Original Article

Evaluation of biochemical markers of kidney function in patients with subclinical hypothyroidism in comparison with euthyroid people

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Abstract

Background: Subclinical hypothyroidism (SCH) as a compensated or preclinical type of primary and overt hypothyroidism (OHT) can affect approximately 4–10% of the general population. Treating SCH can slowdown the progression to OHT, the formation of cardiovascular diseases, neuropsychiatric symptoms, and other miscellaneous problems. **Materials and Methods:** The present study is a case-control study that was conducted on 239 adults who were referred to 501 Imam Reza Hospital from March 2019 up to September 2019. Of the 239 patients and their families admitted to the hospital, 121 (50.6%) were euthyroid (as control group) and the remaining participants (118, 49.4%) were SCH (as case group). The serum levels of thyroid stimulating hormone (TSH), urea, uric acid, creatinine, T3, and T4 were asked to be determined at a single laboratory. Biochemical markers of kidney function and the level of thyroid hormones were compared between the two groups of euthyroid and SCH. **Results:** TSH was significantly higher in SCH (7.25 (4.4-18.15)) compared to euthyroid (1.4 (0.2-3.7)) patients ($P < 0.001$). Among biochemical markers, creatinine ($P < 0.001$) and uric acid ($P = 0.006$) had higher serum levels in the case group. There was no remarkable difference in the thyroxine hormone levels and urea between the euthyroid and SCH patients ($P > 0.05$). Within the SCH group, there was a significant positive correlation between TSH and the level of creatinine ($P = 0.001$, r = 0.302). **Conclusion:** Regular monitoring of the major function of the kidneys in patients with hypothyroidism and SCH can help early diagnosis of kidney dysfunction, thus increasing the chance of restoring normal kidney function.

Keywords: Creatinine, kidney function, subclinical hypothyroidism, urea

Introduction

Biochemical diagnosis of subclinical hypothyroidism (SCH) is crucial since its signs and symptoms are not typical.[1] Typically, SCH as a compensated or preclinical type of primary and overt hypothyroidism (OHT) is categorized with thyroid-stimulating hormone (TSH) level exceeding 4.0 IU/mL in the presence of a normal range of free prohormone thyroxine concentrations, without administering drugs for thyroid disease. It has been shown that SCH can affect approximately 4–10% of the general population. Based on some studies, the prevalence of SCH is more common among women.[2,3] Treating SCH can slowdown the progression to OHT, the formation of cardiovascular diseases, neuropsychiatric symptoms, and other miscellaneous problems. The SCH to OHT progression can be seen in patients with an annual rate of 2–6% within 5–6 years and this can occur based on an initial elevated level of TSH over 10 mIU/L, increased levels of thyroid peroxidase antibodies, and being female sex.[4-6] With regards to the bidirectional interplay of the

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thyroid and renal system, thyroid function below the normal level can confluence renal development and its physiology. Besides, the various kinds of kidney failures negatively affect thyroid activity.[7] There is a direct association between hypothyroidism and the impairment of biochemical markers of kidney function compared to euthyroid people. Increasing levels of urea, uric acid, and creatinine and decreasing level of estimated glomerular filtration rate (eGFR) values are seen in OHT patients.[8] Hitherto, different studies have been related to the association between biochemical markers of kidney function with OHT. However, there is the paucity of data regarding the clinical impacts of SCH on different biochemical markers of kidney in the Iranian adult population. Not much data is available on the impact of SCH on kidney function tests in this region. Therefore, this study is performed to assess the available evidence on the association of SCH with biochemical markers of kidney function compared to euthyroid people and relatively healthy adults.

Materials and Methods

1. Study design

The present study was performed on 239 adults who were referred to 501 Imam Reza Hospital from March 2019 up to September 2020 and divided into two groups—case group (118 adults with SCH) and control group (121 healthy adults). This study was performed under the satisfaction of the research ethics committee of the AJA University of Medical Sciences (JANUARY 2019). For patients referred to our clinics, based on hypothyroidism signs and symptoms and the physician's suspicion for thyroid disorders, the TSH test was performed. Upon recording higher than normal levels of TSH by age, hormonal tests of triiodothyronine (T3) and thyroxine (T4) were requested to be performed on patients. The SCH was diagnosed by an endocrinologist and the test results were interpreted based on the increased levels of TSH, age, race, and normal ranges of T3 and T4. TSH level exceeding 4.0 IU/mL in the presence of a normal range of free prohormone thyroxine concentrations without administering drugs for thyroid disease was labeled as SCH. During history recording, patients treated with steroids, levothyroxine, and drugs that affect kidney functions were excluded from the study. Having proven hypertension, gout, pregnancy, consumption of protein-rich diet, renal disorders, liver disorders, diabetes mellitus, cardiovascular disorders and patients with malignancy or those undergone chemotherapy or radiotherapy were excluded from the rest of our study. In this study, euthyroid patients from the gastroenterology clinic were selected randomly after fulfilling the inclusion criteria. The case and control were adjusted by age, gender, demographic, and baseline features. The consent forms were collected from accepted participants, taking into account the inclusion and exclusion criteria. None of the included participants had known disorders regarding thyroid, hepatic, kidney, oncological, or gastrointestinal function. Anthropometric calculations and brief clinical history were taken by an endocrinologist. Individual physical examinations included body mass index (BMI) (calculated by BW/BH^2 (kg/m^2)), body weight (BW), body height (BH), blood pressure (BP), and waist circumference (WC) were recorded in their forms. Further laboratory tests by means of an auto-analyzer (Hitachi Model 7170 analyzer, Tokyo, Japan) were performed enzymatically that include: fasting glucose (FG), serum uric acid (SUA), blood urea nitrogen (BUN), creatinine (Cr), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). The serum levels of creatinine in the blood, uric acid, urea, TSH, T3, and T4 were determined after eight hours of fasting at the Hospital Lab of Imam Raza. The process of measuring serum levels of TSH, T3, and T4 was performed after receiving 3 mL of a venous blood sample using an enzyme-linked immunosorbent assay (ELISA) reader. Afterward, biochemical methods were used to measure creatinine and uric acid serum levels by an auto-analyzer in a single laboratory.

2.Statistical analysis

Normal and non-normal continuous data were described by mean ± SD, interquartile (IQR), and median (min-max), respectively, and the frequency (percent) of categorical data reported as descriptive statistics. The normality assumption of data was assessed by the Kolmogorov–Smirnov test. In the following, a comprehensive comparison was carried out among the two major study groups by means of independent t-test for normal and Mann–Whitney U test as an alternative nonparametric test applied for abnormal data. The process of evaluation of categorical variables among euthyroid and SCH patients was carried out using the Chi-square test. Correlation tests of Pearson or Spearman's were conducted to evaluate the association among different variables, as appropriate. Whisker and Box charts were outlined to show the distribution of kidney function tests and biochemical markers of kidney function between groups. Finally, Receiver Operating Characteristic (ROC) curve was analyzed to evaluate the biochemical markers of kidney function predictability to classify the SCH from euthyroid patients and to assess the cut-off point values of biochemical markers of kidney function. Sensitivity, specificity, and cut-off points of biochemical markers of kidney function for classifying subjects as SCH were calculated in this analysis. The statistical significance threshold was set at $P < 0.05$. In the present study, the process of data analysis was carried out using the IBM SPSS software version 23.0 (IBM Co., Armonk, NY, USA).

Results

Of the 239 patients and their families admitted to the hospital, 121 (50.6%) were euthyroid (as control group) and the remaining participants (118, 49.4%) were SCH (as case group). The mean age of study participants in both the groups was 50.05 ± 16.40 and 49.86 ± 16.04, respectively. The case and control groups included 51.7% and 50.4% women, respectively. The distribution of base characteristics, anthropometric, and lipid profiles were compared between the two study groups. However, it did not show any significant differences between the euthyroid and SCH groups [Table 1].

Biochemical markers of kidney function and thyroid hormone levels were assessed in both the control and case groups. As indicated in Table 2, the TSH level was significantly higher in SCH (7.25 (4.4–18.15)) compared to the euthyroid (1.4 (0.2–3.7)) patients ($P < 0.001$). Among biochemical markers, uric acid ($P = 0.006$) and creatinine ($P < 0.001$) had significantly higher serum levels in the case group. The values of the thyroxine hormone and urea did not significantly differ between euthyroid ($P = 0.08$) and SCH ($P = 0.07$) patients.

Correlation coefficients (r) between biochemical markers of kidney function and thyroid hormone levels were also calculated separately in euthyroid and SCH patients to find out the existence of any association with them [Table 3]. In euthyroid patients, no significant correlation was found between T3, T4, and TSH levels with any of the kidney function parameters ($P > 0.05$) but a considerable positive correlation was observed among the creatinine level and TSH level in the SCH group (r = 0.302, $P = 0.001$).

Whisker and Box charts were also plotted to compare the differences in thyroid hormone levels and markers of renal function between the control and case groups [Figure 1].

The whiskers present the maximum and minimum values; the boxes possess 50% of values between the percentiles of 25th and 75th; the horizontal line inside the boxes indicates the median. If the data set includes outliers or extreme values, they are plotted separately as points or stars on the chart.

Table 1: Base characteristics between euthyroid and SCH groups

Variables	Total	Euthyroid	SCH	*P*
Age (year)	49.95±16.19	50.05±16.40	49.86±16.04	0.93
Sex				0.84
Male	117 (49.0)	60 (49.6)	57 (48.3)	
Female	122 (51.0)	61 (50.4)	61 (51.7)	
Education				0.45
Primary	123 (51.5)	65 (53.7)	58 (49.2)	
High school	86 (36.0)	44 (36.4)	42 (35.6)	
University	30 (12.5)	12 (9.9)	18 (15.3)	
Marital status				0.96
Single/widow	55 (23.0)	28 (23.1)	27 (22.9)	
Married	184 (77.0)	93 (76.9)	91 (77.1)	
Smoking				0.33
No	202 (84.5)	105 (86.8)	97 (82.2)	
Yes	37 (15.5)	16 (13.2)	21 (17.8)	
Familial CVD				0.79
No	206 (86.2)	105 (86.8)	101 (85.6)	
Yes	33 (13.8)	16 (13.2)	17 (14.4)	
BMI (kg/m^2)	27.61±4.76	27.82±5.35	27.17±4.09	0.48
Waist (cm)	94.60±12.29	94.37±13.35	94.83±11.13	0.77
SBP (mmHg)	116.03±17.74	116.42±16.94	115.63±18.60	0.73
DBP (mmHg)	76.49±9.85	77.05±10.43	75.92±9.22	0.38
CHOL (mg/dL)	189.34±39.23	185.87±37.90	192.90±40.40	0.17
TG (mg/dL)	124 (28-390)	122 (28-291)	127 (50-390)	0.19
HDL (mg/dL)	47.31±12.11	48.16±13.11	46.44±10.98	0.27
LDL (mg/dL)	114.46±32.88	111.65±30.43	117.35±35.11	0.18

Data presented as Mean±SD for normal or median (min-max) for abnormal continuous variables and frequency (percent) for categorical data.

Table 2: The comparison of biochemical markers of kidney function and thyroid hormone levels between euthyroid and SCH groups

Variables	Total	Euthyroid	SCH	*P*
T3 (ng/dl)	102.76±30.68	107.79±38.51	97.60±18.46	0.01
T4 (µg/dL)	7.4 (3.9-18.15)	7.5 (3.9-17.9)	7.25 (4.4-18.15)	0.08
TSH (mIU/L)	2.7 (0.2-9.7)	1.4 (0.2-3.7)	5.4 (2.3-9.7)	<0.001
Urea (mg/dl)	16.41±4.75	15.88±4.78	16.96±4.67	0.07
Creatinine (mg/dl)	1.11 (0.4-1.75)	0.98 (0.4-1.7)	1.20 (0.6-1.75)	<0.001
Uric acid (mg/dl)	4.85±1.40	4.60±1.63	5.10±1.40	0.006

Data are shown as Mean±SD for normal or median (min-max) for abnormal continuous variables. T3='Triiodothyronine, T4='Thyroxine, TSH='Thyroid Stimulating Hormone.

ROC-curve analysis of kidney function tests

ROC analyses were performed to evaluate the thyroid hormones predictability to determine the patient's groups (SCH versus euthyroid) and to assess the cut-off point value of thyroid hormone [Figure 2]. The area under curve was equal to 0.48 (95% CI: 0.41–0.57) for T3, 0.44 (95% CI: 0.36–0.51) for T4, and 0.93 for TSH (95% CI: 0.90–0.97). There was significant predictability of TSH for recognizing SCH patients from the euthyroid group.

The best cut-off point, sensitivity, and specificity of TSH to classify subjects as SCH were 2.7, 90%, and 88%, respectively. The cut-off value of 2.7 indicated that a patient is SCH (with a probability of 90%) if TSH is greater than or equal 2.7 and euthyroidism (with a probability of 88%) if TSH is less than 2.70.

ROC analyses results for evaluating the biochemical factors predictability to determine the patient's groups and to assess optimal cut-off points were displayed in Figure 3. The area under curve equal to 0.56 for urea (95% CI: 0.49–0.64), 0.65 for creatinine (95% CI: 0.58–0.72,) and 0.59 for uric acid (95% CI: 0.51–0.66). There was significant predictability of creatinine and uric acid for recognizing SCH patients from the euthyroid group. The best cut-off point, sensitivity, and specificity of creatinine to classify subjects as SCH were 1.10, 67%, and 62%, respectively. The best cut-off point, sensitivity, and specificity of uric acid to differentiate patients were 4.70, 55%, and 52%, respectively.

Discussion

The main objective of the present study was to assess the effect of SCH on biochemical markers of kidney function and to compare it with euthyroid subjects and also to investigate the correlation of fT4, fT3, and TSH with the biochemical markers of kidney function such as urea, uric acid, and creatinine. As a mild thyroid failure, SCH is a widespread condition that often progresses to OHT. Concerning the high prevalence of the disorder, the outcomes of our study showed higher SCH prevalence rates in women, which is in agreement with the results of previous researches in China and other countries.[9] After a thorough search in PubMed, Medline, EMBASE, and Scopus databases to identify

Table 3: Correlation between the levels of biochemical markers and thyroid hormones of kidney function in clinically euthyroid patients and SCH groups

	Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)
A. Euthyroid			
T3 (ng/dl)	r=-0.058 (P=0.53)	r=-0.158 (P=0.08)	r=-0.066 (P=0.47)
T4 (µg/dL)	r=0.028 (P=0.76)	r=0.069 (P=0.45)	r=-0.044 (P=0.63)
TSH (mIU/L)	r=0.054 (P=0.56)	r=0.079 (P=0.39)	r=0.049 (P=0.59)
B. SCH			
T3 (ng/dl)	r=-0.059 (P=0.52)	r=-0.005 (P=0.96)	r=-0.048 (P=0.61)
T4 (µg/dL)	r=-0.070 (P=0.45)	r=0.008 (P=0.93)	r=0.020 (P=0.83)
TSH (mIU/L)	r=0.115 (P=0.21)	r=0.302 (P=0.001)	r=0.033 (P=0.72)

SCH=Subclinical Hypothyroid, T3=Triiodothyronine, T4=Thyroxine, TSH=Thyroid Stimulating Hormone

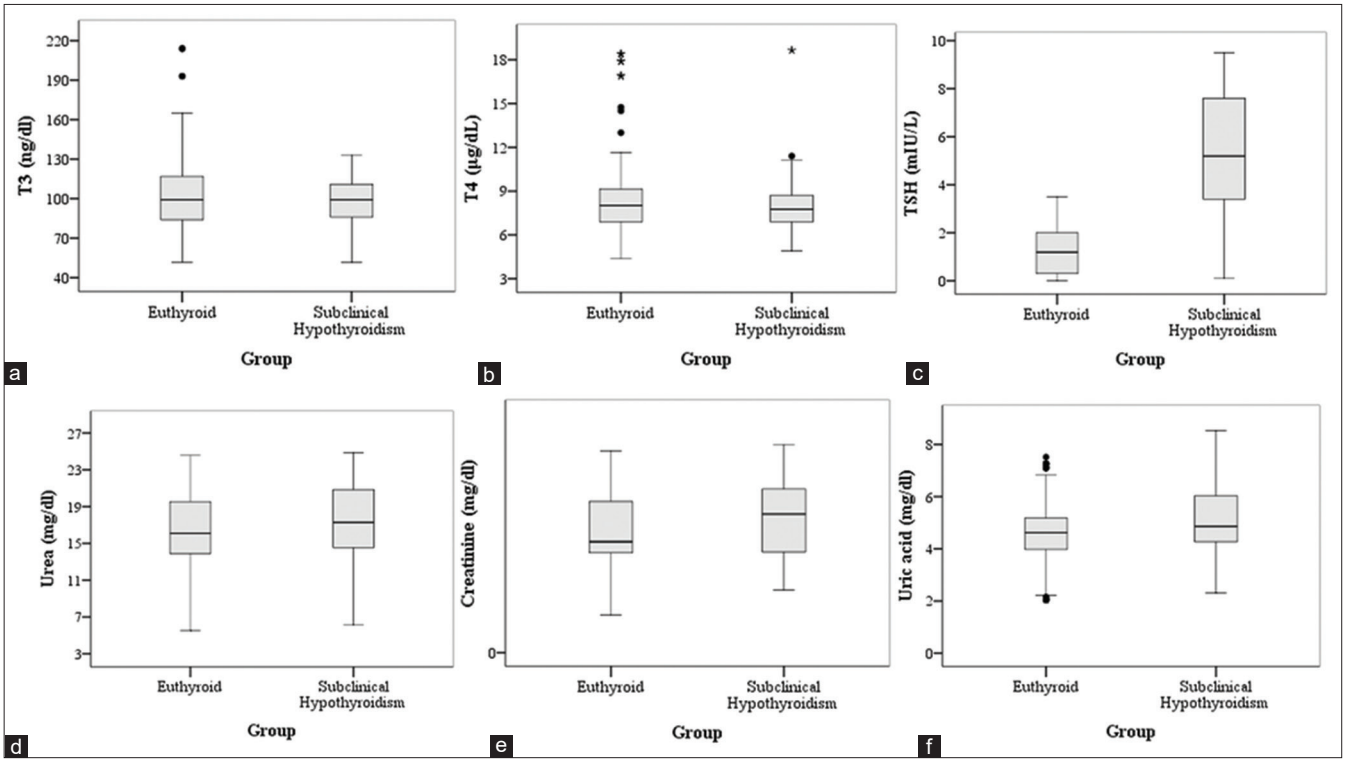

Figure 1: Box and Whisker charts to compare the distribution of a. T3, b. T4, c. TSH, d. Urea, e. Creatinine, and f. Uric acid level, between control and case groups

relevant published studies until February 2020, no relevant studies were found on this subject in Iranian adult patients, and the present study was the first step for the assessment of the possible association between biochemical markers of kidney function and SCH among the Iranian population. In this survey, no significant correlation was found between fT3, fT4 and TSH with the kidney function parameters among euthyroid patients ($P > 0.05$) but there was a significant positive correlation between creatinine level and TSH in the SCH group (r = 0.302, $P = 0.001$) as compared to the euthyroid subjects. The results of the present study demonstrated that in comparison with the control group, there were considerably higher serum levels of creatinine and uric acid in the case group ($P < 0.05$). The significant higher amount of creatinine in our study was on par with Tayal *et al.* study that include 89 patients in the OHT group and 98 patients in the SCH group, and 187 patients within the control group.[10] The increasing degree of hypothyroidism can be considered either as a major culprit in kidney disease or a factor that reflects the actual kidney function impairment. Besides, excretion function and hemodynamics of kidneys are changed, intrarenal vessels are contracted, the resistance of peripheral vessel is increased, and the total volume of blood is decreased; this results in a reduction in renal blood flow, changing secretion function, tubular resorption, and a reduction in eGFR which is reversible by thyroxine treatment.[7,11] Decreased GFR has been described as secondary to the generalized hypodynamic circulation in hypothyroid patients.[9,10] After a reduction in the level of GFR, the flow rate of renal plasma decreased and serum creatinine increased.[12] EGFR improvement with thyroid replacement therapy drives the fact that functional changes are a more important factor in kidney dysfunction than the permanent histological damage.[7,13] This finding is in line with previous studies that the creatinine level shows an obvious increase from

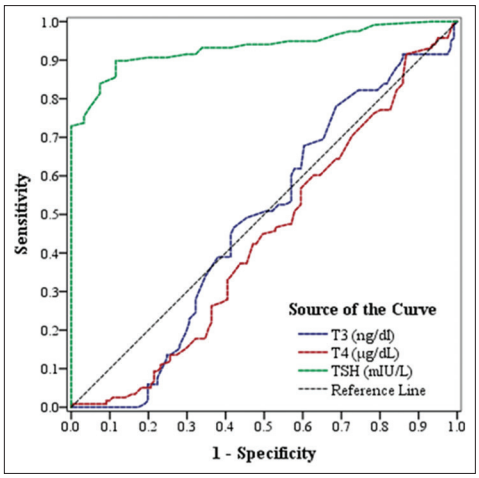

Figure 2: The ROC analysis for evaluating the thyroid hormones cut-off points to differentiate the SCH patients from euthyroid patients

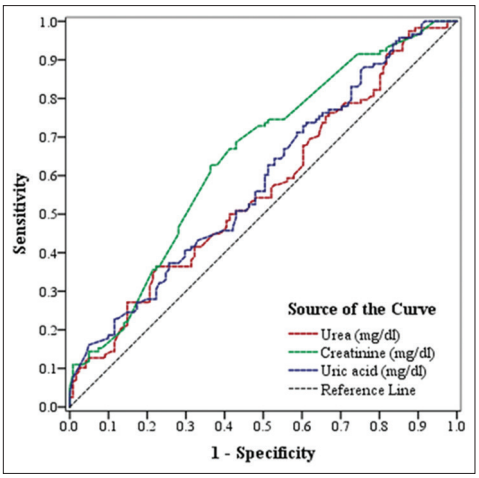

Figure 3: The ROC analysis for evaluating the biochemical factors cut-off points to differentiate the SCH patients from euthyroid patients

the euthyroid to the SCHs as seen in Table 2.[8,14-16] Similarly, the relationship between kidney function and SCH was evaluated by Kaur *et al.* between participants of age 20–70 years. They stated that SCH had a significant association with increased levels of serum creatinine ($P < 0.001$).[8] Similarly, we found a significant and positive correlation between TSH and the level of serum creatinine in our study ($P < 0.001$; R = +0.302); anyway, there was no significant correlation between the serum levels of urea and uric acid and TSH. On the contrary, Tayal *et al.* stated that there was a significant positive correlation between the serum level of creatinine in the OHT group and TSH, but could not find such a correlation in the SCH group.[10] Alternatively, regulating various metabolic pathways in the body is the mainstay of thyroid hormones function. Purine metabolism involves the de novo purine salvage pathway, purine biosynthetic pathway, and degradation can be affected by thyroid hormones. Alteration in these pathways can culminate in uric acid production and impair its degradation.[8,17] Additionally, hyperuricemia may occur secondary to renal plasma flow reduction and impaired GFR.[18] The incongruity of studies regarding significant differences in the level of serum uric acid between the control and case groups can be assigned to available differences among their dietary habits. The case and control groups in our study were not matched in the case of diet.[19] Kaur *et al.* did not report any considerable increases in the level of serum uric acid.[8] Moreover, in a study performed by Liang *et al.*, no significant increase was found in the serum uric acid of patients with SCH but they did not study the serum creatinine between participants.[20] Previous studies showed that the mean level of serum urea in the SCH group was not significantly higher in comparison with the subjects in the control group which was inconsistent with the studies done by ours. SCH as a mild thyroid failure can be a potential risk factor for metabolic syndrome. This notion has been corroborated by a previous study from Chinese researchers. Li M, *et al.* illustrate the correlation between serum thyrotropin and metabolic syndrome components. Given the higher levels of TSH in patients suffering from metabolic syndrome than in those with no metabolic syndrome, SCH can be regarded as a risk factor of metabolic syndrome.[21,22] The results of previous literature show varying conclusions regarding the association between TSH and dyslipidemia[23,24] Among evaluated parameters, lipid profiles were susceptible to get deteriorated from euthyroid cases to patients with SCH or OHT. Interestingly, subtler alterations were seen in the SCH groups compared to OHT cases. Among the studied parameters in this research, TG, LDL-cholesterol, and non-HDL-cholesterol had the most significant differences. However, the values of the aforementioned parameters were not significantly different between euthyroid and SCH patients ($P > 0.05$).[25]

From a clinical point of view, firstly, it is very important to consider the relationship between hypothyroidism and renal function and regular monitoring of renal function among hypothyroidism and SCH patients can help the early diagnosis of kidney dysfunction, thus increasing the chance of restoring normal kidney function. Secondly, it can indirectly emphasize the paramount importance of the SCH groups, and attempts should be made toward finding metabolic risks and reducing cardiovascular diseases (CVD) that are known to be the most critical leading causes of morbidity and mortality. Physicians should be trained in all respects, including its connection with kidney function. To recap, the process evaluation of thyroid function among patients suffering from biochemical abnormalities and deranged kidney function is highly suggested. This study is one of the most studies that evaluate the association of biochemical markers of renal diseases and SCH among the general Iranian population. A few limitations and inherent drawbacks should be mentioned in the current study. First, this study was a single-center and there was the possibility of bias in selection. Moreover, a relatively small sample size, especially for patients in the SCH group, which makes it hard to generalize our results. Thus, multicenter, prospective studies with a larger sample size are required to verify and understand the findings of the present study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in

the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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