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Original Research Article

A Study to Assess the Renal Function in Subclinical Hypothyroid Patients: An Observational Study

Naiyer Azam

Assistant Professor, Department of Biochemistry, L. N. Medical College & Research Centre and J.K. Hospital, Bhopal (MP)

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Corresponding author: Dr. Naiyer Azam
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Abstract

Aim: The aim of the present study was to assess the renal function in subclinical hypothyroid patients.

Methods: The present study was conducted at Department of Biochemistry and all the cases detected with SCH from August 2021 and May 2023 were taken for the study. The data were collected from patients coming to L. N. Medical College & Research Centre and J.K. Hospital, Bhopal (MP) for consultation in outpatient department (OPD) and from medical records. A total of 750 subjects were included in the study.

Results: We found a highly significant difference in the mean values of FT3, FT4, TSH, serum creatinine, eGFR by MDRD, and eGFR by CKD-EPI equation among all the groups. A linear trend of increase in creatinine values from ET controls to SCH to OHT groups. Pearson's correlation studies reveal that TSH levels were well correlated with serum creatinine in the OHT group only. No correlation was found with ET and SCH groups. Similarly, a significant negative correlation between TSH and eGFR was found only in OHT group. We found a very strong positive correlation between eGFR calculated by MDRD and eGFR by CKD-EPI equations in all the subjects. Linear regression analysis in GLM model showed that the linear regression in creatinine based on the TSH values is attributable to the extent of 44.7% among the OHT group.

Conclusion: This study concluded that there is tissue hypothyroidism as manifested by the difference in the creatinine levels and eGFR values in such patients compared to the healthy controls. eGFR calculation by both the formulae has good correlation in the study groups. Hence, either of them can be used for measuring GFR. Furthermore, the linear regression analysis concludes that the TSH values may be used to predict the lower kidney function (higher creatinine values) among the SCH group.

Keywords: renal dysfunction, subclinical hypothyroidism, thyroid-stimulating hormone, tissue hypothyroidism

Introduction

Thyroid disorders are very common with a high prevalence among the general population. Thyroid diseases are associated with many detrimental effects that have a serious impact on various body systems. [1] Thyroid hormones affect renal function by both pre-renal and direct-renal effects. Pre-renal effects are mediated by the influence of thyroid hormones on the cardiovascular system and the renal blood flow. The direct renal effects are mediated by the effect of thyroid hormones on glomerular filtration rate (GFR). Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. [2] Subclinical hypothyroidism (SCH), defined as elevated serum TSH but normal free T4 (FT4) level, is a common endocrine disease. The prevalence of SCH increased with age, about 4 to 10% in adult population [3] and 12.7% in diabetic individuals. [4] Biochemical diagnosis of subclinical hypothyroidism (SCH) is crucial since its signs and symptoms are not typical. [5]

There is an established association between thyroid hormone and renal functions. Thyroid hormones play an important role in the growth, development and physiology of the renal system. [6] Conversely, the kidney is an organ for metabolism and as well as elimination of free T3 and free T4, Thyroid abnormalities can cause significant changes in renal functions and water-electrolyte homeostasis. Hypothyroidism is associated with low GFR, hyponatremia. Excessive level of TSH lowers the glomerular filtration rate and renal blood flow, overall significantly altering the kidney functions. Hypothyroidism is associated with significant alteration in biochemical parameters of kidney function. [7,8] Increased serum creatinine is inversely associated with glomerular filtration rate (GFR) values in overt hypothyroid patients. [6,9,10,11] Renal dysfunction can be assumed as the

reflection of hypothyroidism. Long standing hypothyroidism can cause significant changes in renal function such as decrease in sodium re-absorption in the proximal tubules, impairment in the concentrating and diluting capacities of the distal tubules, a decrease in the urinary urate excretion and a decrease in the renal blood flow and glomerular filtration rate (GFR). These renal abnormalities occur because the deficiency of thyroid hormones (TH) reduces the cardiac output leading to generalized hypodynamic state of the circulatory system. Hypothyroidism also results in increased glomerular capillary permeability of proteins; the consequent proteinuria often precedes the reduction in GFR in hypothyroidism. [12]

SCH cases present with few or no symptoms or signs of thyroid dysfunction and thus by its very nature SCH is a laboratory diagnosis. Due to its asymptomatic nature, the SCH cases are not detected clinically and also its relation to the kidney function is not well established. [13]

The aim of the present study was to assess the renal function in subclinical hypothyroid patients.

Materials and Methods

The present study was conducted at Department of Biochemistry, L. N. Medical College & Research Centre and J.K. Hospital, Bhopal (MP) and all the cases detected with SCH from August 2021 and May 2023 were taken for the study. The data were collected from patients coming to L. N. Medical College & Research Centre and J.K. Hospital, Bhopal (MP) for consultation in outpatient department (OPD) and from medical records. A total of 750 subjects were included in the study.

Inclusion Criteria

The study includes all the subjects in the age group of 18–70 years of either sex attending the OPD.

Exclusion Criteria

Subjects who are known cases of thyroid disorders, on treatment with drugs such as amiodarone, lithium, iodine, antithyroid drugs, patients having renal disorders, liver disorders, diabetes, hypertension, and other chronic inflammatory disorders were excluded from the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards.

A uniform protocol was followed for sample collection and analysis of the tests in the laboratory. 5 mL of blood sample was drawn under aseptic precautions. After 30 min, it was centrifuged and serum separated was sorted in 2 aliquots; one for thyroid profile and the other for estimation of creatinine. The tests were done immediately on the same day.

Methods of Estimation

TSH, FT4, and FT3 were estimated by chemiluminescence immunoassay technology in fully automated immunoassay analyzer from Siemens Advia Centaur CP. The reference range followed in the laboratory for TSH is 0.35–5.5 □IU/L, FT3 is 2.3–4.2 pg/ml, and FT4 is 0.89–1.76 ng/dl.

Creatinine was estimated by modified kinetic Jaffe's method in fully automated Siemens Dimension RXL max chemistry analyzer. Calibrator for creatinine is traceable to isotope-dilution mass spectrometry (IDMS) primary reference measurement procedure. All analyses were performed in accordance with manufacturer's instructions. The reference range followed in the laboratory for creatinine is 0.5–1.3 mg/dl.

The modification of diet in renal disease (MDRD) study equation and the chronic kidney disease epidemiology collaboration (CKD-EPI) equation are the most widely used IDMS traceable equations for estimating GFR in patients aged 18 and over. We have used both the equations for eGFR calculation. [14,15]

The following is the IDMS-traceable MDRD study equation (for creatinine methods calibrated to an IDMS reference method):

The subjects were divided into three groups after laboratory investigations:

• Group 1: SCH: Subjects having higher TSH and free triiodothyronine (FT3), FT4 within the normal reference range

• Group 2: Overt hypothyroid (OHT): Subjects having higher TSH and low FT3 or FT4

• Group 3: Euthyroid (ET): Subjects having TSH, FT3, and FT4 all within the normal reference range.

Statistical analysis

All the findings are expressed as mean ± standard deviation. The $P < 0.05$ was considered statistically significant, $P < 0.01$ as highly significant, and $P < 0.001$ as very highly significant. Analysis was performed by various statistical tests such as general linear model (GLM), ANOVA, Pearson's correlation, and linear regression using IBM® SPSS® statistics version 20.0 (IBM Corporation, New York, USA).

Results

Table 1: Comparison of the various parameters among the three groups by ANOVA

Parameter	SCH		OHT		ET		*P*
	Females	Males	Females	Males	Females	Males	
n	200	115	75	52	200	108	
Age (years)	47±12.38	55±12.36	47±12.98	41±15.35	48±15.25	47±13.67	
FT3 (pg/ml)	2.88±0.42	3.08±0.36	1.87±0.812	1.58±0.86	2.98±0.36	3.24±0.36	<0.001
FT4 (ng/dl)	1.24±0.16	1.27±0.23	0.55±0.25	0.45±0.25	1.34±0.24	1.35±0.25	<0.001
TSH (μIU/ml)	8.24±2.96	8.36±3.36	78±55.42	96.07±55.35	2.52±1.16	2.52±1.10	<0.001
Creatinine (mg/dl)	0.82±0.18	1.08±0.22	0.96±0.24	1.22±0.24	0.76±0.14	0.97±0.13	<0.001
eGFR MDRD	79.19±20.46	75.58±16.96	67.83±22.56	71.79±22.57	84.35±21.57	89.02±22.58	<0.001
eGFR CKD-EPI	87.54±19.64	81.54±19.64	75.51±23.5	79.98±27.05	93.24±22.17	93.38±17.10	<0.001

We found a highly significant difference in the mean values of FT3, FT4, TSH, serum creatinine, eGFR by MDRD, and eGFR by CKD-EPI equation among all the groups.

Table 2: Median values of creatinine observed at the mean values of thyroid-stimulating hormone compared across the groups

Group	*n*	Age (years)	Mean TSH (μIU/ml)	Creatinine (mg/dl)	Creatinine (mg/dl), median	
					Males	Females
OHT	108	44.72	88.84	1.058	1.00	1.00
SCH	310	48.22	8.26	0.918	0.90	0.90
ET controls	332	46.24	2.51	0.856	0.70	0.70

A linear trend of increase in creatinine values from ET controls to SCH to OHT groups.

Table 3: Correlation of thyroid-stimulating hormone with creatinine and estimated glomerular filtration rate in all three groups

TSH	Creatinine (*r*)	*P*	eGFR (MDRD) (*r*)	*P*	eGFR (CKD-EPI) (*r*)	*P*
SCH						
Female	0.03	0.5	−0.004	0.8	−0.03	0.6
Male	0.07	0.3	−0.07	0.5	−0.07	0.5
OHT						
Female	0.58	<0.05	−0.55	<0.001	−0.56	<0.001
Male	0.38	<0.05	−0.35	0.05	−0.33	0.06
ET						
Female	0.02	0.8	−0.12	0.12	−0.09	0.2
Male	0.08	0.3	−0.08	0.32	0.05	0.5

Pearson's correlation studies reveal that TSH levels were well correlated with serum creatinine in the OHT group only. No correlation was found with ET and SCH groups. Similarly, a significant negative correlation between TSH and eGFR was found only in OHT group.

Table 4: Correlation of estimated glomerular filtration rate (modification of diet in renal disease) with estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration)

Group	Female (*r*)	*P*	Male (*r*)	*P*
OHT	0.96	<0.001	0.97	<0.001
SCH	0.98	<0.001	0.98	<0.001
ET controls	0.95	<0.001	0.93	<0.001

We found a very strong positive correlation between eGFR calculated by MDRD and eGFR by CKD-EPI equations in all the subjects.

Table 5: Regression analysis by general linear model

Group	R^2	Adjusted R^2	Residual error
OHT	0.804	0.447	0.044
SCH	0.923	0.484	0.025
ET controls	0.778	0.232	0.023

Linear regression analysis in GLM model showed that the linear regression in creatinine based on the TSH values is attributable to the extent of 44.7% among the OHT group.

Discussion

Subclinical hypothyroidism (SCH) is defined as an elevated serum thyroid-stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxine (fT4) within the reference range. SCH cases present with few or no symptoms or signs of thyroid dysfunction and thus by its very nature SCH is a laboratory diagnosis. The prevalence of SCH in the United States adult population is 4-8.5%. [16] Various epidemiological studies in India show a prevalence rate of SCH varying between 9% and 11.4%. The progression to overt hypothyroidism (OHT) is approximately 2-5% per year. Due to its asymptomatic nature, the SCH cases are not detected clinically and also its relation to the kidney function is not well established. [17]

We found a highly significant difference in the mean values of FT3, FT4, TSH, serum creatinine, eGFR by MDRD, and eGFR by CKD-EPI equation among all the groups. A linear trend of increase in creatinine values from ET controls to SCH to OHT groups. Thyroid has negligible effect upon the synthesis of creatine from its precursors. In hypothyroid state, creatine is retained in the muscle and the stores of both creatine and phosphocreatine are increased; however, the conversion of creatine to creatinine is uncertain. The rate of excretion of creatinine corresponds to a conversion of 2% of the creatine in the body in 24 h. There is no renal threshold for creatinine. Studies done to find the influence of thyroid on the rate of conversion of creatine into creatinine in hypothyroid state did not show convincing results. [18] Pharmacologically induced hypothyroidism in rats resulted in a marked reduction in kidney size and creatinine clearance, thus decreasing GFR. [19] Based on the evidences, we can say that the increased levels of creatinine in SCH and OHT groups are due to changes in renal excretion and not the muscle involvement.

Pearson's correlation studies reveal that TSH levels were well correlated with serum creatinine in the OHT group only. No correlation was found with ET and SCH groups. Similarly, a significant negative correlation between TSH and eGFR was found only in OHT group. We found a very strong positive correlation between eGFR calculated by MDRD and eGFR by CKD-EPI equations in all the subjects. Linear regression analysis in GLM model showed that the linear regression in creatinine based on the TSH values is attributable to the extent of 44.7% among the OHT group. Some authors have called SCH as mild thyroid failure since the thyroid gland is being stimulated by excess TSH to compensate for maintaining the normal thyroid hormone levels. Furthermore, elevated TSH levels could be a compensatory mechanism to prevent excessive catabolism. It is not associated with increased mortality in elderly patients. [20,21] It can be difficult in an individual patient to distinguish a ET subject from one with either mild or overt thyroid disease clinically since all of them have similar constellations of symptoms. Furthermore, when the laboratory reports show a TSH value <10 □IU/L with a normal FT3 and FT4, it is difficult to assess the requirement for treating such patients. There are some studies which have demonstrated evidence of specific neurobehavioral and neuromuscular dysfunction in SCH.

Conclusion

This study concluded that there is tissue hypothyroidism as manifested by the difference in the creatinine levels and eGFR values in such patients compared to the healthy controls. eGFR calculation by both the formulae has good correlation in the study groups. Hence, either of them can be used for measuring GFR. Furthermore, the linear regression analysis concludes that the TSH values may be used to predict the lower kidney function (higher creatinine values) among the SCH group.

References

1. El-Zawawy HT, El-Aghoury AA, Azzam EZ, Deghady AA, Abdellatif MA. Osteopontin as a marker in thyroid disease: relation to body mass index. Endocrine and Metabolic Science. 2020 Jul 1;1(1-2):100049.
2. Emmanouel DS, Lindheimer MD, Katz AI. Mechanism of impaired water excretion in the hypothyroid rat. The Journal of clinical investigation. 1974 Oct 1;54(4):926-34.
3. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocrine reviews. 2008 Feb 1;29(1):76-131.
4. Jia F, Tian J, Deng F, Yang G, Long M, Cheng W, Wang B, Wu J, Liu D. Subclinical hypothyroidism and the associations with macrovascular complications and chronic kidney disease in patients with Type 2 diabetes. Diabetic Medicine. 2015 Aug;32(8): 1097-103.
5. Bensenor IM, Olmos RD, Lotufo PA. Hypothyroidism in the elderly: Diagnosis and management. Clin Interv Aging 2012;7:97.
6. Kimmel M, Braun N, Alscher MD. Influence of thyroid function on different kidney function tests. Kidney and Blood Pressure Research. 2012 Aug 18;35(1):9-17.
7. Saini V, Yadav A, Arora MK, Arora S, Singh R, Bhattacharjee J. Correlation of creatinine with TSH levels in overt hypothyroidism — A requirement for monitoring of renal function in hypothyroid patients? Clin Biochem. 2012;45 (3):212–4.

8. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. Indian J Endocrinol Metab. 2012;16:204.
9. Claus T, Elitok S, Schmitt R, Luft FC, Kettritz R. Thyroid function and glomerular filtration—a potential for Grave errors. Nephrol Dial Transplantat. 2005;20(5):1002–3.
10. Iglesias P, Bajo MA, Selgas R, D´ıez JJ. Thyroid dysfunction and kidney disease: An update. Rev Endocr Metab Disord. 2017;18: 131– 44.
11. Mariani LH, Berns JS. The Renal Manifestations of Thyroid Disease. J Am Soc Nephrol. 2012;23(1):22–6.
12. Mariani LH, Berns JS. The renal manifesta tions of thyroid disease. J Am Soc Nephrol. 20 12;23:22-6.
13. Deshmukh V, Behl A, Iyer V, Joshi H, Dholye JP, Varthakavi PK, et al. Prevalence, clinical and biochemical profile of subclinical hypothyroidism in normal population in Mumbai. Indian J Endocrinol Metab. 2013;17: 454-59.
14. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clinical chemistry. 2007 Apr 1;53(4):766-72.
15. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009 May 5;150 (9):604-12.
16. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. Jama. 2004 Jan 14;291(2):228-38.
17. Deshmukh V, Behl A, Iyer V, Joshi H, Dholye JP, Varthakavi PK. Prevalence, clinical and biochemical profile of subclinical hypothyroidism in normal population in Mumbai. Indian journal of endocrinology and metabolism. 2013 May;17(3):454.
18. Wilkins L, Fleischmann W. Effects of thyroid on creatine metabolism with a discussion of the mechanism of storage and excretion of creatine bodies. The Journal of clinical investigation. 1946 May 1;25(3):360-77.
19. Schmitt R, Klussmann E, Kahl T, Ellison DH, Bachmann S. Renal expression of sodium transporters and aquaporin-2 in hypothyroid rats. American Journal of Physiology-Renal Physiology. 2003 May 1;284(5):F1097-104.
20. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. The journal of clinical endocrinology & metabolism. 2001 Oct 1;86 (10):4585-90.
21. Lu Y, Guo H, Liu D, Zhao Z. Preservation of renal function by thyroid hormone replacement in elderly persons with subclinical hypothyroidism. Archives of Medical Science. 2016 Aug 1;12(4):772-7.