure, BMI-Body Mass Index, BSA-Body Surface Area, UTP-Urinary Total Protein, TSH-Thyroid Stimulating Hormone, TC-Total Cholesterol, HDL-High density lipoprotein, LDL-low density lipoprotein, TG-triglyceride.

Table-II: Distribution of thyroid dysfunction

	Control		Non-Nephrotic (n=42)		Nephrotic(n=52)	
Type of thyroid dysfunction	Number	%	Number	%	Number	%
Subclinical hypothyroidism	0	0	7	16.67	17	32.70
Hypothyroidism	0	0	0	0	0	0
Subclinical hyperthyroidism	1	3.44	1	2.38	0	0
Hyperthyroidism	0	0	0	0	0	0
Low T3	0	0	6	14.28	7	13.46
Total	1	3.44	14	33.33	24	46.16

DISCUSSION

This cross sectional study was carried out with an aim to assess thyroid function in patients with variable degree of proteinuria. A total number of 94 patients with different levels of proteinuria and 29 healthy controls who came to the nephrology unit of Dhaka Medical College Hospital, Dhaka, during the period of January 2016 to December 2016 were included in this study. Patients having fever, urinary infection, heart failure, diabetes mellitus, lupus nephritis, malignancy, pre-diagnosed thyroid diseases and patients taking steroid, oestrogen and other medications that may alter thyroid function e.g. amiodarone, lithium carbonate, were excluded from the study. The present study findings were discussed and compared with previously published relevant studies.

In this study a total of 123 subjects were divided into three groups: 29 in the control group, 42 in non-nephrotic group and 52 in the nephrotic group. Males were predominant in the control and nephrotic group whereas females were predominant in the non-nephrotic group. One study showed male predominance in both control and proteinuric group [1] whereas females were predominant in another study [17].

In this current study it was observed that mean age of the control group was 31±9 years, that of non-nephrotic group was 35±14 years and in nephrotic group was 36±16 years. One study by Groot found the mean age of the patients was 49±17 years[17]. Other study found mean age 52 years ranged between 40-64 in both control and proteinuric group[1]. Our study population were considerably younger than many other studies.

In this current study it was observed that urinary total protein in the control group was 0.07±0.04 gm/24 hrs (ranging 0.02 to 0.14 gm/24 hours), in the non-nephrotic group 1.86±O.59 gm/24 hrs (ranging 1.1 to 3.32 gm/24 hours) and in nephrotic group it was 8.28±3.37gm/24 hrs (ranging 3.51 to 16.13 gm/24hrs). One study showed urinary protein excretion in non-nephrotic subject 1.22 ±0.90 gm/24h and in nephrotic subject 5.07±1.36 gms/24h [6]. Another study found proteinuria level to their

patients 6.6(3.1-10.9) gm/day [1]. Another previous study found urinary protein excretion in 24 hours collection was 7.8±4.5 gm/day [17].

In this study it was found that the serum creatinine was 0.78±0.17mg/dl (ranging 0.53-1.17mg/dl) in the control group, 0.89 ± 0.19 mg/dl (ranging 0.38 to 1.18 mg/dl) in the non-nephrotic group and 0.93±0.19 mg/dl (ranging 0.45 to 1.19 mg/dl) in the nephrotic group. One study showed serum creatinine 99(82-134) µmol/l in the proteinuric group and 83(76-92) µmol/l in the control group [1]. Another study showed serum creatinine level 1.32±0.66 mg/dl in all proteinuric patients [17]. The results of these study slightly differ from our study.

In this current study high TSH level was found in none of the control group, 16.67% in the non-nephrotic group and 32.70% in the nephrotic group. The mean TSH was found 2.02±1.26mIU/L in control group, 3.57±2.04mIU/L in non-nephrotic group, 5.65±3.95 mIU/L in the nephrotic group. Nearly similar observation was found by one previous study [6]. They found TSH value of 2.9±1.2, 2.7±1.0, 5.9±1.8 µIU/mL in the control, the non-nephrotic and the nephrotic group respectively. Other study showed TSH value in the control group was 1.34(range 0.98-1.87) mIU/l and in proteinuric group 1.81(range 1.04-2.81) mIU/l which demonstrated that abnormalities in thyroid function occur in patients with proteinuria [1]. Specifically, TSH levels were higher in patients with proteinuric renal diseases when compared with age and sex-matched controls. These data are consistent with the reports of urinary losses of thyroid hormones in patients with proteinuria. Apparently, these urinary losses of thyroid hormones in patients with proteinuria result in a stimulation of TSH production. One study showed serum TSH 3.2±3.1mIU/m L in the nephrotic group whereas 1.29±0.68 (0.41-2.90) mIU/ml in the control group. [18] Levels differed significantly between control and nephrotic patients.

In this series below normal FT3 level was found in 6(14.28%) of the non-nephrotic group and 7(13.46%) of the nephrotic group. Majority patients had normal serum FT3 level in three groups which was 29(100%) in the control group, 35(83.33%) in the non-nephrotic and 44(84.62%) in the nephrotic group. FT4 value was normal and similar in all three groups. One study found both FT4 and FT3 levels below normal in the nephrotic group while these values were normal in the non-nephrotic group [6]. Another study by Tatar E showed FT3 levels was significantly lower in control group, whereas serum FT4 levels were similar in both control and nephrotic patients groups [18]. There were no differences in FT4 values between nephrotic and non-nephrotic patients that is similar to our study.

The mean serum albumin was found 42.28±4.92 gm/l in controls, 30.31±7.65gm/l in non-nephrotic and 24.49±7.03 gm/l in nephrotic group. One study found serum albumin was 29(22-35) gm/l in proteinuric group and 46(44-48) gm/l in control group [1]. Another study found serum albumin value 22±5 gm/l in nephrotic group [18]. The serum albumin was significantly lower in nephrotic patients in all of these studies.

The patients in nephrotic group showed significantly higher levels of total cholesterol, LDL and triglycerides than non-nephrotic and control groups. Non-nephrotic group showed no significant difference with control except higher levels of triglyceride. One study found total cholesterol was 344±11.1 mg/dl, HDL 52±1.5 mg/dl, LDL 249±10.8 mg/dl and triglyceride 214±11.4 mg/dl [18]. Another study showed total cholesterol was 396.83±10.3 mg/dl, HDL 41.11±4.2 mg/dl, LDL 240.8±3.2 mg/dl, triglyceride 426.99±91.79 mg/dl [18]. These values were slightly different from our study, probably due to ethnic and racial variation in study population.

In this present study it was demonstrated that abnormalities in thyroid function occurs in patients with proteinuria. These were subclinical hypothyroidism and low T3 syndrome. Subclinical hypothyroidism was seen in 7(16.67%) patients in non-nephrotic group, 17(32.70%) patients in nephrotic group compared to 0(0%) patients in control group. So it is seen that TSH levels were higher in patients with proteinuric renal diseases in both non nephrotic and nephrotic when compared with control. In a study of 159 patients with nephrotic syndrome, it was found that 11.3% of the patients had subclinical hypothyroidism and had significantly higher serum TSH levels when compared to the control group [1]. Another study showed six out of thirty three patients had subclinical hypothyroidism which was 18.18% [18]. The frequency of subclinical hypothyroidism were slightly higher in our study compared to those studies. In this study low T3 syndrome was observed in 6(14.28%) patients in non nephrotic group, 7(13.46%) patients in nephrotic group; no patients had low T3 in control group. One study showed eleven of the patients (33%) had low T3 level syndrome that was higher from our study [18]. No subclinical hyperthyroid was found in nephrotic group but there was 1(3.3%) patient in control group and 1(2.88%) patient in non-nephrotic group which was different from the study done by another previous study where they found 1(0.6%) patient in proteinuric group, 0(0%) patient in control group [1]. Our results also showed difference with the result by other study where they found 1(3.03%) patient with this respect. [18] Our study showed no patient with overt hypothyroidism in any group that was different from another study where they found 1(0.6%) patient with overt hypothyroid in proteinuric group and no patient 0(0%) in control group [1]. Another study also found 1(3.3%) patient with overt hypothyroid in proteinuric group [18]. Total thyroid dysfunction found in our study were 1(3.44%) patients in control group, 14(33.33%) patients in non-nephrotic group, and 24 (46.16%) patients in nephrotic group. One study showed thyroid abnormalities in 21(63.6%) patients with proteinuria [18]. Thyroid dysfunction was not present in control group. Another previous study found total thyroid dysfunction in 20(12.5%) patients with proteinuria compared to 18(2%) patients in control [1].

CONCLUSIONS

This study was undertaken to assess the thyroid function in patients with variable degrees of proteinuria. Serum TSH level was higher in proteinuric patients. Serum FT3 level was lower in proteinuric patients. Thyroid dysfunction especially subclinical hypothyroidism and low T3 syndrome were more common in proteinuric patients. Serum albumin was lower and lipid profile abnormalities were found in proteinuric patients especially in nephrotic group. Serum TSH was negatively correlated with serum albumin. FT3 level was negatively correlated with serum albumin especially nephrotic group. All patients with proteinuria and particularly nephrotic syndrome should be assessed for thyroid dysfunction.

REFERENCES

1. *Gilles R, Heijer MD, Ross AH, Sweep FCGJ, Hermus ARMM, Wetzels JFM. Thyroid function in patients with proteinuria. Netherlands Journal of Medicine. 2008; 66(11): 483-485.*
2. *Afrasiabi MA, Vaziri ND, Gwinup G, Mays DM, Barton CH, Ness RL, et al. Thyroid function studies in the nephrotic syndrome. Ann Int Med .1979; 90(3): 335-8.*
3. *Adlkofer F, Hain H, MeinholH, Kraft D, Ramsden D, Herrmann J, etal. Thyroid function in patients with proteinuria and normal or increased serum creatinine concentration. ACTA Endocrinoligica.1983; 102(3): 367-76.*
4. *Liappis N, Rao S. Behavior of the levels of free triiodothyronine, free thyroxine, thyroxine, thyrotropin and thyroxine- binding globulin in*

the serum of children with nephrotic syndrome. Klin Padiatr. 1985; 197(5): 423-6.

5. *Fonseca V, Thomas M, Katrak A, Sweny P, Moorhead JF. Can urinary thyroid hormone loss cause hypothyroidism? The Lancet .1991; 338(8765): 475-6.*
6. *SangitaU, ChandranS,AlmediaAF,Rajan G. Correlation between oxidative stress and thyroid function in patients with nephrotic syndrome. Int J Nephrol. 2011;5 : 256-420.*
7. *Ochs N, Auer R, Bauer DC. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Annals of Internal Medicine (Meta-analysis) 2008; 148 (11): 832–45.*
8. *Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical Practice Guidelines for Hypothyroidism in Adults. Thyroid. 2012; 22 (12):1200–1235.*
9. *Song SH, Kwak IS, Lee DW, Kang YH, Seong EY, Park JS, et al. The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone. Nephrol Dial Transplant .2009;24(5): 1534-1538.*
10. *Zoccali C, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P. Low triiodothyronine and survival in end-stage renal disease. Kidney Int. 2006; 70(3):523-528.*
11. *Carrero JJ, Qureshi AR, Axelsson J, Yilmaz MI, Rehnmark S, Witt MR, et al. Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. J Intern Med. 2007;262(6): 690-701.*
12. *Pfister R, Strack N, Wielckens K, Malchau G, Erdmann E, Schneider CA. The relationship and prognostic impact of low-T3 syndrome and NT-pro-BNP in cardiovascular patients. Int J Cardiol. 2010;144(2):187-190.*
13. *Ozen KP, Asci G, Gungor O, Carrero JJ, Kircelli F, Tatar E, et al. Nutritional state alters the association between free triiodothyronine levels and mortality in hemodialysis patients. Am J Nephrol. 2011;33 (4):305-312.*
14. *Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987; 317(17): 1098.*
15. *Glassock RJ. 2001.Glomerular Diseases. In: Massry, SG Glassock.*
16. *Strachan,M.W.J. and Walker,B.B., 2014. Endocrine disease. In : Colledge NR, Walker BR, Ralston SH. Davidson Principles and Practice of Medicine. 2014. 22nd Edition: pp:738-746. Publisher: Churchill Livingstone.*
17. *Groot De LJ. Dangerous dogmas in medicine: The nonthyroidal illness syndrome. J clin Endocrinol Metab.1999; 84: 151-164.*
18. *Tatar E, Isikyakar T, GunGor O, Yeniay KP, Tasli F, et al. Low T3 Syndrome in Adult Patients with Nephrotic Syndrome. Turkish J Nephrol. 2014; 23(2):137-141.*