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ORIGINAL ARTICLE

Thyroid-Stimulating Hormone and Estimated Glomerular Filtration Rate

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Abstract

Background: Hypothyroidism has been identified as a comorbidity related to chronic kidney disease (CKD). The retrospective study investigated thyroid function and CKD and assessed the relationship between TSH and urine albumin/creatinine ratio (ACR), the slope of estimated glomerular filtration rate (eGFR), stratified by CKD grades.

Methods: This retrospective cohort study was conducted in a community nephrology clinic established with clinical and demographic data, from April 1, 2015, until December 30, 2019. Hypothyroidism prevalence, eGFR slope and ACR were the outcomes of interest and were analyzed by using unconditional and adjusted generalized linear (GLM) and logistic regression models.

Results: The overall demographics of the 312 subjects were 58.3% were male, 12.8% had hypothyroidism and 43.3% had diabetes mellitus, with the median age of 73 years (IQR (interquartile range) 29-99). The hypothyroidism prevalence was 9.4%, 11.5%, 15%, and 17.5% for the CKD categories defined as Grade 1 and 2 combined, Grade 3, Grade 4, and Grade 5, respectively. The overall median eGFR slope was -0.0027 (IQR -0.158 - 0.602). With GLM models, the adjusted odds ratio of 1.052 (95% CI: 1.006-1.100) was calculated for TSH level > 5 µIU/L (Q2), per unit ml/min/day decline in eGFR slope. The overall median urine ACR was 10.2 mg/mmol (IQR 0.24-1414). In a multivariate logistic regression model with the 75th percentile for urine ACR, the adjusted odds ratio of TSH level of > 1.8 µIU/l (50th percentile) was 1.803 (95% CI: 0.986-3.296).

Conclusions: The prevalence of hypothyroidism increased with worsening eGFR grades from 9.4% to 17.4% at baseline. The higher TSH levels were associated with faster decline in eGFR and higher levels of albuminuria. Furthermore, prospective studies are needed to evaluate the effect of hypothyroidism treated on renal function.

Keywords

Thyroid-stimulating hormone, Chronic kidney disease, Proteinuria, Estimated glomerular filtration rate

Background

In the general population, there are 10-13.4 percent individuals diagnosed with chronic kidney disease (CKD) [1,2]. In addition to hypertension, anemia, cardiovascular disease and congestive heart failure, hypothyroidism has been identified as a comorbidity related to chronic kidney disease, which is usually accompanied by metabolic syndrome. The prevalence of hypothyroidism accompanied by CKD ranges between 3 and 25% [3]. TSH levels of 3 to 5 mIU/L, 5 to 10 mIU/L and greater than 10 mIU/L were associated with incrementally increased mortality risk of time-adjusted hazard ratios (95% CI) 1.27 (1.22-1.32) and 1.13 (1.02-1.25), respectively [4].

The primary objective of this study is to assess the relationship of hypothyroidism to urine albumin/creatinine ratio, slope of eGFR, hypothyroidism and different grades of CKD.

These objectives were met in a retrospective cohort, compiled from a nephrology clinic of a community hospital in Quebec. A random sample of 312 subjects was entered into an electronic database from the following data sources: Laboratory data from the Reflections database, clinical examination, medication list and demographical data from clinic charts, ECG data from Cardiology data management electronic database

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and radiological data from web-based PACs database.

Methods

The inclusion criteria for sample size were an age of ≥ 18, a diagnosis of CKD as represented by three eGFR readings of ≤ 90 ml/min/1.73 m^2 and a life expectancy of more than 6 months. The subjects were excluded if the individuals were noted to have acute kidney injury, expected to require renal replacement therapy within 3 months, or transferred to another health care facility.

Age, gender, race, diabetes status, cause of renal disease, comorbidities, height, weight, blood pressure, baseline eGFR, baseline CKD grade, hemoglobin, sodium, potassium, calcium, phosphate, TSH, hemoglobin A1c, proteinuria and uric acid were the variables collected for the database. Absolute hemoglobin A1c was calculated by multiplying hemoglobin A1c by the hemoglobin in g/L [5].

Sample size calculation

For the calculation of sample size using logistic regression for albuminuria, the assumption of 10% hypothyroidism prevalence compared with 15% of hypothyroidism prevalence in the effect size of 0.5, power of 80% and alpha error of 0.05, the required sample size is 329. Similarly, if the effect size is 0.04, the power is set at 80%, alpha error of 0.05, for the desired linear regression analysis for slope of eGFR, with the anticipated TSH level above the 50th percentile (Q2) the required sample size is 274 [6].

Sample size acquisition

The research team identified a random sample of 312 medical charts from a nephrology clinic of a community hospital were identified by the nephrology team and all data were collected and entered into an electronic excel database.

Outcomes

Estimated GFR slopes were calculated for individual patients using three or more eGFR values collected over time of follow up and the linear regression models. Significant urine albumin/creatinine levels at baseline were defined as 75th percentile (Q3).

Hypothyroidism was diagnosed as TSH level above 5 µIU/l (Q2). The TSH levels were categorized by greater than 50th (Q2) and 75th percentiles (Q3), as well.

Results

Of the 312 subjects, 58.3% (182/312) were male, 12.8% had a diagnosis of hypothyroidism (40/312), 43.3% (135/312) of a diagnosis of diabetes mellitus, with a median age of 73 (IQR 29-99) (Table 1). Their baseline eGFR was 34 ml/min/1.73 m^2 (IQR 9-93). The duration

Table 1: Baseline characteristics.

Demographics	Number of Subjects	Median/Proportion	IQR/Ratio
Age (years)	312	73	29-99
Gender: Male		58.33%	124/212
Height (meters)	297	1.68 meters	0.91-1.7
Weight (kilograms)	299	78.4 kg	34-150
BMI (kilograms/meters squared)	294	27.8	16.8-48.8
Race	312		
Caucasian		59%	184
Arab		11.5%	36
Asian		16.4%	51
Black		6.4%	20
Europe		5.1%	16
South American		1.6%	5
Comorbidities			
Diabetes mellitus	312	43.3%	92
Dementia	312	2.2%	5
Pacemaker	312	6.1%	13
Gout	312	14.4%	31
GERD	312	9.9%	21
Atrial fibrillation	312	12.5%	27
Peripheral vascular disease	312	11.5%	24
Cerebrovascular disease	312	9.9%	21
Coronary artery disease	312	26%	55

Congestive heart failure	312	13.5%	42
Cancer	312	31%	66
Liver disease	312	2.2%	7
COPD	312	16.7%	35
Deep venous thrombosis	312	4.2%	9
Dyslipidemia	312	43.2%	92
Hematuria	312	30.7%	65
Proteinuria	312	43.2%	134
Hypothyroidism	312	12.8%	40
Clinic Variable			
Systolic blood pressure (mmHg)	306	141	88-239
Diastolic blood pressure (mmHg)	306	75	40-104
Heart rate (beats per minute)	307	71	32-140
Medication			
Levothyroxine (mcg)	39	88	0-225
Laboratory			
Thyroid stimulating hormone (μIU/l)	211	1.85	0.06-109.5
Baseline eGFR ml/min/1.73 m^2	312	34	9-93
Hemoglobin < 100 g/l > Or = 100 g/l	312	14.1% 85.9%	30 182
Serum creatinine (μmol/L)	312	147	63-626
Hemoglobin (g/L)	307	123	76-172
Serum sodium (mmol/L)	306	139	132-145
Serum potassium (mmol/L)	306	4.5	2.6-6.2
Serum bicarbonate (mmol/L)	265	26	14-33
Blood urea (mmol/L)	280	10.4	2.9-42.8
Serum albumin (g/L)	295	39	19.5-47
Serum uric acid (μmol/L)	289	391	117-879
Total cholesterol	269	4.31	1.92-8.63
HDL (mmol/L)	264	1.14	0.54-2.64
LDL (mmol/L)	264	2.29	0.56-5.85
Serum calcium (mmol/L)	218	2.38	2.16-2.76
Ionized calcium (mmol/L)	78	1.26	1.13-1.39
Serum phosphate (mmol/L)	291	1.2	0.63-2.26
C reactive protein (mg/L)	241	5.5	2.03-293
Ferritin (μg/l)	279	72	2.22-1022
HbA1c (percent)	275	5.8	4.8-11.3
Absolute hemoglobin a1c (percent)	273	7.3	4.1-15.1
Urine albumin/creatinine (mg/mmol)	270	10.2	0.24-1414
eGFR slope (ml/min/1.73 m^3/day)	306	-0.00270	-0.158 - 0.602
Radiology			
Right Kidney cm	289	9.9	3.2-27.5
Left Kidney cm	294	10	5-28.2
Average Kidney cm	289	9.8	4.8-27.9
Total kidney volume ml^3	294	257.8	66-3765.4

of the follow up period was 24.4 (IQR 0.93-103.5) months (Table 1). When the subjects were divided into CKD categories (less than 15 ml/min/1.73 m^2, 15-30 ml/min/1.73 m^2, 30-60 ml/min/1.73 m^2 and > 60 ml/min/1.73 m^2) a progressive increase in the proportion with the diagnosis of diabetes mellitus, diagnosis of dementia, proteinuria and ferritin was observed with statistical significance (Table 2). Conversely, there was a statistically significant progressive decline in eGFR, serum albumin and hemoglobin, also evident.

Table 2: Baseline characteristics by CKD grades.

Demographics	**CKD 1-2** **N = 19**	**CKD 3** **N = 112**	**CKD 4** **N = 66**	**CKD 5** **N = 15**
Age (years)	63.5 (29-92)	72 (31-93)	78 (37-93)	74 (45-99)
Gender male	53% (10)	60% (67)	58% (38)	57% (9)
Race				
Caucasian	3.9%	30.1%	20.5%	4.5%
Arab	2.9%	4.8%	3.2%	0.64%
Asian	1.3%	8.7%	4.8%	1.6%
Black	1.3%	3.9%	1.3%	0
European	0.6%	2.2%	1.9%	0.3%
South American	0.3%	0.6%	0.3%	0.3%
Height (meters)	1.65 (IQR 1.03-1.9)	1.68 (IQR 1.5-1.96)	1.68 (IQR 1.47-1.96)	1.67 (IQR 1.4-1.8)
Weight (kilograms)	78.5 (IQR 53.3-130.6)	80 (IQR 43-150)	73.5 (IQR 34-131.5)	77.7 (IQR 50.9-123.6)
Bmi (kilograms/meters squared)	28.3 (IQR 18.9-43.2)	27.9 (IQR 17-53.2)	27.2 (IQR 20.2-45.9)	27.9 (IQR 20.3-43.8)
Comorbidities				
Diabetes Mellitus$^{\Psi}$	31.2%	38.2%	56%	39.1%
Dementia$^{\Psi}$	3.13	0	4	8.7
Pacemaker	0.32	2.56	2.88	0.32
Gout	0.96	5.77	6.73	0.96
GERD	1.92	5.77	1.28	0.96
Atrial fibrillation	0.96	6.41	4.81	0.32
Peripheral Vascular disease	0	6.41	4.49	0.64
Cerebrovascular disease	0.96	4.17	4.49	0.32
Coronary artery disease	0.96	13.78	8.97	2.24
Congestive heart failure	2.4(1)	47.6(20)	38.1(16)	11.9(5)
Cancer$^{\Psi}$	18.8%	29.3%	34%	43.5%
Liver disease	0	1.28	0.64	0.32
COPD	1.28	8.97	4.49	1.92
Deep venous thrombosis	0.32	3.21	0.64	0
Dyslipidemia	1.92	17.63	11.86	3.21
Hematuria	36.7	28.4	27.8	52.4
Proteinuria$^{\Psi}$	30	31.3	60.8	90.5
hypothyroidism$^{\Psi}$	9.4%	11.5%	15%	17.4%
Clinic				
Systolic blood pressure (mmHg)	137 (IQR 101-188)	142 (IQR 92-239)	143 (IQR 88-195)	139 (IQR 107-200)
Diastolic blood pressure (mmHg)	76.5 (IQR 60-102)	76 (IQR 49-102)	71 (IQR 41-104)	77 (IQR 40-100)
Heart rate (beats/minute)	73 (IQR 51-104)	70 (IQR 49-123)	70.5 (IQR 49-114)	74 (IQR 62-106)
Laboratory				
Thyroid stimulating hormone (μIU/l)	1.6 (IQR 0.78-6.18)	1.83 (IQR 0.18-109.5)	1.8 (IQR 0.06-9.5)	2.51 (IQR 0.26-6.39)
eGFR ml/min/1.73m2$^{\Psi}$	67.5 (IQR 60-93)	41 (IQR 30-59)	24 (IQR 15-29)	11 (IQR 9-14)
Serum creatinine (μmol/L)	88.5 (IQR 63-128)	132 (IQR 80-193)	208 (IQR 130-349)	393 (IQR 241-626)
Hemoglobin (g/l)$^{\Psi}$	133 (IQR 102-162)	127 (IQR 77-172)	115 (IQR 82-171)	106 (IQR 76-151)

Serum sodium (mmol/L)	139 (IQR 133-143)	139 (IQR 127-148)	138.5 (IQR 134-145)	139 (IQR 133-142)
Serum potassium (mmol/L)	4.3 (IQR 3.7-4.9)	4.5 (IQR 2.6-5.6)	4.6 (IQR 3.4-6.2)	4.8 (IQR 3-5.9)
Serum bicarbonate (mmol/L)	26.5 (IQR 21-30)	26 (IQR 20-33)	25 (IQR 14-31)	23.5 (IQR 18-28)
Blood urea (mmol/L)	5.95 (IQR 2.9-16.2)	8.7 (IQR 3.1-29)	14.7 (IQR 6.7-28.7)	19.6 (IQR 2.9-42.8)
Serum albumin (g/l)Ψ	41.5 (IQR 34-46)	41 (IQR 19.5-47)	37 (IQR 23-46)	36 (IQR 22-41)
Serum uric acid (mmol/L)	380 (IQR 235-588)	397 (IQR 117-879)	392 (IQR 225-690)	409 (IQR 201-555)
Total cholesterol (mmol/L)	4.75 (IQR 2.77-7.33)	4.43 (IQR 2.06-7.32)	3.98 (IQR 1.92-6.55)	3.93 (IQR 2.39-11.65)
HDL (mmol/L)	1.18 (IQR 0.73-2.06)	1.17 (IQR 0.54-2.02)	1.08 (IQR 0.58-1.99)	1.06 (IQR 0.6-2.71)
LDL (mmol/L)	2.61 (IQR 1.32-4.89)	2.39 (IQR 0.02-5.55)	2.06 (IQR 0.56-5.85)	2.09 (IQR 1.08-8.5)
Serum calcium (mmol/L)	2.45 (IQR 2.25-2.46)	2.39 (IQR 1.27-2.71)	2.38 (IQR 1.19-2.76)	2.39 (IQR 1.84-2.66)
Ionized calcium(mmol/L)	1.27 (IQR 1.16-1.32)	1.25 (IQR 1.17-1.39)	1.27 (IQR 1.17-1.41)	1.27 (IQR 1.13-1.32)
Serum phosphate (mmol/L)Ψ	1.26 (IQR 0.9-1.51)	1.15 (IQR 0.63-1.73)	1.29 (IQR 0.86-2.26)	1.495 (IQR 0.95-2.26)
C reactive protein (mg/l)	4 (IQR 2.03-18.8)	4 (IQR 4-293)	5.7 (IQR 4-122)	6.7 (IQR 4-47.1)
Ferritin (µg/l)Ψ	50 (IQR 10-417)	71 (IQR 3-486)	79 (IQR 7-1022)	119.5 (IQR 2.22-743)
HbA1c (percent)	5.8 (IQR 5-9.6)	5.7 (IQR 5.2-11.3)	6.2 (IQR 5.2-9.6)	5.5 (IQR 6-9)
Absolute HbA1c (percent)Ψ	7.6 (IQR 4.4-128)	7.6 (IQR 5.3-15.1)	7.2 (IQR 5-14.4)	6.4 (IQR 4.1-9.9)
Urine Albumin/creatinine (mg/mmol)Ψ	1.32 (IQR 0-324.14)	5.13 (IQR 0-725.6)	31.9 (IQR 0-1413.97)	110.3 (IQR 5.2-978.8)
eGFR slope (ml/min/1.73 m^3/day)	0.014 (IQR -1.03-0.102)	-0.003(IQR -0.158-0.246)	0.00016 (IQR -0.15-0.60)	-0.0019 (IQR -0.014 to -0.016)
Radiology				
Right Kidney cm	11 (IQR 8.5-14.2)	10.1 (IQR 5.2-24)	9.5 (IQR 4.9-27.5)	9.5 (IQR 3.2-11.8)
Left Kidney cm	11 (IQR 6.6-14)	10.3 (IQR 5.6-23)	9.8 (IQR 5.9-28.2)	9.3 (IQR 5-11.8)
Average Kidney cm	10.8 (IQR 8.6-13.5)	9.95 (IQR 4.8-23.5)	9.65 (IQR 6.8-27.85)	8.925 (IQR 5.6-11.8)
Total kidney volume (ml^3)	238.3 (IQR 66-693.4)	271 (IQR 75.2-1707.4)	338.4 (IQR 84.5-3765.5)	223.1 (IQR 112.7-445.1)

Ψp value < 0.05.

Table 3A: Unadjusted odds ratio for eGFR slope.

Variable	Odds ratio	95% CI	P value
Baseline eGFR	0.999	0.998-1.000	0.0976
TSH > 5 µIU/l	1.007	0.989-1.025	0.4311
TSH ≤ 5 µIU/L (reference)	1.0		
Systolic blood pressure (mmHg)Ψ	0.999	0.999-1.000	0.0028
Urine nephrotic range (g/l)Ψ	0.970	0.947-0.994	0.0493
Urinalysis: Urine overt proteinuria	0.986	0.971-1.002	
Urinalysis: Urine trace proteinuria	0.988	0.969-1.007	
Urinalysis: Reference negative proteinuria	1.0		

Ψp value < 0.05.

Table 3B: Adjusted multivariate model for eGFR slope.

Variable	Odd ratio	95% CI	P value
Baseline eGFRΨ	0.999	0.998-1.000	0.0029
TSH > 5 µIU/lΨ	1.052	1.006-1.100	0.0275
TSH ≤ 5 µIU/L (reference)	1.0		
Systolic blood pressure (mmHg)Ψ	0.999	0.999-1.000	0.0066
Urine nephrotic range (g/l)Ψ	0.966	0.942-0.990	0.0053
Urinalysis: Urine overt proteinuria	0.985	0.969-1.001	0.0754
Urinalysis: Urine trace proteinuria	0.983	0.964-1.002	0.0873
Urinalysis: Reference negative proteinuria	1.0		

Ψp value < 0.05.

The overall median eGFR slope was -0.0027 (IQR -0.158 - 0.602) (Table 1). When generalized linear regression models were applied for the decline in eGFR slope, an odds ratio of 1.052 (95% CI: 1.006-1.100) was calculated for a TSH level greater than 5 µIU/l (Q2), after adjusting for systolic blood pressure, proteinuria, and baseline eGFR (Table 3A and Table 3B). Absolute hemoglobin A1c was not included due to not being an a priori objective.

The overall median urine albumin/creatinine ratio was 10.2 mg/mmol (IQR 0.24-1414) (Table 4). When the 75th percentile for urine ACR ratio was assessed in a

Table 4: Patient characteristics by urine albumin/creatinine ratio.

Demographics	**Urine Albumin/Creatinine Ratio Less Than or Equal 64 mg/mmol N = 230**	**Urine Albumin/Creatinine Ratio Greater Than 64 mg/mmol N = 64**
Age (years)	73 (IQR 29-99)	72 (IQR 31-92)
Gender male	56.6% (138)	64.7% (44)
Race		
Caucasian	59.4%	57.4%
Arab	10.7%	14.7%
Asian	15.6%	19.2%
Black	6.7%	4.4%
European	5.3%	4.4%
South American	2%	0%
Height (meters)	1.68 (IQR 1.03-2.0)	1.68 (IQR 1.6-1.9)
Weight (kilograms)	77.3 (IQR 34-150)	83 (IQR 50.9-125)
Bmi (kilograms/meters squared)	27.7 (IQR 15.8-93.2)	28.3 (IQR 20.3-48.8)
Comorbidities		
Diabetes Mellitus$^{\Psi}$	38.5(94)	60.3(41)
Dementia	1.6(4)	4.4(3)
Pacemaker	7(17)	3(2)
Gout	13.5(33)	17.7(12)
GERD	11.5(28)	4.4(3)
Atrial fibrillation	13.9(34)	7.4(5)
Peripheral Vascular disease	11.9(29)	10.3(7)
Cerebrovascular disease	9.8(24)	10.3(7)
Coronary artery disease	24.2(59)	32.4(22)
Congestive heart failure	12.3(30)	17.7(12)
Cancer	32.8(80)	23.5(16)
Liver disease	2.5(6)	1.5(1)
COPD	15.6(38)	20.6(14)
Deep venous thrombosis$^{\Psi}$	5.2(13)	0
Dyslipidemia	32.8(80)	41.2(28)
Hematuria	84.9(163)	92.2(47)
Proteinuria	44.9(68)	97.1(66)
hypothyroidism	13(32)	11.8(8)
Clinic		
Systolic blood pressure (mmHg)$^{\Psi}$	139 (IQR 88-239)	154.5 (IQR 106-200)
Diastolic blood pressure (mmHg)	75 (IQR 41-104)	72 (IQR 40-100)
Heart rate (beats/minute)	71 (IQR 49-123)	71.5 (IQR 50-103)
Laboratory		
Thyroid stimulating hormone (µIU/l)	1.78 (IQR 0.06-109.5)	2.03 (IQR 0.2-13.4)
eGFR ml/min/1.73 m^2	37 (IQR 10-93)	24 (IQR 9-82)
Serum creatinine (umol/L)$^{\Psi}$	139 (IQR 63-496)	210.5 (IQR 65-626)

Hemoglobin (g/l)Ψ	126 (IQR 77-172)	111.5 (IQR 76-171)
Serum sodium (mmol/l)	139 (IQR 130-145)	139 (IQR 133-145)
Serum potassium (mmol/l)Ψ	4.5 (IQR 2.6-5.6)	4.6 (IQR 3.5-6.2)
Serum bicarbonate (mmol/l)Ψ	26 (IQR 18-33)	24 (IQR 14-31)
Blood urea (mmol/l)Ψ	9.3 (IQR 2.9-32)	14.2 (IQR 4.6-42.8)
Serum albumin (g/l)Ψ	39 (IQR 19.5-47)	37 (IQR 23-44)
Serum uric acid (mmol/l)	389 (IQR 172-879)	406 (IQR 117-591)
Total cholesterol (mmol/l)	4.3 (IQR 2.06-7.33)	4.23 (IQR 1.92-8.63)
HDL (mmol/l)Ψ	1.16 (IQR 0.54-2.06)	1.04 (IQR 0.6-2.04)
LDL (mmol/l)	2.35 (IQR 0.56-5.55)	2.09 (IQR 0.72-5.85)
Serum calcium (mmol/l)	2.38 (IQR 2.1-2.76)	2.38 (IQR 1.19-2.65)
Ionized calcium(mmol/l)	1.26 (IQR 1.13-1.54)	1.27 (IQR 1.17-1.3)
Serum phosphate (mmol/l)Ψ	1.18 (IQR 0.63-1.73)	1.34 (IQR 0.9-1.88)
C reactive protein (mg/l)	4 (IQR 2.03-293)	6.0 (IQR 4-36.5)
Ferritin (µg/l)	69 (IQR 2.22-924)	84 (IQR 9-1022)
HbA1c (percent)Ψ	5.7 (IQR 5-11.3)	6.3 (IQR 4.6-14.7)
Absolute HbA1c (percent)	7.3 (4.1-15.1)	7.3 (4.1-14.4)
Urine Albumin/creatinine (mg/mmol)Ψ	5.2 (IQR 0.17-55.7)	162.5 (IQR 64.2-1414)
eGFR slope (ml/min/1.73 m^3/day)Ψ	-0.0015 (IQR -1.577-0.602)	-0.010 (IQR -0.149 to 204)
Radiology		
Right Kidney cm	9.9 (IQR 3.2-24)	10 (IQR 6.4-27.5)
Left Kidney cm	10 (IQR 5.6-23)	9.8 (IQR 5-28.2)
Average Kidney cm	9.8 (IQR 4.8-23.5)	9.9 (IQR 7.4-27.9)
Total kidney volume (ml^3)	255.1 (IQR 66-1707)	275.6 (IQR 112.7-3765.5)

Ψp value < 0.05.

Table 5A: Unadjusted odds ratio for Urine albumin/creatinine ratio.

Variable	Odds ratio	95% CI	P value
TSH > 1.8 µIU/l	1.619	0.935-2.801	0.0851
History of diabetesΨ	2.421	1.398-4.201	0.0016
Body mass index (kg/m^2)	1.003	0.964-1.042	0.8915
Chronic kidney disease categories			
eGFR < 30 ml/minΨ			
eGFR 30-60 ml/min	8.654	1.975-37.926	< 0.0001
eGFR > 60 ml/min	2.316	0.515-10.415	0.5902
reference group	1		

Ψ p value < 0.05.

multivariate logistic regression model, the TSH greater than 1.8 µIU/l (50th percentile) had an odds ratio of 1.803 (95% CI: 0.986-3.296), after adjusting for diabetes mellitus history, body mass index and chronic kidney disease grade at baseline presentation (Table 5A and Table 5B).

Discussion

It has been reported that the prevalence of hypothyroidism in CKD has ranged between 3 and 25% [2]. Our study findings show a similar progressive increase in the prevalence of hypothyroidism with worsening eGFR grades from 9.4% to 17.4%. Both the studies of Kalantar-Zadeh, et al. and Lo JC, Chertow GM, Go AS, et al. confirmed an increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease [7,8]. Their findings were again indicative of the progressive increase in the prevalence of hypothyroidism with the increasing CKD Grades [8].

Treatment for hypothyroidism resulted in a slower decline in renal function than untreated hypothyroidism [9]. Lower T3 levels in the renal transplant literature have shown to be linked with faster renal transplant graft loss [10]. Our study shows similar results but because of a small effect size, it marks an association of 5% increase in odds ratio of elevated TSH levels with a negative eGFR slope.

Table 5B: Multivariate adjusted model for urine albumin/creatinine ratio.

Variable	Odds ratio	95% CI	P value
TSH > 1.8 μIU/l^{Y}	1.803	0.986-3.296	0.0555
History of diabetes^{Ψ}	2.422	1.217-4.132	0.0096
Body mass index (kg/m^2)	1.004	0.960-1.050	0.8768
Chronic kidney disease categories			
eGFR < 30 ml/min^{Ψ}			
eGFR 30-60 ml/min	6.883	1.572-31.027	0.0004
eGFR > 60 ml/min	2.031	0.442-9.325	0.5724
reference group	1		

^{Ψ}p value < 0.05; ^{Y}p value < 0.1

Proteinuria has been reported with both hyperthyroidism and hypothyroidism. Hyperthyroidism is associated with tubulointerstitial disease [3]. Immune complex renal disease and minimal change disease have also been reported in Hashimoto thyroiditis [3]. Nephrotic syndrome can cause thyroxine binding protein loss such as thyroglobulin binding protein, then can lead to higher TSH levels and subclinical hypothyroidism [11].

Hypothyroidism has multiple effects on renal tubules. It is linked to a decrease activity of the renin-angiotensin II - aldosterone axis, the proximal tubule Na/Phosphate pump, the Na - hydrogen pump and the sodium potassium ATPase pump [3]. The increased levels of ADH are noted in hypothyroidism, resulting in hyponatremia. Low thyroxine levels have been reported to decrease cardiac output and decreased renal blood flow which in turn lowers GFR [3]. Conversely, hyperthyroidism increases cardiac output, increases renal blood flow and results in renal hyperfiltration [3].

Another possible biological explanation for worsening renal function with hypothyroidism could be due to hypercalciuria and nephrocalcinosis. In both humans and animal models, there is a documented relationship with elevated TSH and hyperparathyroidism, resulting in hypercalcemia that can develop ultimately nephrocalcinosis [12].

The limitations of the study include retrospective bias, as well as the selection bias of sampling one nephrologist clinical practice. The study, like retrospective cohorts, is unable to account for all unperceived confounding factors. The results are limited in significance because of the relatively small sample size. Given the smaller effect size of TSH levels associated with eGFR slope, the results are limited in significance due to a relatively small sample size. The tetraiodothyronine (T4) levels were not available for all subjects, because the institution did not include this thyroid function test.

Conclusions

In clinical practice, the thyroid tests for prognosis and/or renal function stabilization should be considered in the management chronic kidney disease. Further studies are needed to determine whether treatment of hypothyroidism reverses the progression of chronic kidney disease and improves the albuminuria.

Declarations

- Ethics Approval obtained from the St. Mary's Hospital Research Ethics Board SMHC-20-03 in accordance to the Helsinki declaration.
- For a retrospective, database study individual patient consent was not required.
- There are no competing interests.
- There was no formal funding.

Author Contributions

S Iqbal, C Scheede-Bergdahl and K Rafat Zand were involved in the conceptualization of the project, study design, and critical review of manuscript; S Iqbal and D Yang were key players for acquisition of data, and analysis and interpretation; S Iqbal wrote the main manuscript and prepared the tables; S Iqbal and D Barama critically reviewed the manuscript and completed the final approval.

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