The Levels of Cystatin C and Markers of Kidney Function in Hypothyroidism

Suyash Saxena[1], Jyoti Batra[2], Gladys Rai[3], Sudeep Kumar[4]

ABSTRACT

Introduction: Thyroid hormones affect kidneys in various ways ranging from their development to their functions. The present study aims to evaluate the effects of hypothyroidism (subclinical and overt) on the markers of kidney function.

Material and Methods: In this cross-sectional study 368 subjects were recruited and divided in three categories euthyroid, subclinical and overt hypothyroid subjects. All the subjects were analysed for Thyroid function (Total T_3, T_4 TSH) and Kidney Function (Blood Urea, Creatinine, Cystatin C, eGFR).

Results: Statistical analysis revealed a significant rise in BUN and serum creatinine was observed in both subclinical and overt hypothyroid patients as compared to euthyroids. Serum Cystatin C and eGFR were significantly decreased.

Conclusion: The study shows that there are negative effects of hypothyroidism on kidney functions.

Keywords: Kidney function, CKD, Hypothyroidism, Thyroid Dysfunction, Cystatin C, Creatinine, Blood Urea, Glomerular Filtration Rate

INTRODUCTION

In past few years Chronic Kidney Disease (CKD) has emerged as a prevalent and serious threat. According to a recent study the prevalence of CKD was observed to be 17.2% out of which 7% were with only stage.[1] There is a special relation of thyroid and kidneys. Thyroid dysfunction can alter Renal Blood Flow (RBF), Glomerular Filtration Rate (GFR), electrolyte homeostasis, tubular function and kidney structure; on the other hand, kidney has a key role in the metabolism, degradation and excretion of thyroid hormone and its metabolites. The hypothyroidism can affect kidneys by decrease in RBF due to decreased cardiac output by the negative chronortropic and inotropic effects.[2] In hypothyroidism there is intrarenal vasoconstriction[3], reduced renal response to vasodialators[4] and increased peripheral vascular resistance.[5] Along with that there is decreased angiotensin II and impaired RAAS activity in hypothyroidism which results in reduced GFR.[6] It should be emphasized and taken care of by the primary care physicians to screen for early kidney damage in cases of hypothyroidism.

In hypothyroidism the GFR is reversibly reduced by about 40% in more than 55% of adults.[7] Very limited data is available on the effects of hypothyroidism on renal function tests.[8,9,10] Serum creatinine and Blood urea are the traditional markers to assess kidney function but both of them can be affected by various other factors.

Cystatin C is a low molecular weight, non glycosylated protein that acts as a cysteine protease inhibitor. Cystatin C is produced at a constant rate by nucleated cells and released into the bloodstream with a half-life of ~2h.[11] Cystatin C is freely filtered and almost completely taken up and degraded, but not secreted, by proximal tubular cells. Compared to serum creatinine, CysC has a lower variability and is not affected by lean tissue mass, age and gender.[12,13] CysC has been proved to be a reliable marker of glomerular filtration rate (GFR) in healthy adults and children as well as in patients with renal disorders of neoplastic, rheumatologic, hepatic, and nephrologic origin.[14,15,16,17]

So the present study aimed to evaluate the levels of traditional biochemical markers of kidney function and serum cystatin C in patients of hypothyroidism.

MATERIAL AND METHODS

This was a cross-sectional study. The study was conducted in the Department of Biochemistry, Santosh Medical College and Hospital, Ghaziabad, Delhi-NCR region. A total 368 subjects were recruited from the medicine OPD and divided in 3 groups. (i) Euthyroid (100subjects) (ii) Subclinical Hypothyroid (118 subjects) (iii) Overt Hypothyroid (150 subjects). The ethical approval was taken from local ethics committee.

The newly detected cases whose diagnosis was confirmed following clinical and biochemical investigations were included in the study group whereas the subjects having Diabetes mellitus, Hypertension, Coronary Heart Diseases, other endocrine disorders, alcohol abusers, pregnant women and patients who were already on Thyroid treatment or CKD treatment were excluded from the study.

Blood samples were collected after 12 hrs overnight fasting by venipuncture in clean test tubes. The samples were

[1]Ph.D. Scholar, Department of Biochemistry, Santosh Medical College, Ghaziabad, [2]Professor and Vice-Dean (Research), Department of Biochemistry, Santosh Medical College, Ghaziabad, [3]Professor and HOD, Department of Biochemistry, School of Medical Sciences and Research, Greater Noida, [4]Ph.D. Scholar, Department of Biochemistry, Santosh Medical College, Ghaziabad, India

Corresponding author: Suyash Saxena, Deaprtment of Biochemistry, Santosh Medical College, Santosh University, Ghaziabad, U.P., India

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centrifuged for 15 minutes at 2500 rpm and aliquots of serum were used to analyze different parameters.

Following Biochemical parameters were analyzed in the study group:

Serum T3 and T4 were performed using competitive ELISA technique and serum TSH was performed using sandwich ELISA technique using the reagent kit by Monobind, Lake forest, USA

Serum urea was analyzed by enzymatic urease glutamate dehydrogenase method using the reagent kit by Erba diagnostics Mannheim Germany.

Creatinine was analyzed by modified Jaffe's method using the reagent kit by Autospan liquid gold creatinine (Aarkay healthcare, India).

Cystatin c was analysed by quantitative turbidimetric immunoassay using the reagent kit by Quantia Cystatin C(Tulip Diagnostics, India)

eGFR was calculated by Cock-croft Gault Formula

STATISTICAL ANALYSIS

All the data is shown as mean and standard deviation. The difference between groups was compared by Student's t Test. The correlation between different parameters for thyroid and kidney function was analyzed by Pearson's correlation coefficient.

RESULTS

The level of TSH in euthyroids was 2.55µIU/ml ± 1.14. As compared to euthyroids there is a significant rise in the levels of TSH in subclinical hypothyroids(15.24µIU/ml ± 4.51) and overt hypothyroids (36.29µIU/ml ± 12.1); however there was a significant decrease in the level of T_3 in subclinical hypothyroids(0.88ng/ml ± 0.30) and overt Hypothyroids (0.38ng/ml ± 0.15) as compared to euthyroids (1.02ng/ml ± 0.12) (Table 1).

The level of T_4 in euthyroids was 8.04µg/dl ± 1.9. As compared to euthyroids there is a significant decrease in the levels of T_4 in subclinical hypothyroids(7.33µg/dl ± 1.87) and overt Hypothyroids (2.81µg/dl ± 1.05) (Table 1). The markers of kidney function like Blood Urea and Serum Creatnine were found to be also statistically significantly increased in both Subclinical hypothyroids and overt hypothyroid patients as compared to euthyroids. There was an increase of 31.41% in blood urea and 74.71% increase in the level serum creatinine in case of overt hypothyroidism from euthyroids(Table 1).

Similarly there was a statistically significant decrease in serum Cystatin C in both Subclinical hypothyroids (0.65mg/L ± 0.21) and overt hypothyroid patients (0.39mg/L ± 0.12) as compared to euthyroids (0.83 mg/L ± 0.0.19) (Table 1).

The eGFR of all the patients, calculated by Cock-croft Gault formula was analysed statistically and a significant fall was observed in both subclinical and overt hypothyroidism as compared to euthyroids.

All the parameters of kidney function were compared with markers of thyroid function for any statistical correlation. In Subclinical hypothyroidism and overt hypothroidism there was a significant positive correlation found between TSH and serum creatinine along with eGFR. Serum Cystatin C was found to be reduced significantly showing a negative correlation with TSH. Blood urea and T_3 in overt hypothyroidism were found to be negatively correlated. None of the other markers were found correlated statistically.

Parameters	Euthyroid (1)	Subclinical Hypothyroid (2)	Two sample t test with p value (1) Vs (2)	Overt Hypothyroid (3)	Two sample t test with p value 1 vs 3
T_3 (ng/ml)	1.02 ± 0.12	0.88 ± 0.30	(P>0.05)	0.38 ± 0.15	(P <0.0001)*
T_4 (µg/dl)	8.04 ± 1.9	7.33 ± 1.87	(P<0.05)**	2.81 ± 1.05	(P <0.0001)*
TSH (µIU/ml)	2.55 ± 1.14	15.24 ± 4.51	(P<0.0001)*	36.29 ± 12.1	(P <0.0001)*
Blood Urea (mg/dl)	19.99 ± 5.38	20.45 ± 4.84	(P >0.05)	26.87 ± 5.50	(P <0.0001)*
Creatinine (mg/dl)	0.87 ± 0.25	1.09 ± 0.36	(P <0.05)**	1.52 ± 0.30	(P <0.0001)*
Cystatin C (mg/L)	0.83 ± 0.19	0.65 ± 0.21	(P <0.0001)*	0.39 ± 0.12	(P <0.0001)*
eGFR (ml/min)	97.97 ± 25.92	80.11 ± 28.11	(P<0.0001)*	54.97 ± 16.53	(P <0.0001)*
T3=Tri idothyronine, T4=Thyroxine, eGFR= Estimated Glomerular filtration rate, P<0.05,P<0.001= significant result					

Table-1: Level of different biochemical parameters in euthyroid, subclinical hypothyroid and overt hypothyroid patients

Parameters		Blood Urea	Creatinine	Cystatin C	eGFR
T_3	Euthyroid	r= -0.0553	r=-0.0074	r=0.0563	r=0.0774
	Subclinical hypothyoid	r=-0.0479	r=-0.1429	r=-0.1539	r=0.1059
	Overt hypothyroid	r=0.2807*	r=0.0924	r=0.1131	r=-0.0729
T_4	Euthyroid	r=-0.0232	r=0.082	r=0.1594	r=-0.1451
	Subclinical hypothyoid	r=0.1468	r=0.0368	r=0.0551	r=-0.0518
	Overt hypothyroid	r=0.1877	r=0.1179	r=0.1284	r=-0.1497
TSH	Euthyroid	r=0.2750*	r=0.0329	r=0.0548	r=0.0137
	Subclinical hypothyoid	r=0.1084	r=0.2645*	r=0.3877*	r=0.2736*
	Overt hypothyroid	r=0.1340	r=0.2599*	r=0.2188*	r=0.4273*
*=P<0.05, Significant Result					

Table-2: Correlation between the markers of Thyroid and Kidney Function in different thyroid states

DISCUSSION

The aim of present study was to evaluate the consequence of subclinical hypothyroidism and overt hypothyroidism on markers of kidney function and to compare them with euthyroids.

The study shows that there is a significant rise in the levels of serum creatinine and blood urea in both the groups i.e. subclinical and overt hypothyroidism. When compared with euthyroids, all these changes were statistically significant. Similar results of increase in serum creatinine have been reported in some previous studies also.[9,10,18,19] A study reports that infants with congenital hypothyroidism show higher creatinine level in proportion to the severity of hypothyroidism.[20] The increase in creatinine and urea may be due to decrease in GFR, myopathies and rhabdomyolosis. The downfall in GFR is found in our study also. The decrease in GFR results from decrease in cardiac output, intrarenal vasoconstriction[4], reduced renal response to vasodialators[5] and increased peripheral vascular resistance.[6] The study shows that the levels of serum cystatin C were significantly decreased in both groups i.e. subclinical and overt hypothyroidism. It was speculated before that in hypothyroidism, there is decreased production of cystatin C in the nucleated cells due to decreased cellular metabolism. But in our view, since after glomerular filtration, Cystatin C is completely reabsorbed in proximal tubule and is catabolised there. The reduction in overall reabsorbing capacity of the renal tubules in hypothyroidism[21,22,23], leads to no absorption in proximal tubules and results in the secretion of cystatin C through urine. This can be the plausible cause of decrease in the level of cystatin C in hypothyroidism. It shows that hypothyroidism can have negative effects on kidney function. Knowledge of association between change in biomarkers of kidney function and hypothyroidism is very important for clinicians. This would help the clinicians in better treatment of hypothyroidism and its deleterious on kidneys. The assessment of kidney function should be done routinely in the patients of hypothyroidism.

CONCLUSION

By the results of our study, it can be concluded that there is some relation in progression of hypothyroidism and the deterioration in kidney function. Some studies have given the possible reasons like thickening of basement membrane in kidney, decreased renal blood flow and generalized hypodynamic state of circulatory system. But the exact mechanism behind hypothyroidism and its negative effect on kidney is yet to be established and this leads to various questions for the further studies in future. As the prevalence of chronic kidney disease increases, all cases of hypothyroidism should be routinely screened for deteriorating kidney functions, which will help the clinicians in better management of kidney dysfunction.

REFERENCES

1. Singh et al. Epidemiology and risk factors of chronic kidney disease in India- results from the SEEK (Screening and early evaluation of kidney disease) study. BMC Nephrology 2013;14:114
2. Crowley WF Jr, Ridgway EC, Bough EW, Francis GS, Daniels GH, Kourides IA, et al. Noninvasive evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. N Engl J Med 1977;296:1-6.
3. Singer MA. Of mice and men and elephants: Metabolic rate sets glomerular filtration rate. Am J Kidney Dis 2001;37:164-78.
4. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501-9.
5. Diekman MJ, Harms MP, Endert E, Wieling W, Wiersinga WM. Endocrine factors related to changes in total peripheral vascular resistance after treatment of thyrotoxic and hypothyroid patients. Eur J Endocrinol 2001;144:339-46.
6. Asmah BJ, Wan Nazaimoon WM, Norazmi K, Tan TT, Khalid BA. Plasma renin and aldosterone in thyroid diseases. Horm Metab Res 1997;29:580-3.
7. Montenegro J, Gonzalez O, Saracho R, Aguirre R, Martinez I. Changes in renal function in primary hypothyroidism. Am J Kidney Dis 1996;27:195-8.
8. Kreisman SH, Hennessey JV. Consistent reversible elevations of serum creatinine levels in severe hypothyroidism. Arch Intern Med 1999; 159:79-82.
9. Tayal Devika, Chawla Ranjana, Arora Sarika, Gupta VK, Sohi JS, Mallika V. Dynamic Changes in Biochemical Markers of Renal Function with Thyroid Status – A Study in Indian Population. Internet Journal of Medical Update 2009;4:36-41.
10. Kaur V, Singh K and Verma M, Changes In Biochemical Markers Of Renal Function In Subclinical And Overt Hypothyroidism, International Journal of Bioassays, 2015;4:3799-3802.
11. Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez-Bru C, Grubb A. Cystatin C as a marker of GFR-history, indications, and future research. Clin Biochem 2005;38:1–8.
12. Keevil BG, Kilpatrick ES, Nichols SP, Maylor PW: Biological variation of cystatinC: Implications for the assessment of glomerular filtration rate. Clin Chem 1998; 44:1535–1539.
13. Vinge E, Lindergard B, Nilsson-Ehle P, GrubbA: Relationships among serum cystatin C, serum creatinine, lean tissue mass and glomerular filtration rate in healthy adults. Scand J Clin Lab Inves 1999;59:587–592.
14. Galteau MM, Guyon M, Gueguen R, Siest G: Determination of serum cystatinC: Biologica lvariation and reference values. Clin Chem Lab Med 2001; 39:850–857.
15. Mangge H, Liebmann P, Tanil H, et al: Cystatin C, an early indicator for incipient renal disease in rheumatoid arthritis. Clin Chim Acta 2000; 300:195–202.
16. Stickle D, Cole B, Hock K, et al: Correlation of plasma concentrations of cystatin C and creatinine to inulin clearance in a pediatric population. Clin Chem 44:1334–1338, 1998.
17. Woitas RP, Stoffel-Wagner B, Flommersfeld S, et al: Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. Clin

Chem 2000; 46:712–715.
18. den Hollander JG, Wulkan RW, Mantel MJ, et al. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol (Oxf). 2005;62: 423- 7.
19. Nakahama H, Sakaguchi K, Horita Y, et al. Treatment of severe hypothyroidism reduced serum creatinine levels in two chronic renal failure patients. Nephron. 2001;88:264-7.
20. Asami T, Uchiyama M. Elevated serum creatinine levels in infants with congenital hypothyroidism: reflection of decreased renal function? Acta Paediatr. 2000; 89:1431-4.
21. Zimmerman RS, Ryan J, Edwards BS, Klee G, Zimmerman D, Scott N, et al. Cardiorenal endocrine dynamics during volume expansion in hypothyroid dogs. Am J Physiol 1988;255: R61-6.
22. Garg LC, Tisher CC. Effects of thyroid hormone on Na-K-adenosine triphosphatase activity along the rat nephron. J Lab Clin Med 1985;106:568-72.
23. Marcos Morales M, PurchioBrucoli HC, Malnic G, Gil Lopes A. Role of thyroid hormones in renal tubule acidification. Mol Cell Biochem 1996;154:17-21.

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