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Subclinical and Clinical Hypothyroidism in Proteinuric Nephropathies: Amelioration of Proteinuria and Preservation of Renal Function by Thyroid Hormone Replacement Therapy

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ABSTRACT

Background: Emerging evidence shows a bi-directional talk between the kidney and thyroid; yet to date, sparse data exist as to the screening and treatment of hypothyroid states, whether Subclinical Hypothyroidism (SCH) or Clinical Hypothyroidism (CHT), in Chronic Kidney Disease (CKD) patients.

Objectives: The aim of the current study was to examine the association between thyroid hypofunction (whether subclinical or clinical) and proteinuric CKD (low eGFR and/or proteinuria), and to assess the impact of treating thyroid hypofunction on the progression of CKD.

Patients and methods: We conducted a prospective cohort study on 100 participants with baseline proteinuric CKD who were subcategorized according to their thyroid status into three groups: 20 euthyroid, 40 (SCH), 40 (CHT). All subjects were then followed up for 2 years after receiving Thyroid Hormone Replacement Therapy (THRT) according to their thyroid status.

Results: At baseline, we found a highly statistically significant association between SCH/CHT and low eGFR and proteinuria (P-value < 0.001 for both) in univariate and multivariate analyses. After THRT, we found a statistically significant reduction in CKD progression as evidenced by preservation of mean eGFR and decrease in proteinuria in both groups with SCH and CHT (P-value < 0.001 and 0.016 respectively) after the first 6 months of treatment that persisted over the remainder of 2-year follow-up period at a P-value <0.001.

Conclusion: The current study demonstrated a strong association between baseline proteinuric CKD and hypothyroid states and showed that THRT significantly halted CKD progression in hypothyroid patients who achieved euthyroid state.

Keywords: Chronic Kidney Disease (CKD)**,** Proteinuria, Subclinical Hypothyroidism (SCH), Thyroid Hormone Replacement Therapy (THRT).

INTRODUCTION

Growing evidence from epidemiological and experimental studies has consistently demonstrated the co-existence of CKD and hypothyroid states in an incremental and bi-directional pattern; yet, the mechanistic pathways linking the two disorder, to prove causality, are still evolving [(1-4)].

In CKD, low T3 levels are the most commonly reported thyroid abnormality and SCH is the most frequent thyroid disorder [(5)]. The uremic milieu in CKD can adversely affect thyroid functions due to altered thyroid hormone synthesis, metabolism, and regulation especially in proteinuric states via: decreased TSH release from hypothalamic-pituitary axis, increased thyroid hormone displacement, decreased T4 to T3 peripheral conversion, and increased thyroid-binding proteins' clearance [(5)].

Hypothyroid states, on the other hand, have been demonstrated in contemporary studies to adversely affect renal functions, the hunt study found that low thyroid function, even within the clinically low normal range, is associated with reduced GFR [(4)]. Hypothyroid-CKD interaction has been contributed to a variety of mechanisms including: preglomerular vasoconstriction, reduced renal perfusion and increased vascular resistance hence decreased GFR, decrease in renal sodium reabsorption, and volume depletion [(6-7)]. Furthermore, hypothyroidism has been shown to cause increased capillary permeability to proteins and cause edema which is reversed by THRT [(8)].

In animal models [(9-11)] using isotopic renal functions have shown decreased GFR mainly through hemodynamic changes. Furthermore, exogenous THRT in hypothyroid patients has been demonstrated to increase renal perfusion and improve creatinine clearance [(12-15)].

In addition, autoimmune conditions provide another common link where hypothyroidism has been reported with multiple glomerulopathies, chief among them is membranous nephropathy [(16)]**.**

The present study aimed at assessing the thyroid status in patients with proteinuric CKD and studying the impact of correction of the hypothyroid states on halting the progression of CKD.

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PATIENT AND METHODS

Between July 2018 and December 2020, a total of 322 patients from Benha University Hospital clinics were assessed for eligibility, patients were initially screened for CKD, increased urinary Albumin-Creatinine ratio (ACR) and thyroid functions including (TSH, Free T3, Free T4 levels). Among them, 100 patients were eligible for enrollment in the study. CKD was defined as per the 2012 KDIGO guidelines as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD was classified based on cause, GFR category, and albuminuria category (CGA) [17]. Subclinical hypothyroidism (SCH) was defined as an elevation in serum thyroid-stimulating hormone (TSH) concentration (normal range 5–10 μIU/mL) with a normal serum FT4 concentration, whereas clinical primary hypothyroidism was defined as thyroid-stimulating hormone (TSH) concentrations above the reference range and FT4 concentrations below the reference range [18].

The variables that were collected and followed up during the study included: age, sex, body height and weight, body mass index (BMI) calculated as weight divided by height squared, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean arterial pressure (MAP) and comorbidities. Additionally, laboratory data included: Serum creatinine (SCR), estimated Glomerular Filtration Rate (eGFR) (ml/min/1.73m^2) using the Modification of Diet in Renal Disease Study (MDRD) equation, Urinary Albumin-Creatinine Ratio (ACR), serum cholesterol, serum triglycerides, Fasting Blood Glucose (FBS), Glycated Hemoglobin (HbA1c), and serum albumin.

In all participants, serum free T3, free T4, and TSH; thyroid function tests were performed using chemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland).

One hundred Proteinuric CKD patients were identified: 20 patients were euthyroid, 40 had subclinical hypothyroidism and received L. thyroxine and 40 patients had overt hypothyroidism were also treated with L. thyroxine and all the participants were followed up for 24 months with no dropout. All the variables were measured at baseline then every 6 months to the end of the study. Noteworthy, other lines of treatment for proteinuric CKD were individualized.

Ethical approval:

The study was performed in accordance with the principles and regulations of the Helsinki's declaration. The study protocol was approved by the Ethical Committee of Benha University on 24/6/2018, with approval number 3089/2286. All the participants gave informed written consents in the Arabic language fully explaining the study and highlighting the potential hazards and benefits of Thyroid Hormone Replacement Therapy (THRT).

Inclusion criteria:

Age ≥ 18 years, patients with proteinuric CKD

Exclusion criteria:

History of previous hyperthyroidism, history of THRT before the study, history of autoimmune disease, pregnancy, malignancy, chronic liver disease, heart failure, renal transplant, or ESRD.

Thyroid Hormone Replacement Therapy (THRT):

Levothyroxine used was (synthetic thyroid hormone, L-Thyroxine, GlaxoSmithKline pharmaceutical ***(UK)*** with concentration 25, 50,100 mcg). L-thyroxine was given orally once daily on empty stomach 30 minutes -1 hour before breakfast. The treated patients were initially administered L-thyroxine with the lowest dose necessary to normalize serum TSH level, usually 12.5 to 25 μg/d. After the start of thyroid hormone supplement, serum TSH concentration was remeasured for follow-up. If the level of TSH remained above or below the normal reference range, the dose of L-thyroxine was adjusted by 12.5 to 25 μg/d until the patient's thyroid function tests were brought to the normal reference range. In the present study, 90% of patients have achieved the targets in the first 3 months and 97% have achieved the targets by the first 6-month time.

Statistical methods

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical Package for the Social Sciences) version 26. Quantitative data were represented as mean±standard deviation (SD) when parametric and were compared by one-way ANOVA test or as median and interquartile range (IQR) when nonparametric and were compared by Kruskal-Wallis test for more than 2 groups or Wilcoxon signed-rank test for paired data**.** Post-hoc Bonferroni test was used for multiple comparison when comparing more than 2 groups. Qualitative data were represented as frequency and percentage and were compared by X^2 test. A multivariate regression analysis was conducted on the dependent and independent variables to adjust for any interaction between thyroid functions and CKD to explore whether thyroid hypofunction was independently associated with CKD. A P value <0.05 was considered statistically significant (*) while a P value <0.01 was considered highly significant (**) in all analyses.

RESULTS

As shown in table (1), compared to patients with euthyroid state, those with subclinical and overt hypothyroidism had no statistically significant difference regarding age, sex, or blood pressure values.

Table 1: Comparison between the studied groups according to baseline demographics

Characteristic	Euthyroid group (20)		Subclinical hypothyroidism (40)		Overt hypothyroidism (40)		Statistical test (F)	P value
	Mean	±SD	Mean	±SD	Mean	±SD		
Age	47.7	9.41	45.2	11.37	44.6	7.35	0.73	0.49
BMI	23.28	2.83	24.87	2.6	24.8	2.51	2.84	0.06
Blood Pressure (BP):								
SBP	133.25	10.29	130.0	10.13	133.0	8.83	1.23	0.30
DBP	83. 75	6.26	85.8	4.27	86.5	4.21	17.0	0.11
MAP	100.3	7.03	98.8	7.49	101.8	5.88	5.59	0.15
	No	%	No	%	No	%	Chi square	P value
Sex Male Female	 10 10	 50.0 50.0	 24 16	 60.0 40.0	 16 24	 40.0 60.0	3.2	0.20

(BMI: Body Mass Index, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: Mean arterial pressure).

As summarized in table (2), univariate analysis showed that compared to patients with euthyroid state, those with subclinical and overt hypothyroidism had a highly statistically significant difference as regard serum creatinine, eGFR, urinary ACR, serum albumin, total cholesterol, and TG.

Table 2: Comparison between studied groups according to baseline laboratory values

Variable	Euthyroid group (20)		Subclinical hypothyroidism (40)		Overt hypothyroidism (40)		Post-hoc test	(Kruskal-Wallis) test	P value
	Median	IQR	Median	IQR	Median	IQR			
Creatinine (mg/d L)	1.0	0.90-1.1	1.2	1.1-1.4	1.6	1.5-1.8	abc	50.97	<0.001**
eGFR (min/ml/1.73m^2)	75	72.3-79.8	63.74	43.22-78.6	56.2	45.2-67.57	ab	24.92	<0.001**
ACR (mg/g)	432	351.7-537.7	991	978-1035	1110	980-1160	abc	54.77	<0.001**
TSH (mIU/L.)	3.6	2.63- 4.0	8.75	7.6- 8.9	10.1	9.2- 11.4	abc	66.29	<0.001**
FT3 (ng/dL.)	0.95	0.80-1.18	0.91	0.90-1.1	0.30	0.20-0.40	bc	71.92	<0.001**
FT4 (ng/dL.)	1.1	0.80- 1.2	1.0	0.8- 1.2	0.35	0.21-0.47	bc	70.24	<0.001**
S albumin (g/dL.)	3.9	3.63- 4.18	3.5	3.3- 3.7	3.3	3.1- 3.8	ab	20.37	<0.001**
Cholesterol (mg/dL.)	210	197.2-227.7	198	187.0-230	247.0	242- 255	bc	60.82	<0.001**
STG (mg/dL.)	129	113.5-150.7	156	120-158	162.5	154- 170	abc	34.90	<0.001**
FBS (mg/dL.)	100.0	89- 104	98.0	88- 105	95.0	90- 130		0.89	0.64
HbA1c	6.0	5.9- 6.1	5.95	5.8- 6.2	6.1	5.8- 7.0		2.21	0.33
Uric acid (mg/dL.)	5.45	4.43-5.98	5.6	4.0- 6.1	5.5	5.0- 6.9		2.84	0.24

a: Euthyroid and SCH b: Euthyroid and CHT c: SCH and CHT

(eGFR: estimated Glomerular Filtration Rate, ACR: urinary Albumin-Creatinine Ratio, TSH: Thyroid Stimulating Hormone, FT3, FT4: Free Thyroid Hormones, S.TG: Serum Triglycerides, FBS: Fasting Blood Sugar, HbA1c: Glycated Hemoglobin).

Even after adjustment of other baseline variables by multivariate regression analysis of eGFR and proteinuria among euthyroid, SCH, and CHT groups, (P-for- trend remained <0.001), showing higher standardized coefficient Beta values for baseline TSH compared to other risk factors for low eGFR/proteinuria in both SCH/CHT, whereas standardized coefficient Beta for FT4 levels was significant only in CHT (Tables 3-6).

Table 3: Multivariate linear regression of eGFR among SCH groups against other variables at baseline

eGFR (min./ml/1.73m^2)	**Standardized coefficient Beta**	**t**	**value**	**Lower limit of 95% CI**	**Upper limit of 95% CI**
TSH (mIU/L.)	0.871	8.070	<0.001	0.1	0.6
FT4 (ng/dL.)	0.509	7.808	<0.001	0.5	0.9
ACR (mg/g)	0.678	7.960	<0.001	0.010	0.016
MAP	-0.558-	-7.227-	<0.001	-1.356-	-0.760-
DBP	-0.655-	-7.227-	<0.001	-1.356-	-0.760-
FBS (mg/dL.)	0.629	7.409	<0.001	0.333	0.642
HbA1c	0.429	-5.272-	<0.001	0.451	1.295
s.TG (mg/dL.)	0.306	3.293	0.002	0.162	0.688
s. Cholesterol (mg/dL.)	0.306	-8.315-	<0.001	1.91	2.45
Age	0.112	43.667	<0.001	16.12	19.22
Sex	0.019	35.435	0.002	-3.564-	-1.263
BMI	0.123	49.239	<0.001	14.521	17.721
R square	0.81				
Adjusted r square	0.77				
F test	22.95				
P value	<0.001**				

(eGFR: estimated Glomerular Filtration Rate, ACR: urinary Albumin-Creatinine Ratio, TSH: Thyroid Stimulating Hormone, FT3, FT4: Free Thyroid Hormones, S.TG: Serum Triglycerides, FBS: Fasting Blood Sugar, HbA1c: Glycated Hemoglobin)

Table 4: Multivariate linear regression of ACR among SCH groups against other variables at baseline

ACR (mg/g)	**Standardized coefficient Beta**		**P value**	**Lower limit of 95% CI**	**Upper limit of 95% CI**
TSH (mIU/L.)	1.383	554.628	<0.001	124.718	125.640
FT4 (ng/dL.)	0.100	11.421	<0.001	568.841	816.585
eGFR (min./ml/1.73m^2)	0.978	7.960	<0.001	0.19	0.87
FBS (mg/dL.)	0.589	116.453	<0.001	23.558	24.399
HbA1c	0.329	-4.203-	<0.001	0.651	2.295
DBP	0.607	114.210	<0.001	33.931	35.166
MAP	-0.858-	-7.227-	<0.001	-1.356-	-2.760-
S.TG (mg/dL.)	-0.775-	-300.04-	<0.001	-56.869-	-56.100-
S. Cholesterol (mg/dL.)	0.189	35.709	<0.001	13.613	15.264
Age	0.012	12.667	<0.001	11.01	13.36
Sex	0.024	14.329	<0.001	-2.046-	-2.03
BMI	-0.684-	-224.78-	<0.001	-205.745-	-202.040-
R square	1.0				
Adjusted r square	1.0				
F test	127713.7				
P value	<0.001**				

(eGFR: estimated Glomerular Filtration Rate, ACR: urinary Albumin-Creatinine Ratio, TSH: Thyroid Stimulating Hormone, FT3, FT4: Free Thyroid Hormones, S.TG: Serum Triglycerides, FBS: Fasting Blood Sugar, HbA1c: Glycated Hemoglobin)

Table 5: Multivariate linear regression of eGFR among CHT group against other baseline variables

eGFR (min./ml/1.73m^2)	**Standardized coefficient Beta**	**t**	**P value**	**Lower limit of 95% CI**	**Upper limit of 95% CI**
TSH (mIU/L.)	-2.563	398.359	<0.001	0.89	1.45
FT4 (ng/dL.)	-2.126-	-363.827-	<0.001	-154.895-	-153.168-
ACR (mg/g)	-.516-	-184.785-	<0.001	-0.006-	-0.006-
S. Cholesterol (mg/dL.)	1.308	334.508	<0.001	0.986	0.998
FBS (mg/dL.)	-0.769-	-225.157-	<0.001	-0.906-	-0.889-
HbA1c	0.295	-45.272-	<0.001	0.96	2.952
DBP	1.301	201.420	<0.001	5.187	5.293
MAP	-1.028-	-5.709-	<0.001	-1.536-	-3.605-
ACR (mg/g)	-1.216-	-184.785-	<0.001	-0.36-	-1.56-
S.TG (mg/dL.)	0.249	84.878	<0.001	0.204	.214
R square					1.0
Adjusted r square					1.0
F test					83815.1
P value					<0.001**

(eGFR: estimated Glomerular Filtration Rate, ACR: urinary Albumin-Creatinine Ratio, TSH: Thyroid Stimulating Hormone, FT3, FT4: Free Thyroid Hormones, S.TG: Serum Triglycerides, FBS: Fasting Blood Sugar, HbA1c: Glycated Hemoglobin)

Table 6: Multivariate linear regression of ACR among CHT group against other baseline variables

ACR (mg/g)	**Standardized coefficient Beta**		**P value**	**Lower limit of 95% CI**	**Upper limit of 95% CI**
TSH (mIU/L.)	4.158	162.265	<0.001	323.061	331.285
FT4 (ng/dL.)	-2.662-	-286.690-	<0.001	-0.518-	-0.919-
eGFR (min./ml/1.73m^2)	-2.099-	-321.969-	<0.001	-176.090-	-173.873-
FBS (mg/dL.)	-0.891-	-521.549-	<0.001	-1.356-	-2.765-
HbA1c	-0.765	-345.954-	<0.001	-2.654-	-2.576-
DBP	-1.09-	-230.085-	<0.001	-1.26-	-2.18-
MAP	1.109	196.078	<0.001	602.474	615.140
S. cholesterol (mg/dL.)	0.410	297.042	<0.001	520.325	527.519
S. TG (mg/dL.)	0.158	162.265	<0.001	323.061	331.285
Age	-0.406-	-463.053-	<0.001	-224.956-	-222.983-
BMI	-0.141-	-52.539-	<0.001	-588.653-	-544.658-
R square					1.0
Adjusted r square					1.0
F test					1435091.9
P value					<0.001**

(eGFR: estimated Glomerular Filtration Rate, ACR: urinary Albumin-Creatinine Ratio, TSH: Thyroid Stimulating Hormone, FT3, FT4: Free Thyroid Hormones, S.TG: Serum Triglycerides, FBS: Fasting Blood Sugar, HbA1c: Glycated Hemoglobin).

The impact of THRT on eGFR (at 6, 12, 18, 24 months) is summarized in table (7) showing that in patients with subclinical hypothyroidism and clinical hypothyroidism, there was a highly
statistically significant improvement of eGFR from baseline values along all the follow- up period (all p values <0.001); nevertheless, the most clinically significant improvement was noticed early on after the first 6 months, then the trend continued to improve afterward albeit steeply.

Table 7: Differences of estimated GFR from baseline and along follow up periods after thyroid replacement therapy among subclinical and overt hypothyroidism

Subclinical hypothyroidism (40)	**eGFR (min./ml/1.73m^2)**		**Base line and**	
	Median	**IQR**	Wilcoxon signed-rank test	**P**
Base line	63.74	43.22- 78.68		
After 6 months follow up	71.39	51.63- 81.94	5.24	<0.001**
After 12 months follow up	71.39	51.4- 87.23	5.52	<0.001**
After 18 months follow up	71.80	51.83- 87.33	5.54	<0.001**
After 24 months follow up	72.0	51.59- 87.40	5.22	<0.001**
Overt hypothyroidism (40)	**eGFR (min./ml/1.73m^2)**		**Base line and**	
	Median	**IQR**	Wilcoxon signed-rank test	**P**
Base line	56.20	45.2- 67.57		
After 6 months follow up	60.86	49.57- 71.16	5.52	<0.001**
After 12 months follow up	60.62	49.39- 71.41	5.22	<0.001**
After 18 months follow up	61.09	49.80- 71.60	5.24	<0.001**
After 24 months follow up	61.22	50.88- 71.99	5.12	<0.001**

e GFR: estimated Glomerular Filtration Rate, IQR: Inter Quartile Range, MWZ test: Mann-Wilcoxon-Whitney test

In table (8), the impact of THRT on urinary ACR comparing baseline values with values at 6, 12, 18, 24 months is listed showing a similar trend for proteinuria reduction to that of improved eGFR along the time, whereas in the subclinical hypothyroid and clinical hypothyroid groups we found a highly statistically significant reduction of ACR from a baseline along follow up period, that was again most clinically significant after the first 6 months, then continued afterwards albeit at a steeper rate of proteinuria reduction.

Table 8: Differences in urinary Albumin-Creatinine Ratios (ACR) from baseline and along follow up periods after thyroid replacement therapy among subclinical and overt hypothyroidism

Subclinical hypothyroidism (40)	**ACR (mg/g)**		**Base line and**	
	Median	**IQR**	Wilcoxon signed-rank test	**P**
Base line	991.0	978.0- 1035.0		
After 6m follow up	596.5	554.0- 670.0	5.52	<0.001**
After 12m follow up	575.0	534.0- 660.0	5.52	<0.001**
After 18m follow up	565.0	522.0- 644.0	5.12	<0.001**
After 24m follow up	556.0	490.0- 630.0	5.56	<0.001**
Overt hypothyroidism (40)	**ACR (mg/g)**		**Base line and**	
	Median	**IQR**	Wilcoxon signed-rank test	**P**
Base line	1110.5	980.0-1160.0		
After 6m follow up	822.0	756.0- 944.0	5.52	<0.001**
After 12m follow up	795.0	745.0- 867.0	5.52	<0.001**
After 18m follow up	742.0	699.0- 845.0	5.5	<0.001**
After 24m follow up	716.5	550.0- 830.0	5.12	<0.001**

ACR: urinary Albumin-Creatinine Ratio, IQR: Inter Quartile Range, MW$_Z$ test: Mann-Wilcoxon-Whitney test

DISCUSSION

The findings of the current study demonstrating an association between CKD and SCH/CHT come in agreement with previous observational cross-sectional studies [1-4]. Nevertheless, a significant limitation of the previous studies showing such association comes from their inherently limited ability to establish a mechanistic link for temporal causality. The present study demonstrated a statistically significant association between baseline proteinuric CKD and SCH/CHT. We conducted a univariate analysis and a multivariate analysis to adjust for the interaction of the baseline risk factors for CKD (Low eGFR/ Proteinuria), in both univariate and multivariate models, SCH/CHT were associated with CKD.

Long considered a physiological adaptation in CKD, evolving evidence on hypothyroid states challenges this notion suggesting that low thyroid hormone levels, left untreated, might be a risk factor for both incident CKD and CKD progression [19-21]. Therefore, we examined the impact of correcting thyroid hypofunction to an euthyroid state by THRT on the progression of baseline CKD, we found that THRT in both SCH and CHT was associated with a statistically significant improvement in eGFR levels and decrease in proteinuria levels along the follow-up, the beneficial effect of THRT started and was most clinically significant after the first 6 months on treatment and continued all over the 2-year follow-up period. Several studies have shown a beneficial effect on reversing hypothyroid state on halting the progression of CKD [11-14]. In CKD patients with SCH, unresolved SCH was found as an independent predictor of CKD progression, interestingly enough, in this same study, spontaneous resolution of SCH even without treatment has led to less decline in eGFR [19]. Our current study findings confirm and strengthen the favorable kidney outcomes conveyed by exogenous THRT in both SCH and CHT groups with baseline proteinuric CKD.

Whilst the consensus in Endocrinology Society dictates starting THRT for patients with CHT albeit in small increments in elderly patients, in SCH, indications for starting THRT are rather individualized based on the risk for progression to CHT if TSH levels> 10 μIU/mL or in the presence of thyroid peroxidase antibodies (TPO) or symptoms or comorbidities. Yet, there is no explicit recommendations in endocrinology, nor in nephrology guidelines regarding the screening or treatment of hypothyroid states in CKD despite the growing evidence suggesting a causal interplay between the two entities even independent of conventional risk factors [21].

Proteinuric CKD in patients with SCH even poses a more important clinical question regarding the benefit of starting HTRT merely for preservation of renal functions in the absence of other traditional indications. **Shin *et al.*** [22-23], showed that patients with subclinical hypothyroidism who received THRT had a lower risk of CKD progression compared to their counterparts with SCH who did not receive treatment even after adjusting for other conventional risk factors for CKD progression. Our current study showed a similar effect of THRT for halting CKD progression. Taken together, the question that springs to mind is whether the presence of CKD alone (reduced eGFR/ Proteinuria) could be a novel indication for treatment of subclinical hypothyroidism? Obviously, further larger and longer studies are needed to explore this potential.

In addition, the cut offs used in our present study as well as previous studies to define hypothyroid status are derived from studies conducted on general population [1-4]. CKD patients are well-known to have distinct features that distinguish them from the normal population. Hence, if we are to accurately distinguish true thyroid disorders from non-thyroidal illness in CKD patients, further research is warranted to identify more sensitive and specific methods to classify thyroid disorders in CKD population. Furthermore, the dosing and targets of THRT in CKD patients need to be further explored in future studies.

Taken together, our results demonstrate the benefit and call for the screening and treatment of thyroid hypofunction states in patients with proteinuric CKD as a potential untraditional risk factor for CKD progression.

LIMITATIONS

It is fair to acknowledge that our study has some salient limitations including:

1- The average age in our cohort was around late forties, relatively a young population, hence no adverse events regarding ischemia, arrhythmias, or bone mineral disorders were reported with THRT; nevertheless, this should be kept in mind when deciding on elderly patients with SCH who are more liable for side effects of THRT.
2- A small number of patients with a short follow-up period, therefore, larger studies with longer follow-up periods are needed to further explore our findings.
3- In the present study, we used MDRD equation as a surrogate for eGFR. Notwithstanding their imperfections and limitations of performance of e GFR equations, our findings are consistent with the results of studies that have used radio-isotope imaging for measuring GFR in hypothyroid states and their treatment [12-13].
4- Screening for thyroid peroxidase (TPO) was not routinely ordered in our cohort, however, the HUNT

study did not find a difference between those with or without TPO in terms of CKD [4].

CONCLUSION

Our findings strengthen and support the previous reports on the reciprocal relation between CKD and hypothyroid states; and demonstrate that THRT can be safely advocated to preserve renal functions in proteinuric CKD patients with SCH/CHT suggesting a potential for halting CKD progression after THRT in both SCH/CHT that warrants to be confirmed in future studies.

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