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Subclinical Hypothyroidism as a Risk Factor for Vascular Calcification in ESRD Patients

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Abstract
Background: Subclinical hypothyroidism (SCH) is defined as the absence of symptoms accompanied by an increase in thyroid-stimulating hormone (TSH) levels and normal free T3 and free T4 levels. End-stage renal disease (ESRD) is the last stage of chronic kidney disease (stage 5), characterized by an irreversible, gradual loss of renal function. Vascular calcification is the abnormal and pathological deposition of calcium salts inside vascular tissues.
Aim and objectives: To evaluate how vascular calcifications in ESRD patients are affected by SCH and study the relationship between them.
Subjects and methods: In this cross-sectional study, 100 patients were enrolled and diagnosed by ESRD patients on regular hemodialysis. All the included patients were subjected to investigate Thyroid stimulating hormone (TSH), carotid artery atherosclerosis, arterial stiffness, and vascular calcification at Aswan University Hospital, Internal Medicine Department, Faculty of Medicine.
Results: Carotid and its Correlates (age, SCH, PTH, TSH, T3, and T4) and the independent effect of SCH on carotid calcification (CAAC) differed significantly among the examined population (PTH, TSH, and SCH).
There was an insignificant difference between the studied population regarding Carotid and its Correlates (sex, DM, and PH) and the independent effect of SCH on CAAC (age, sex, T3, and T4).
Conclusion: With high sensitivity and specificity, SCH is a risk factor for vascular calcification in ESRD patients.
Key Words: Subclinical Hypothyroidism, Vascular Calcification, ESRD

Introduction

Chronic kidney disease (CKD) is characterized by structural or functional renal problems that have persisted for more than three months in the context of a glomerular filtration rate of less than 60 mL/min and a urine albumin concentration of greater than 30 mg per gramme of creatinine **(1)**.
End-stage renal disease (ESRD): is the final stage of chronic kidney disease (stage 5) marked by irreversible progressive deterioration in renal function in which the body fails to maintain the normal metabolic state and fluid and electrolyte balance, resulting in uremia or azotemia and necessitating dialysis or renal transplantation for survival **(2)**.

Vascular calcification is the improper and harmful deposition of calcium salts inside the vascular tissues. This can occur with normal aging but increases with diabetes mellitus, certain hereditary diseases, and CKD. One of the most prevalent causes of vascular calcification is CKD **(3)**. This unneeded calcification of the arterial wall will raise vessel stiffness, and lead to increased pulse pressure, left ventricular hypertrophy, and several cardiovascular diseases **(4)**.

Intima and media of the artery wall are susceptible to vascular calcification. Endothelial tissues. In the intimal layer of the artery, endothelial cells are surrounded by elastic fibers. Calcification of the intima is linked to dyslipidemia and, together with inflammation and intimal layer thickness, leads to the development of atherosclerosis. This process forms unstable, rupture-prone plaques on the inner vessel wall. Additionally, they may result in thrombus formation and occlusive disease. Additionally, they may result in thrombus formation and occlusive disease. The media layer is composed of smooth muscle cells in a framework of loose connective tissue, and calcification in this layer is frequently caused by diabetes or CKD. This is known as medial calcification and occurs in the absence of luminal constriction **(5)**.

In patients with ESRD, abnormal serum phosphate, calcium-phosphate ion product, and parathyroid hormone levels are independent risk factors for cardiovascular disease. Aortic stiffness is an independent predictor of total and cardiovascular mortality, coronary artery disease, and fatal stroke in hypertensive patients. **(6)**.

The clinical manifestations of hypothyroidism are overt or subclinical. Subclinical hypothyroidism (SCH) is described as the absence of symptoms accompanied by a rise in thyroid-stimulating hormone (TSH) levels and normal free T3 and free T4 levels **(7)**.

The association between SCH and cardiovascular disease in adults may be mediated by elevated cholesterol levels, inflammatory markers, increased oxidative stress, insulin resistance, elevated systemic vascular resistance, arterial stiffness, altered endothelial function, and activation of thrombosis and hypercoagulability **(8)**.

The work aimed to assess how vascular calcifications in ESRD patients affected by SCH and study the relationship between them.

Patients and Methods

In this cross-sectional study, 100 patients were enrolled and diagnosed by ESRD patients on regular hemodialysis. All the included patients were subjected to investigate TSH, carotid artery atherosclerosis, arterial stiffness, and vascular calcification at Aswan University Hospital, Department of Internal Medicine, Faculty of Medicine.

Inclusion Criteria

Age: > 16 years old, Sex: males and females and Patients with DM

Exclusion Criteria

Patients with DM, Patients with secondary hyperparathyroidism, Patients on antithyroid medications, Patients with Hyperphosphatemia, and Patients with chron.

Methods

Every participant in the study underwent a complete medical history, a clinical examination, and laboratory tests.

Informed consent

A participant's informed consent form was a permanent part of their study records and was maintained similarly to other documents.

Statistical analysis

Data were analyzed using SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA) *. Descriptive statistics: Means, standard deviations, medians, ranges, frequency, and percentages were calculated. The normality of continuous variables was tested using Kolmogorov–Smirnov test/Shapiro–Wilk test as appropriate. The Chi-square/Fisher's exact test was used to compare distribution differences of frequencies among groups. The Student t-test/Mann Whitney U was used to compare the means/medians of dichotomous data. The clinical and demographic factors with proven statistical significance from the univariate analyses were further included in the multivariable logistic regression models. Analyzed as area under the curve (AUC), standard error (SE), and 95% confidence interval (CI), the diagnostic performance of ceramide level for prediction of unfavorable cardiac outcome was depicted as a ROC curve, with AUC, SE, and 95% CI. It was determined the validity statistics (sensitivity, specificity, positive and negative predictive value –PPV & NPV-). p values 0.05 are regarded as significant.

Results

Table 1: Baseline Characteristics of the Studied Cohort

Parameters	Category	n = 91
Age/years	**Mean ± SD**	46.21 ± 11.1
	Median (Range)	46 (26 – 66)
Sex	**Female**	42 (46.2%)
	Male	49 (53.8%)
DM	**Yes**	5 (5.5%)
	No	86 (94.5%)

This table showed that demographic data of ESRD patients on regular hemodialysis with mean age 46.21 ± 11.1 years, ranging from 26 years to 66 years, sex varied among male and female, 49 patients 53.8% were males and 42 patients 46.2% were female, DM was detected in 5.5% of patients as represented in **Table (1)**.

Table 2: Laboratory Findings of the Studied Cohort

Parameters	Category	n = 91
PH	**Mean ± SD**	3.86 ± 0.9
	Median (Range)	3.8 (1.5 – 5.8)
PTH (pg/ml)	**Mean ± SD**	122.88 ± 83.1
	Median (Range)	121 (8.7 – 300)
TSH (mIU/L)	**Mean ± SD**	3.06 ± 2.5
	Median (Range)	2.1 (0.3 – 11.4)
T3 (nmol/L)	**Mean ± SD**	3.02 ± 0.9
	Median (Range)	3 (0.9 – 6.5)
T4 (nmol/L)	**Mean ± SD**	9.95 ± 6.1
	Median (Range)	9 (0.5 – 27.6)

This table showed that laboratory findings; the mean PH 3.86 ± 0.9 ranging from 1.5 to 5.8 with median 3.8, the mean PTH 122.88 ± 83.1 pg/ml ranging from 8.7 to 300 pg/ml with median 121 pg/ml, the mean TSH 3.06 ± 2.5 mIU/L ranging from 0.3 to 11.4 mIU/L with median 121 mIU/L, the mean T3 3.02 ± 0.9 nmol/L ranging from 0.9 to 6.5 nmol/L with median 3 nmol/L and T4 9.95 ± 6.1 nmol/L ranging from 0.5 to 27.6 nmol/L with median 9 nmol/L as represented in **Table (2)**.

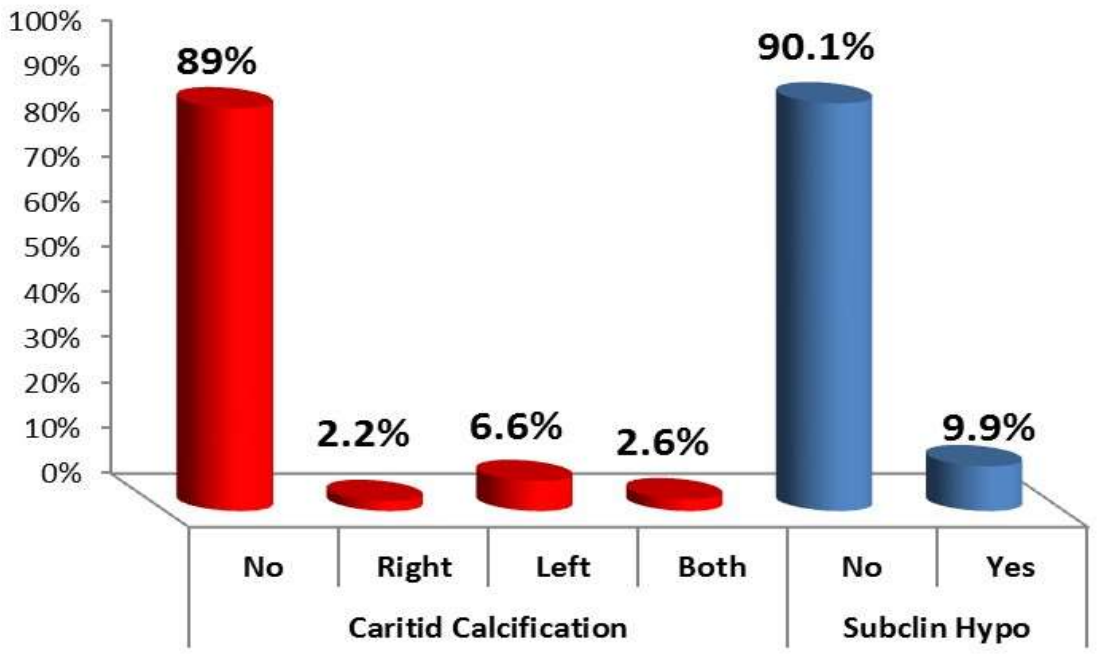

Figure (1): Outcome Data of the studied Cohort
This table showed that clinical findings; Carotid artery Calcification (CAAC) were categorized to (No) 80 patients 89% out of 91 patients, (right side) 2 patients 2.2% out of 91 patients, (left side) 6 patients 6.6.% out of 91 patients and both were represents 2 patients 2.2 % out of 91 patients. Aortic calcification represents 91 patients 100% and SCH represents (no) 82 patients 90.1% out of 91 patients and (yes) 9 patients 9.9% as represented in **Figure (1)**.

Table 3: Relationship between CAAC **and its Correlates (A)**

	Carotid Calcification		**P-value**
	No (n = 81)	**Yes (n = 10)**	
Age/years	45.56 ± 11.3	51.50 ± 7.2	**= 0.037***
Sex			
□ **Male**	43 (53.1%)	6 (60%)	= 0.472**
□ **Female**	38 (46.9%)	4 (40%)	
Subclinical Hypothyroidism			
□ **No**	80 (100%)	1 (10%)	**< 0.001*****
□ **Yes**	0 (0%)	9 (90%)	

DM			
□ **No**	76 (93.8%)	10 (100%)	= 0.551***
□ **Yes**	5 (6.2%)	0 (0%)	

This table showed that the mean age for (no = 81) was 46.21 ± 11.1 years and (yes = 10) 51.50 ± 7.2 years with p-value = 0.037*, sex for (no = 81) 43 (53.1%) males and 38 (46.9%) female and (yes = 10) 6 (60%) males and 4 (40%) female with p-value = 0.472*, the mean SCH for (no = 81) no 80 (100%) and yes 0 (0%) and (yes = 10) no 1 (10 %) and yes 9 (90%) with p-value < 0.001***, the mean DM for (no = 81) no 76 (93.8%) and yes 5 (6.2%) and (yes = 10) no 10 (100 %) and yes 0 (0%) (P= 0.551)***, **Table (3)**.

Table 4: Relationship between CAAC **and its Correlates (B)**

	Carotid Calcification		**P-value**
	No (n = 81)	**Yes (n = 10)**	
PH			
□ **Mean ± SD**	3.87 ± 0.9	3.79 ± 0.8	= 0.665*
□ **Median (Range)**	3.8 (1.5 – 5.8)	3.7 (2.8 - 5)	
PTH (pg/ml)			
□ **Mean ± SD**	118.57 ± 86.1	157.75 ± 42.9	**= 0.029****
□ **Median (Range)**	103 (8.7 – 300)	158 (77.5 - 220)	
TSH (mIU/L)			
□ **Mean ± SD**	2.46 ± 1.9	7.97 ± 0.7	**< 0.001****
□ **Median (Range)**	1.8 (3 – 11.5)	8 (7 - 9)	
T3 (nmol/L)			
□ **Mean ± SD**	3.10 ± 1.0	2.41 ± 0.8	**= 0.038****
□ **Median (Range)**	3 (1.1 – 6.5)	2.8 (0.9 - 3)	
T4 (nmol/L			

Mean ± SD	10.29 ± 6.4	7.25 ± 2.1	**= 0.021****
Median (Range)	10 (0.5 – 27.5)	7.5 (4 - 10)	

This table shows the relationship between carotid calcification and correlates B; the mean PH 3.86 ± 0.9 ranging from 1.5 to 5.8 with a median of 3.8 with (p-value = 0.665), the mean PTH 122.88 ± 83.1 pg/ml ranging from 8.7 to 300 pg/ml with median 121 pg/ml with (p-value = 0.029), the mean TSH 3.06 ± 2.5 mIU/L ranging from 0.3 to 11.4 mIU/L with median 121 mIU/L with (p-value < 0.001), the mean T3 3.02 ± 0.9 nmol/L ranging from 0.9 to 6.5 nmol/L with median 3 nmol/L with (p-value = 0.038) and T4 9.95 ± 6.1 nmol/L ranging from 0.5 to 27.6 nmol/L with median 9 nmol/L with (p-value = 0.021) **Table (4)**.

Table 5: Independent Effect of SCH **on** CAAC**: Multivariable Logistic Regression**

Predictor	**OR* (95% CI**)**	**P-value**
Age/years	1.065 (0.909 – 1.248)	= 0.433
Sex(Male)	0.741 (0.193 – 2.837)	= 0.661
PTH	1.023 (1.001 – 1.047)	**= 0.047**
TSH	3.887 (1.474 – 10.245)	**= 0.006**
T3	0.313 (0.015 – 6.456)	= 0.452
T4	1.165 (0.749 – 1.811)	= 0.498
Subclinical hypothyroidism	7.201 (4.139 – 12.542)	**< 0.001**

*OR=Odds Ratio **CI=Confidence Interval

SCH patients after adjusting for all correlates, had 7.2 times more probability of having CAAC (AOR=7.20, 95% CI: 4.14–12.54) and this was significant. For the other correlates; with one pg/ml increase in the level of PTH with a 2.3% increase in the risk of having CAAC (AOR=1.023, 95% CI: 1.001–1.047) and this was significant. Moreover; with one mIU/L increase in the level of TSH with a 3.9 times

increase in the liability of having CAAC (AOR=3.887, 95% CI: 1.474–10.245) and this was significant. **Table (5)**.

Table 6: Diagnostic criteria of SCH **for** CAAC **Prediction**

Diagnostic Criteria	Subclinical Hypothyroidism
AUC	**0.950**
95% CI	**0.841 - 1.000**
SE**	**0.056**
P-value***	**< 0.001**
Accuracy	**98.8%**
Sensitivity%	**90%**
Specificity%	**100%**
PPV%	**100%**
NPV%	**98.7%**

The diagnostic performance criteria of SCH for the prediction of CAAC are illustrated in Table 7 and Figure 15. The findings showed that AUC was excellent (0.950; 95% CI: 0.841 - 1.000, p=0.001). Moreover, the accuracy was 98.8% (which means the ability of the test to diagnose accurately cases and controls), sensitivity which means the ability of the test to pick up true positives among all patients was (90%), specificity; which means the ability of detect negative results among all control was (100%). Also, PPV was 100% and NPV was (98.7%) as represented in **Table (6)**.

Discussion

This cross-sectional study was performed on 91 ESRD patients on regular hemodialysis with a mean age of 46.21 ± 11.1 years, ranging from 26 years to 66 years. 53.8% were males. DM was detected in 5.5% of patients.

Supporting this study, El-Ballat et al. showed that the average age of patients with ESRD in one Egyptian governorate was 52.80 ±13.82 years, with a range of 16 to 90 years.39.6 percent of patients were female, while 60.4% were male **(9)**.

Among ESRD patients included in this study, the mean PTH level was 122.88 ± 83.1 pg/ml. The mean TSH was 3.06 ± 2.5 mIU/L. The mean concentrations of T3 and T4 were 3.02 ±0.9 and 9.95 ±6.1 nmol/L, respectively. The mean PH was 3.86 ± 0.9.

Among the 120 hemodialysis patients evaluated by Tajbakhsh and colleagues, serum PTH level was 274.34 ± 286.53 pg/mL**(10)**.

Tatar et al detected that the mean fT3 level in hemodialysis patients was 3.70 ± 1.23 pmol/L **(11)**.

Among 104 hemodialysis Patients in Rhee and colleagues' study, the mean TSH value was 2.29 ± 1.88 mIU/L **(12)**.

CAAC was detected in 11% of this study's patients. 6.6% of them were on the left side 2.2% were on the right side and 2.2% on both sides.
Among 133 patients on hemodialysis included in Nakayama et al, CAAC was found in 94 patients (71%) **(13)**.
SCH was found in 9.9% of this study's patients. Shantha et al. found a significant prevalence of SCH (24.8%) among ESRD patients. **(14)**.
In a study by Lim, the prevalence of goiter in ESRD was 0–58% and of SCH 0–9.5% **(15)**.
In agreement with Pamuk et alfinding .'s that hypoparathyroidism induces an increase in arterial stiffness, old age was a key determining factor **(16)**.
Regarding sexual orientation, there was no substantial difference between patients with and without CAAC. SCH correlated significantly with CAAC. 9% of patients with CAAC had SCH, while no SCH was found in patients without CAAC.
The presence of DM had an insignificant effect on the occurrence of CAAC among ESRD patients undergoing chronic dialysis therapy.
In a cohort of prevalent hemodialysis patients who underwent assessment of multiple thyroid markers and CAC assessments using coronary CT scanning, Rhee et al. observed that decreased thyroid function, as indicated by an increase in blood TSH, was associated with higher CAC **(17)**.
As regards PH insignificant difference was found between patients with and without CAAC .Concerning the mean PTH level among the patients in this study, a significant difference was found between those with and without CAAC (157.75 ± 42.9 pg/ml and 118.57 ± 86.1 pg/ml, respectively) .
In the present study, patients with CAAC had a higher mean TSH level (7.97 0.7 mIU/L) than those without CAAC (2.46 1.9 mIU/L).
The mean T3 and T4 levels were significantly lower in patients with CAAC (2.41 ± 0.8 nmol/L and 7.25 ± 2.1 nmol/L, respectively) than those without CAAC (3.10 ± 1.0 nmol/L and 10.29 ± 6.4 nmol/L, respectively).
Meuwese et al. found, in this study, that fT4 and TSH levels were inversely linked with CAC scores in ESRD patients **(18)**.
In this study patients with SHT had 7.2 times more probability of having CAAC and this was significant.
According to this study results analysis, it was found that with one pg/ml increase in the level of PTH, there was a 2.3% increase in the risk of having CAAC and this was significant .
Moreover; with one mIU/L increase in the level of TSH there was a 3.9 times increase in the liability of having CAAC and this was significant .
The diagnostic accuracy of SCH for prediction of CAAC was 98.8%, with 90% sensitivity and 100% specificity. Also, it had a 100% ability to predict positives among all test positives (PPV) and it had 98.7% NPV.

Conclusion

With high sensitivity and specificity, SCH is a risk factor for vascular calcification in ESRD patients

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