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Evaluation of renal function in subclinical hypothyroidism

Vijayetha P. Patil, Alagilwada S. Shilpasree, Vidya S. Patil, Kangokar R. Pravinchandra[1], Deepti G. Ingleshwar, Axita C. Vani

Abstract:

INTRODUCTION: Patients with subclinical hypothyroidism (SCH) have a few or no symptoms or signs of thyroid dysfunction and thus by its very nature, SCH is a laboratory diagnosis. Serum creatinine is elevated and glomerular filtration rate (GFR) values are reversibly reduced in overt hypothyroid patients. We hypothesize that SCH also may be associated with low GFR.

AIMS AND OBJECTIVES: The objective of this study was (1) to know the effect of SCH on kidney function, (2) to find the correlation between the renal function parameter creatinine, estimated GFR (eGFR), and thyroid-stimulating hormone (TSH), and (3) to know if creatinine values can be predicted by TSH values in SCH cases.

MATERIALS AND METHODS: This is a hospital-based cross-sectional study for 1 year. A total of 608 subjects of either sex were included in the study and were divided into 3 groups: (1) SCH, (2) overt hypothyroidism (OHT), and (3) euthyroidism (ET). TSH, free triiodothyronine, free thyroxine, and serum creatinine were estimated and eGFR was calculated using modification of diet in renal disease study equation and the chronic kidney disease epidemiology collaboration equations.

RESULTS: Serum creatinine levels were higher and eGFR was lower significantly in the subclinical hypothyroid group when compared to the control ET group ($P < 0.001$). The overtly hypothyroid group had significantly higher levels of serum creatinine and lower eGFR when compared to both the groups ($P < 0.001$). Significant correlation between TSH, creatinine, and eGFR was found in OHT group only. Linear regression analysis showed the regression in creatinine upon TSH is attributable to 44.5% among OHT group, 48.2% in SCH group.

CONCLUSION: It can be concluded that the SCH group behaves biochemically similar to OHT group and changes in serum creatinine reflect tissue hypothyroidism in SCH cases.

Key words:

Creatinine, estimated glomerular filtration rate, renal dysfunction, subclinical hypothyroidism, thyroid-stimulating hormone, tissue hypothyroidism

Introduction

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%.[1] Various epidemiological studies in India shows a prevalence rate of SCH varying between 9% and 11.4%.[2] The progression to overt hypothyroidism (OHT) is approximately 2%–5%/year. Due to its asymptomatic nature, the SCH cases are not detected clinically[2] and also its relation to the kidney function is not well established. There is paucity of data in Indian population. Patients with SCH report more symptoms than ET individuals, but fewer symptoms than overtly hypothyroid participants.[1] There is controversy in management of patients with a serum TSH level <10 μIU/L. There

Departments of Biochemistry and [1]Community Medicine, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India

Address for correspondence:
Dr. Vijayetha P. Patil, Department of Biochemistry, SDM College of Medical Sciences and Hospital, Sattur, Dharwad, Karnataka, India.
E-mail: drvijayetha@gmail.com

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is inadequate literature in this area and statements may often be an expert panel opinion rather than strictly evidence based.

There is a well-known interaction between thyroid and kidney functions. Thyroid hormones are involved in the growth, development, and physiology of the kidney.[3] Hypothyroid state is associated with significant derangement in biochemical parameters of renal function.[4,5] Serum creatinine is elevated and glomerular filtration rate (GFR) values are reversibly reduced in overt hypothyroid patients than in ET subjects.[3,6-9] We hypothesize that SCH also may be associated with low GFR. Renal dysfunction can be actually emphasized as the reflection of tissue hypothyroidism. There is insufficient or no evidence to support an association between SCH and its systemic effects.[1] The basis for treatment in SCH is not clear yet. This investigation would help us to find out whether SCH manifests on the organ function, i.e., renal function. If so, it would help in planning the treatment for SCH.

Hence, this study was taken up to evaluate the renal function by estimating serum creatinine and estimated GFR (eGFR) in SCH patients with the following objectives:

- To know the effect of SCH on kidney function
- To find the correlation between the renal function parameter creatinine, eGFR, and TSH
- To know if creatinine values can be predicted by TSH values in SCH cases.

Materials and Methods

It is a retrospective cross-sectional study. All the cases detected with SCH for 1 year were taken for the study. The data were collected from patients coming to SDM hospital for consultation in outpatient department (OPD) and from medical records. From all the patients who had undergone blood tests for creatinine and thyroid function testing between January 2015 and January2016, one set of results was collected.

Inclusion criteria

The study includes all the subjects in the age group of 18–70 years of either sex attending the OPD in SDM hospital, Dharwad. 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 and
- Group 3: Euthyroid (ET): Subjects having TSH, FT3, and FT4 all within the normal reference range.

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.

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 μIU/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.[10,11]

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

GFR (mL/min/1.73 m^2) =175× $(S_{cr})^{-1.154}$× $(Age)^{-0.203}$× (0.742 if female) × (1.212 if African American) [Table 1].

The chronic kidney disease epidemiology collaboration (CKD-EPI)equation for estimating glomerular filtration rate is given in Table 1.

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). Licensed officially to SDM College of Medical Sciences, Dharwad - 580 009, India, by IBM-SPSS Corporation, Bengaluru.

Ethical clearance has been obtained from the Institutional Ethical Clearance Committee, SDM College of Medical Sciences and Hospital, Dharwad. 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.

Results

A total of 608 subjects were included in the study. Table 2 shows the results of one-way ANOVA for comparison of means of investigation reports between overall groups under study. 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 as shown in Table 2. Similar findings were also seen in *post hoc* test. Table 3 shows 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 ($r = 0.54$, $P < 0.001$) in the OHT group only. No correlation was found with ET and SCH groups ($r = 0.034$, $r = 0.06$, respectively). Similarly, a significant negative correlation between TSH and eGFR was found only in OHT group. The results are summarized in Table 4.

We found a very strong positive correlation between eGFR calculated by MDRD and eGFR by CKD-EPI equations in all the subjects ($r = 0.96$, $P < 0.001$) as shown in Figure 1. Correlation of the same in different groups is shown in Table 5.

Table 1: The following is the chronic kidney disease epidemiology collaboration equation for estimating glomerular filtration rate for white and other races

Sex	Serum creatinine (mg/dl)	CKD-EPI equation
Female	<0.7	$GFR=144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>0.7	$GFR=144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	<0.9	$GFR=141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>0.9	$GFR=141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

GFR = Glomerular filtration rate, CKD-EPI = Chronic kidney disease epidemiology collaboration

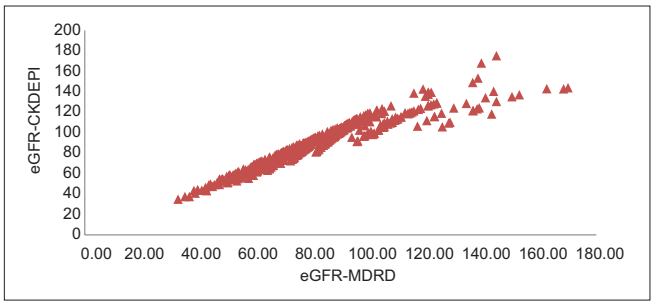

Figure 1: Correlation between estimated glomerular filtration rate - modification of diet in renal disease and estimated glomerular filtration rate - chronic kidney disease epidemiology collaboration in all three groups. $R = 0.96$, $P < 0.001$ highly significant

Table 2: Comparison of the various parameters among the three groups by ANOVA

Parameter	SCH		OHT		ET		*P*
	Females	Males	Females	Males	Females	Males	
n	160	97	60	31	160	100	
Age (years)	46±12.39	54±13.32	45±11.99	40±14.37	46±14.27	48±14.66	
FT3 (pg/ml)	2.87±0.40	3.07±0.38	1.86±0.81	1.57±0.84	2.99±0.38	3.22±0.39	<0.001*
FT4 (ng/dl)	1.23±0.17	1.28±0.22	0.54±0.24	0.44±0.26	1.33±0.22	1.34±0.20	<0.001*
TSH (μIU/ml)	8.22±2.94	8.35±3.35	79±56.41	97.08±54.34	2.50±1.15	2.52±1.10	<0.001*
Creatinine (mg/dl)	0.83±0.16	1.07±0.20	0.98±0.26	1.21±0.26	0.78±0.14	0.96±0.14	<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*

**P*<0.001 - highly significant, Same findings by *post hoc* tests. ET = Euthyroid, OHT = Overt hypothyroid, SCH = Subclinical hypothyroid, FT3 = Free triiodothyronine, FT4 = Free thyroxine, eGFR = Estimated glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic kidney disease epidemiology collaboration, TSH = Thyroid stimulating hormone

Table 3: Median values of creatinine observed at the mean values of thyroid-stimulating hormone compared across the groups

Group	*n*	Mean			Creatinine (mg/dl), median	
		Age (years)	TSH (μIU/ml)	Creatinine (mg/dl)	Males	Females
OHT	91	43.71	88.84	1.058	1.00	1.00
SCH	257	49.24	8.26	0.918	0.90	0.90
ET controls	260	47.24	2.51	0.856	0.70	0.70

TSH = Thyroid-stimulating hormone, ET = Euthyroid, OHT = Overt hypothyroid, SCH = Subclinical hypothyroid

Table 4: 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	0.04	0.5	−0.003	0.9	−0.03	0.6
Male	0.09	0.3	−0.05	0.5	−0.07	0.5
OHT						
Female	0.56	<0.05*	−0.54	<0.001**	−0.56	<0.001**
Male	0.39	<0.05*	−0.34	0.05	−0.33	0.06
ET						
Female	0.01	0.8	−0.11	0.15	−0.09	0.2
Male	0.09	0.3	−0.09	0.31	0.05	0.5

*P<0.05 - significant, **P<0.001 - highly significant. TSH = Thyroid-stimulating hormone, ET = Euthyroid, OHT = Overt hypothyroid, SCH = Subclinical hypothyroid, eGFR = Estimated glomerular filtration rate, MDRD = Modification of diet in renal disease, CKD-EPI = Chronic kidney disease epidemiology collaboration

Table 5: 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	0.95	<0.001*	0.98	<0.001*
SCH	0.97	<0.001*	0.99	<0.001*
ET controls	0.94	<0.001*	0.92	<0.001*

*Highly significant. ET = Euthyroid, OHT = Overt hypothyroid, SCH = Subclinical hypothyroid

Table 6: Regression analysis by general linear model

Group	R^2	Adjusted R^2	Residual error
OHT	0.801	0.445	0.043
SCH	0.927	0.482	0.024
ET controls	0.779	0.231	0.022

ET = Euthyroid, OHT = Overt hypothyroid, SCH = Subclinical hypothyroid

Linear regression analysis in GLM model [Table 6] shows that the linear regression in creatinine based on the TSH values is attributable to the extent of 44.5% among the OHT group (adjusted R^2 = 0.445 with residual error of 0.043). However, the model fits best in the SCH group where 48.2% can be attributed (adjusted R^2 = 0.482 with residual error 0.024) indicates a regression model comparable to the OHT group if not better. This compares better in the OHT group than in the control ET group where adjusted R^2 = 0.23 only. The residual error of 0.024 which is half of the error in OHT group, 0.043 also indicates a better model fit.

The regression coefficients have been shown in Table 7 in respect of OHT and SCH groups only since the control ET group has very low adjusted R^2. Gender offers a significant covariate contribution in the model of OHT group. Hence, its effect has been eliminated by calculating the regression coefficient separately for the genders. Similarly, the same gender-wise segregation has been done in the SCH group for calculating the regression coefficient to fit into the model. The same is proved in the residual P-P plots shown in Figure 2.

Discussion

In this cross-sectional study, we observed that though the serum creatinine levels were within the normal reference range, it was higher and eGFR was lower significantly in the SCH group when compared to the control group.[3,12]The overtly hypothyroid group had much higher levels of serum creatinine and lower eGFR when compared to both the groups. This is in accordance with other studies.[3,12,13] It is seen that the creatinine values show a definite trend of increase from the ET cases to the SCHs and finally to the OHT cases as seen in Table 3.

The cause for this difference in the serum creatinine and eGFR in the SCH group and OHT could be due to reduced renal blood flow[12] and tubular function as a result of tissue hypothyroidism. The differences in SCH group and OHT group could explain the severity of the disease. Thyroid hormones influences cardiac output, and hence, in hypothyroid state, there is decreased cardiac output and increased peripheral resistance resulting in an overall decrease in systemic blood volume, thereby decreasing renal blood flow, which can decrease the eGFR. Studies have shown an improvement in eGFR with thyroid replacement therapy indicating that renal dysfunction is predominantly caused by functional changes rather than by permanent histological damage.[3,14-16]

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.[17]

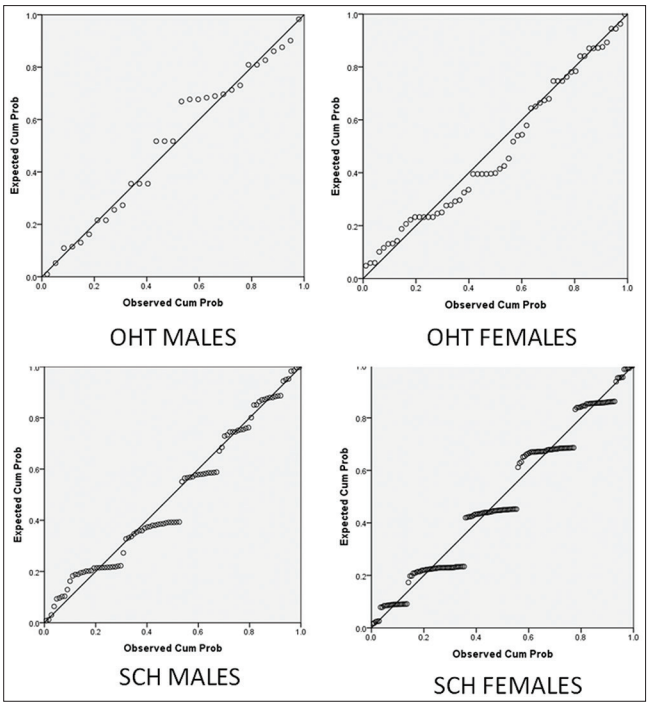

Figure 2: Residual P-P plot for overt hypothyroid and subclinical hypothyroid groups. (dependent variable is creatinine for variable thyroid-stimulating hormone)

Table 7: Beta-coefficients that evaluated association between creatinine as dependent variable and thyroid-stimulating hormone in overt hypothyroid and subclinical hypothyroid groups

	n	Constant	Beta coefficient	*R*	Adjusted R^2	Significance
OHT						
Males	31	1.011	0.002	0.393	0.125	<0.05*
Females	60	0.777	0.003	0.557	0.298	<0.001**
SCH						
Males	97	1.023	0.006	0.094	−0.002	NS
Females	160	0.807	0.002	0.043	−0.005	NS

*Significant, **Highly significant. NS = Not significant, OHT = Overt hypothyroid, SCH = Subclinical hypothyroid

Pharmacologically induced hypothyroidism in rats resulted in a marked reduction in kidney size and creatinine clearance, thus decreasing GFR.[18] 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.

We have used calculated eGFR using creatinine-based equation for assessing the changes in renal function. There are many studies that have performed clearance studies using ^{51}Cr-ethylenediaminetetraacetic acid clearance, ^{131}I-hippuran clearance for measuring GFR and have reported that changes in levels of serum creatinine in patients with thyroid disorders do reflect actual changes in GFR.[10]

We have used both MDRD study equation and CKD-EPI equations which are the most widely used IDMS traceable equations for estimating GFR in patients aged 18 and over. Data from various studies showed that the CKD-EPI creatinine equation is more accurate than the MDRD study equation across a wide variety of populations and clinical conditions.[19] We have got a very strong significant positive correlation between eGFR calculated by MDRD and eGFR calculated by CKD-EPI equations [Table 5 and Figure 1]. Hence, either of the equations could be used for estimating eGFR in these groups.

Linear regression analysis using GLM model is shown in Table 6, which shows there is high-adjusted R^2 and low residual error in SCH group, where genders are segregated in comparison to OHT group. The positive correlations in the OHT group are found compelling one to work out the regression coefficients of the creatinine values upon the TSH values. It is observed that the TSH values considered gender-wise yield much better regression with the creatinine values in the SCH group than in the control ET group and comparable to the regression values in the OHT group. Hence, regression coefficients have been shown in the Table 7 for OHT and SCH groups but not control ET group. The residual P-P plots shown in Figure 2 demonstrate that the GLM model shows a good fate in respect of the OHT group as well as the SCH group. It can be concluded from these observations that the SCH groups behave biochemically similar to 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.[15,16] 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 μIU/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. A recent study involving subjects from a Chinese population found a higher TSH level in patients with metabolic syndrome compared to that in the nonmetabolic syndrome group suggesting that SCH may be a risk factor for metabolic syndrome.[20] Some authors have found SCH to be an independent and equivalently important risk factor for myocardial infarctions, at least in subjects having TSH values >10 μIU/L.[15,21] According

to Tsuda *et al*., SCH is associated with CKD and also TSH is an independent factor for determining renal function in ET individuals.[22]

Conclusion

In this cross-sectional study, we have evaluated one more objective parameter to assess the impact of SCH on the renal system by estimating serum creatinine values and eGFR. This study clearly shows 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. This is an important conclusion of this paper that there is probably scope for reversing the decline in renal function among the SCH group. The large samples in this study which shows a definite linear trend of creatinine as a dependent variable on the TSH values is a significant observation. SCH is a common disorder that frequently progresses to OHT. Given the high prevalence of SCH, treatment with thyroid hormone replacement needs to be addressed in an appropriately powered randomized controlled trial. As of now based on the findings of this study, patients with SCH need to be monitored and treated individually based on the symptoms and laboratory investigations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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