Research Article

iMedPub Journals
http://www.imedpub.com

Journal of Nephrology and Urology

2021
Vol. 5 No.4: 20

The Role of Thyroid Stimulating Hormone in Nephrolithiasis Associated with Chronic Kidney Disease

Sameena Iqbal[1*], Sero Andonian[1], Davine Yang[2], Celena Scheede-Bergdahl[2] and Khashayar Rafat Z[1]

[1]Department of Medicine, McGill University, CUISSS West Island, Pointe Claire, QC, Canada
[2]Department of Kinesiology, McGill University, CUISSS West Island, Pointe Claire, QC, Canada

***Corresponding author:** Sameena Iqbal, Department of Medicine, McGill University, CUISSS West Island, Pointe Claire, QC, Canada, E-mail: sameena.iqbal@mcgill.ca

Citation: Iqbal S, Andonian S, Yang D, Bergdahl SC, Rafat ZK, et al. (2021) The Role of Thyroid Stimulating Hormone in Nephrolithiasis Associated with Chronic Kidney Disease. J Nephrol Urol Vol.5 No.4:20.

Abstract

Introduction: The prevalence of nephrolithiasis in Chronic Kidney Disease (CKD) is 5%-10%. To better understand the relationship between thyroid function and nephrolithiasis in the CKD population, we conducted a retrospective study with the main objective to identify the prevalence of nephrolithiasis in CKD and explore the relationship between TSH hormone level and nephrolithiasis.

Methods: A retrospective cohort study was conducted in a community nephrology clinic in Quebec, Canada that included clinical and demographic data collection in an electronic format. The clinical information collected was from April 1, 2015 until December 30, 2019. The outcome of interest was the prevalence of nephrolithiasis, and the exposure variable of TSH level greater than 2.22 µIU/l was analysed by applying unconditional and adjusted generalized linear and logistic regression models.

Findings: The 310 charts were reviewed. The subjects had a median age of 73 years (IQR (interquartile range) 29-99), 58.3% was male, 12.8% had a diagnosis of hypothyroidism and a diagnosis of diabetes mellitus was made in 43.3%. The overall prevalence of nephrolithiasis 10.2% and was 9.4%, 14%, 6%, and 4.4% within the CKD groups combined, Grade 1 and 2,3,4 and 5 respectively. When certain generalized linear regression models were applied, an adjusted odds ratio of 2.38 (CI 95%: 1.08-5.27) was calculated for a TSH level>2.22 µIU/L (Q2), for the presence of nephrolithiasis on baseline CT scan of the abdomen.

Discussion: Our study shows a significant prevalence of nephrolithiasis in CKD, with a higher proportion of kidney stones in the early stages of the renal disease. TSH levels above 2 uIU/L have more than a two-fold higher risk of forming kidney stones. Further studies that address the target thyroxine level to resolve kidney stone formation will be important.

Keywords: Nephrolithiasis; Chronic kidney disease; Thyroid stimulating hormone

Received: October 01, 2021; **Accepted:** October 15, 2021; **Published:** October 22, 2021

Introduction

Among Canadians with the Chronic Kidney Disease (CKD) population that make up 10%-12.5% of the population, the rates of asymptomatic nephrolithiasis are unknown [1]. In the general population, one study showed that 8.6% had asymptomatic kidney stones in the retrospective cohort of 1353 studies using radiological data [2]. In the community, the formation of nephrolithiasis is a result of urinary supersaturation of elements such as calcium, phosphate, oxalate, uric acid or cysteine [3]. Certain dietary components, such as reduced fluid and calcium intake, increased intake of carbohydrates, and excessive sodium and protein in the daily consumption, augment the risk of nephrolithiasis development and recurrence [4]. Higher body index and decreased physical activity are also been documented as risk factors for nephrolithiasis [3]. Hypothyroidism is related to insulin resistance, and to hyperuricemia [5]. The relationship of hypothyroidism to nephrolithiasis is not well described.

The aims of the present study were

- To determine the prevalence of asymptomatic nephrolithiasis in patients attending chronic kidney disease clinic.
- To compare thyroid stimulating hormone levels to presence of nephrolithiasis on radiological examination.

Materials and Methods

The study protocol was granted research ethics approval from the St. Mary's Hospital Research Ethics Board, meeting the criteria for Helsinki declaration. We conducted a retrospective study

utilizing a cohort of individuals followed at a nephrology clinic of a community hospital in Quebec. From over 1000 clinic charts, a random sample of 333 patients from the nephrology clinic of a community hospital was identified by the nephrology team and all data was collected and entered into an electronic system. Those subjects who met the inclusion criteria were 310. The subjects were entered in an electronic database which collected data from the following data sources laboratory data from Reflections database, clinical examination, medication list and demographical data from clinic charts, and radiological data from web-based PACs (Picture Archiving and Communication Systems) database. The period of collection was from April 1, 2015 until December 30, 2019.

The inclusion criteria were age ≥ 18 years, diagnosis of CKD as described with three consecutive eGFR readings of less than or equal to 90 ml/min/1.73 m^2 and life expectancy of greater than 6 months. Six hundred and ten individuals were excluded if they were noted to have acute kidney injury, expected to require renal replacement therapy within 3 months, or moved to another health care facility. Cohort entry was defined as the date the individual met the diagnostic criteria of CKD.

The variables collected at cohort entry were as follows: age (at baseline assessment), gender (male or female), race (Caucasian, Arab, Asian, Black, Europe, South American), diabetes mellitus status (yes) cause of renal disease as documented in the chart, comorbidities (coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, hypertension, pacemaker, chronic obstructive pulmonary disease, sleep apnea, cirrhosis, autoimmune disease, cancer history, deep venous thrombosis, dyslipidemia, dementia, hypothyroidism, gastroesophageal reflux, gout, and atrial fibrillation), height (m^2, weight (kg), blood pressure (mmHg), baseline eGFR (ml/min/1.73 m^2), baseline CKD grade, hemoglobin (mg/L), sodium (mmol/L), potassium (mmol/L), calcium (mmol/L), phosphate (mmol/L), TSH µIU/L, hemoglobin A1c (%), proteinuria (mg/L) and uric acid umol/L).

Sample size calculation

For calculation of sample size using logistic regression for presence of stone, the assumption of 5% proportion of individuals with TSH level above 2.22 IU/L compared to 10% of those with TSH level above 2.22 IU/L in the effect size of 0.5 and power of 90% and alpha error of 0.05, sample size required is 263.

Outcomes

The prevalence of asymptomatic nephrolithiasis by radiological report was calculated in the overall population and by CKD grades. The TSH levels were categorized by greater than 60th percentile (Q2) as well. Nephrolithiasis was defined as stone reported in the urinary tract on the first CT Scan of the abdomen after the first visit at the nephrologist office.

Statistical analyses

All prevalence data was estimated as a percentage with 95% confidence intervals using binomial proportions. Continuous variables were summarized as medians, ranges, means and standard deviations. The effect size and statistical significance for TSH level percentiles was explored for 10th, 25th, 33rd, 50th, 55th, 60th, 66th, 75th, 95th percentiles. Due to the largest effect size and statistical significance, the relationships between TSH level by 60th percentile and nephrolithiasis were utilized by applying unconditional and adjusted generalized linear regression and logistic regression models, respectively. Variables found statistically significant in the bivariate analyses were included in the final logistic regression models.

Results

The 310 subjects had a median age of 73 (IQR 29-99) years, male gender 58.3% (182/312), 12.8% had a diagnosis of hypothyroidism (40/312) and a diagnosis of diabetes mellitus was made in 43.3% (135/312) (**Table 1**). Their baseline eGFR was 34 ml/min/1.73 m^2 (IQR 9-93). The follow up period was 24.4 (IQR 0.93-103.5) months (**Table 1**). When the subjects were divided into chronic kidney disease 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 decrease in proportion of nephrolithiasis prevalence (**Figure 1**). The overall prevalence of nephrolithiasis 10.2% and was 9.4%, 14%, 6%, and 4.4% within the CKD groups combined, Grade 1 and 2, Grade 3, Grade 4 and Grade 5, respectively.

Table 1: Overall, patient demographics, comorbidities, clinic visit, laboratory, and radiological data for study population.

Demographics	Number of subjects	Median/ Proportion	IQR/ratio
Age	310	73	29-99
Gender: Male	310	58.1%	180
Height	297	1.68 meters	0.91-1.7
Weight	299	78.4 kg	34-150
BMI	294	27.8	16.8-48.8
Race Caucasian other	310	40.6%	184 126
Comorbidities			
Haemoglobin <100 g/l	310	15.5%	48
Diabetes mellitus	310	43.2%	134
Dementia	310	2.3%	7
Pacemaker	310	6.1%	19
Gout	310	14.2%	44
GERD	310	10%	31
Atrial fibrillation	310	12.3%	38
Peripheral vascular disease	310	11.3%	35
Coronary artery disease	310	26%	80
Congestive heart failure	310	13.5%	42
Cancer	310	31%	95
Liver disease	310	2.3%	7
COPD	310	16.8%	52

Deep venous thrombosis	310	4.2%	13
Dyslipidemia	310	34.5%	107
Hematuria (microscopic)	296	32.4%	96
Proteinuria	296	45%	148
Hypothyroidism	310	12.9%	40
History of kidney stone	310	15.8%	49
Urological intervention	310	0	0-9
Clinic variable			
Systolic blood pressure	304	141	88-239
Diastolic blood pressure	304	75	40-104
Heart rate	305	71	49-123
Medication			
Levothyroxine	39	88	0-225
Laboratory			
Thyroid stimulating hormone	211	1.85	0.06-109.5
Baseline eGFR ml/min/1.73 m^2	312	34	9-93
CKD grade 2	32	10.3%	
CKD grade 3	157	50.0%	
CKD grade 4	100	32.3%	
CKD grade 5	23	7.4%	
Serum creatinine	312	147	63-626
Parathyroid hormone	227	9.1	1.4-107.4
Vitamin D 25 OH	175	83	5-362
Vitamin D 1-25 OH	120	90	18-278
Haemoglobin	305	123	76-172
Serum sodium	304	139	132-145
Serum potassium	304	4.5	2.6-6.2
Serum bicarbonate	263	26	14-33
Blood urea	278	10.4	2.9-42.8
Serum albumin	293	39	19.5-47
Serum uric acid	287	393	117-879
Total cholesterol	267	4.3	1.92-8.63
HDL	262	1.14	0.54-2.64
LDL	262	2.3	0.71-5.85
Serum calcium	216	2.38	1.19-2.76
Ionized calcium	78	1.3	1.13-1.39
Serum phosphate	290	1.2	0.63-2.26
C reactive protein	239	5.5	2.03-293
Ferritin	277	72	2.22-1022
Hb A1c	273	5.8	4.8-11.3
Urine albumin/ creatinine	269	10.2	0.17-1414

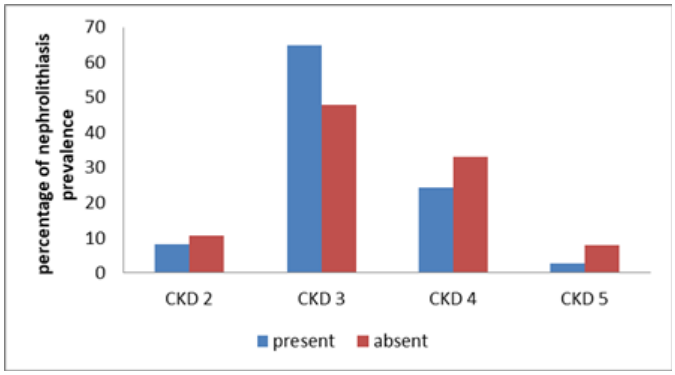

Figure 1: Asymptomatic nephrolithiasis prevalence in percentage by CKD Grade, n=310, p value>0.05.

Table 2: Patient demographics, comorbidities, clinic visit, laboratory and radiological data for study population categorized by nephrolithiasis status n=310.

		Nephrolithiasis		Absence of nephrolithiasis		P value
Demographics	**Number of subjects**	**Median/ Proportion**	**IQR/ratio**	**Median/ proportion**	**IQR/ratio**	
Age (years)	310	74	42-88	73	29-99	0.7671
Gender: Male	310	73%	27/37	56%	153/280	0.0502
Height (meters)	297	1.68	1.52-1.85	1.67	0.91-1.7	0.5829
Weight	299	75	50.9-108.4	78.7	34.02-150	0.6987
BMI	294	28.3	20.3-38.7	27.8	16.8-48.8	0.7369
Race Caucasian other	310	32.4	25/37	58.2 41.8	159/276	0.4002
Comorbidities						
Hemoglobin<100 g/l	310	8.11	3/37	16.5	45/273	0.2317
Diabetes mellitus	310	46	17/37	42.9	117/273	0.7219
Dementia	310	0		2.6%	7/273	1.0000
Pacemaker	310	2.7%	1/37	6.6	18/273	0.3545
Gout	310	18.9%	5/37	13.6%	40/273	0.3801
GERD	310	8.1%	3/37	10.3	28/273	1.0000

Atrial fibrillation	310	10.8	4/37	12.5	34/273	0.7748
Peripheral Vascular disease	310	5.4	2/37	12.1	33/273	0.4026
Coronary artery disease	310	21.6%	8/37	26.4%	72/273	0.5353
Congestive heart failure	310	5.6%	2/37	14.5%	40/276	0.1395
Cancer	310	34%	12/37	30.4%	83/273	0.8016
Liver disease	310	0		2.7%	7/273	1.0000
COPD	310	16.2%	6/37	16.9	46/273	0.9229
Deep venous thrombosis	310	8.3	3/37	3.7	10/273	0.1930
Dyslipidaemia	310	48.7%	18/37	32.6	89/273	0.0540
Haematuria	310	32.4%	15/37	30.5	79/182	0.1529
Proteinuria	310	40.5%	15/37	46	119/273	0.0819
Hypothyroidism	310	10.8%	3/37	13.21%	37/273	0.6858
History of Stone^	310	100%	37/37	4.4%	12/273	<0.0001
Urological intervention*	310	0	0-9	0	0	<0.0001
Clinic variable						
Systolic blood pressure	306	140	92-191	141	88-239	0.8928
Diastolic blood pressure	306	74	54-100	75	40-104	0.8865
Heart rate	307	72	52-102	71	49-123	0.6587
Medication						
Levothyroxine	39	50	50-112	50	0-225	0.3603
Laboratory						
Thyroid stimulating hormone	211	2.3	0.65-6.56	1.82	0.06-109.5	0.3768
TSH hormone greater than 2.22 IU/L*	310	40.5%	15/36	24.9%	68/276	0.0439
Baseline eGFR ml/ min/1.73 m^2	310	37	13-86	34	9-93	0.1317
Serum creatinine	310	139	81-319	148	63-626	0.2517
Parathyroid hormone*	227	5.6	1.4-37.7	9.4	1.4-107.4	0.0026
Vitamin D 25 OH	175	77	27-149	83.5	5-362	0.4843
Vitamin D 1-25 OH	120	92	39-278	90	18-254	0.6842
Haemoglobin	307	123	96-160	123	76-172	0.3918
Serum sodium	306	139	132-148	139	130-145	0.9880
Serum potassium	306	4.4	3.8-5.8	4.5	2.6-6.2	0.2179
Serum bicarbonate	265	26	20-30	26	14-33	0.4173
Blood urea	280	9.2	4.6-26	10.7	2.9-42.8	0.0623
Serum albumin	295	39	28-44	39	19.5-47	0.4783
Serum uric acid	289	373	172-604	397	117-879	0.0779
Total cholesterol*	269	4.0	2.35-6.24	4.4	1.92-8.63	0.0261
HDL	264	1.11	0.6-1.98	1.15	0.54-2.64	0.1040
LDL*	264	2.06	0.56-3.48	2.36	0.72-5.85	0.0136
Serum calcium	218	2.38	2.1-2.63	2.38	1.19-2.76	0.9800
Ionized calcium	78	1.25	1.21-1.29	1.27	1.13-1.39	0.4353
Serum phosphate*	291	1.105	0.69-1.59	1.23	0.63-2.26	0.0004
C reactive protein	241	4	4-72.2	5.6	2.03-293	0.2614
Ferritin	279	61	9-486	73	2.22-1022	0.5127
HbA1c	275	5.8	4.4-9.6	5.8	4.8-11.3	0.7584
Urine albumin/ creatinine	270	61	0.41-681	12.5	0.17-1414	0.1453
Note:*p value<0.05						

On the bivariate analysis, there was a tendency toward statistical difference in both decreased LDL cholesterol, presence of haematuria and higher serum phosphate level and parathyroid hormone level of greater than 17.1 pmol/l that was associated with nephrolithiasis presence on the report (**Table 2**). There was statistically significant difference on the serum phosphate and urine albumin/creatinine ratio on the identification of nephrolithiasis on the radiological results (**Table 2**).

The 60th percentile for TSH level was 2.22 uIU/L. TSH greater than 2.22 uIU/l had an unadjusted odds ratio of 2.06 (CI 95%: 1.01-4.19) and an adjusted odds ratio of 2.38 (CI 95%: 1.08-5.27) for nephrolithiasis on the CT scan of the abdomen or ultrasound at baseline assessment (**Table 3**).

Table 3: Unadjusted and adjusted logistic regression models for TSH level greater than 2.22 IU/L and nephrolithiasis N=277.

Variable	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	P value
TSH>2.22 uIU/l	2.06 (1.01-4.19)	2.38 (1.08-5.27)	0.0324
TSH ≤ 2.22 uIU/l (reference)	1.0		
Age (years)	1.01 (0.98-1.04)	1.01 (0.98-1.04)	0.5807
Parathyroid hormone>17.1 pmol/l	0.71 (0.24-2.12)	0.94 (0.27-3.26)	0.9194
eGFR at baseline	1.014 (0.994-1.034)	1.004 (0.98-1.03)	0.7564
Serum phosphate	0.04 (0.01-0.29)	0.04 (0.004-0.35)	0.0040
Serum uric acid	0.996 (0.993-1.000)	1.00 (0.99-1.00)	0.0706
Gender female	0.47 (0.22-1.01)	0.69 (0.29-1.62)	0.3958

The multivariate logistic regression model was adjusted for baseline eGFR, age, serum phosphate, parathyroid hormone above 17.1 pmol/l and serum uric acid (**Table 3**).

Discussion

Interestingly, the prevalence of asymptomatic nephrolithiasis in CKD is similar to the symptomatic nephrolithiasis in the general population. As the CKD Grade at clinic presentation increased in severity, the prevalence of asymptomatic stone disease decreased. One plausible explanation is decreased eGFR to leads less filtration of elements such as calcium, phosphate, uric acid, and oxalate that result in decrease supersaturation of urine. Another is healthier individuals eat and maintain muscle mass, whereas those who develop malnutrition have decreased appetite and poor intake of the above stone forming elements. It is well-recognized in the literature that nephrolithiasis results in kidney scarring and decreased renal function [6].

Hypothyroidism is associated with hyperparathyroidism, and radiation exposure is considered as one possible cause [7]. Another possibility is the low vitamin D 25 hydroxyl levels that have been reported in subclinical hypothyroidism that can facilitate the development of secondary hyperparathyroidism and hypercalcaemia [8]. Vitamin D supplementation improves the TSH levels. TSH levels are increased in individuals with insulin resistance, the mechanism is unclear. TSH has been shown to stimulate the Glucose transporter 2 of ß2 cells of pancreas that further promotes the secretion of insulin [9]. Hyperinsulinemia is also associated with clinically significant hypercalcaemia with a theory of diminished resorption of calcium from the proximal renal tubule, postprandial. With the relationship of obesity and diabetes, hypothyroidism is associated with hyperuricemia and uric acid stones. Decreased renal perfusion resulting in decreased glomerular filtration rate seen in hypothyroidism is postulated to be due to the thyroxine deficient state resulting in a bradycardic effect on the sinus node and ultimately lowering the cardiac output. Another potential mechanism for TSH to affect stone formation is the effect it may have to the calcium sensitive receptors on the ureters that control ureteric peristalsis [10].

Conclusion

The limitations of the study include the method of diagnosis was radiologist dependent with one reader observation. The retrospective nature of the study in a specialized nephrology clinic for CKD will represent a higher proportion of nephrolithiasis. The small sample size and cross-sectional design only allows identification of an association between TSH levels and nephrolithiasis not a definite causal relationship.

Further studies are required to re-evaluate the target TSH level and treatment goals for hypothyroidism in renal disease.

Disclosures

None

Funding

None

Acknowledgments

None

References

1. Arora P, Vasa P, Brenner D, Iglar K, McFarlane P, et al. (2013) Prevalence estimates of chronic kidney disease in Canada: results of a nationally representative survey. Can Med Assoc J 185: E417-E423
2. Bansal DA, Hui J, Goldfarb SD (2009) Asymptomatic nephrolithiasis detected by ultrasound. Clin J Am Soc Nephrol 4: 680-684
3. Bao Y, Tu X, Wei Q (2020) Water for preventing urinary stones. Cochrane Database Syst Rev. 11: CD004292
4. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ, et al. (1997) Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med 126: 497-504
5. Aune D, Mahamat-Saleh Y, Norat T, Riboli E (2018) Body fatness, diabetes, physical activity and risk of kidney stones: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol 11: 1033-1047

6. D'Costa M, Savcic-Kos R, Huang J, Rule AD, Murali N, et al. (2016) Urological procedures in urolithiasis and their association with chronic kidney disease. Clin Med Res 14: 75-82

7. Ahi S, Dehdar MR, Hatami N (2020) Vitamin D deficiency in non-autoimmune hypothyroidism: A case-control study. BMC Endocr Disord. 20: 41

8. Talaei A, Ghorbani F, Asemi Z (2018) The Effects of vitamin D supplementation on thyroid function in hypothyroid patients: A randomized, double-blind, placebo-controlled trial. Indian J Endocrinol Metab 22: 584-588

9. Cortizo AM, Chazenbalk GD, Gagliardino de EE, Garcia ME, Pisarev MA, et al. (1987) Thyroid hormone binding and deiodination by pancreatic islets: relationship with the in vitro effect upon insulin secretion. Acta Endocrinol 116: 66-72

10. Burdyga T, Lang RJ (2019) Excitation-contraction coupling in ureteric smooth muscle: mechanisms driving ureteric peristalsis. Adv Exp Med Biol 1124: 103-119