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Original Paper

Prevalence of Subclinical Hypothyroidism in Patients with End-Stage Renal Disease and the Role of Serum Albumin: A Cross-Sectional Study from South India

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Key Words
Albumin · Chronic kidney disease · Serum albumin · Subclinical hypothyroidism

Abstract
Background/Aim: Subclinical hypothyroidism (SCH) and end-stage renal disease (ESRD) are independent risk factors for cardiovascular mortality. We aimed to study the prevalence of SCH in ESRD patients and assessed its associated risk factors. ***Methods:*** This cross-sectional study was conducted at 2 tertiary-care centers in Chennai, India, over a 3-year period. The study group comprised 137 patients with ESRD on thrice weekly regular maintenance hemodialysis. Free thyroxine (FT_4) and thyroid-stimulating hormone (TSH) were measured using an electrochemiluminescence immunoassay. SCH was defined as TSH ranging between 4.5 and 10 mIU/l with normal FT_4 (0.93–1.7 ng/dl). Patients with overt hypothyroidism, SCH and overt hyperthyroidism, those on medications affecting thyroid function and pregnant women were excluded from the study. ***Results:*** Of 137 ESRD patients (mean age: 43 ± 13.38 years), 107 were males (78.1%), 45 diabetics (32.8%), 127 hypertensives (92.7%), and 38 smokers (27.7%). Prevalence of SCH was 24.8%. In unadjusted (OR: 3.37, 95% CI: 1.91–5.21) and adjusted (for age, gender, HbA_{1C}, and albumin/creatinine ratio; OR: 3.11, 95% CI: 2.15–4.98) logistic regression analysis, serum albumin was significantly associated with SCH. Further, multiple linear regression identified that for every 1 g/dl drop in serum albumin TSH increased by 4.61 mIU/l (95% CI: 2.75–5.92). ***Conclusion:*** We observed a high prevalence of SCH in our ESRD patients. Also, serum albumin was significantly associated with SCH in our study.

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Introduction

The estimated prevalence rates of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in India are 800 and 200 per million inhabitants, respectively [1]. In South India, the main causes of CKD in decreasing order of prevalence are diabetic nephropathy (29.6%), chronic interstitial nephritis (20.4%), chronic glomerulonephritis (17.4%), and hypertensive nephropathy (11%) [2]. Studies have clearly demonstrated an association between CKD and increased cardiovascular mortality. Ryan et al. [3] reported an increase in the risk of cardiovascular mortality with decreasing glomerular filtration rate (GFR), with a marked increase when the estimated GFR was <45 ml/min/1.73 m^2.

Subclinical hypothyroidism (SCH) is diagnosed when the serum thyroid-stimulating hormone (TSH) level is high (range: 4.2–10 μIU/ml) but the corresponding serum-free thyroxine (FT_4) level is within normal limits (range: 0.93–1.7 ng/dl). A recent review has observed that SCH was prevalent in 4–8% of the general population in western countries, and in women who were >60 years of age it was prevalent in up to 15–18% [4]. SCH is recognized as a risk factor for atherosclerotic cardiovascular disease (CVD), hyperlipidemia, low-grade inflammation and hypercoagulability [5–7]. As ESRD and SCH are independent risk factors for CVD mortality, it is possible that patients suffering from both disease entities may have a higher CVD risk.

Previous studies have consistently shown an increased prevalence of SCH in CKD patients compared to normal controls [8–11]. There is a paucity of Indian data with respect to SCH prevalence in patients with ESRD. Also, factors associated with SCH in ESRD have not yet been clearly defined. Hence, this study is our effort to identify the prevalence of SCH in ESRD patients from South India and its associated risk factors.

Patients and Methods

This was a cross-sectional study conducted at 2 tertiary-care centers in South India. The study was conducted over a 3-year period (August 2007 to July 2010). Patients with overt hypothyroidism, SCH and overt hyperthyroidism, those on medications affecting thyroid function, e.g. lithium and high-dose steroids (hydrocortisone >100 mg or equivalent dose of other commonly used steroids), and pregnant women were excluded from the study. Hence, from a total of 176 patients (91 from center 1 and 85 from center 2) who underwent hemodialysis during this period, 39 patients with the above-mentioned features were excluded. Consequently, the remaining 137 consecutive patients with ESRD (70 from center 1 and 67 from center 2) receiving thrice weekly maintenance hemodialysis formed the study cohort. Demographic characteristics (age, gender, diabetes mellitus, current smoking, and duration of dialysis), laboratory variables [hemoglobin, blood urea nitrogen, serum levels of creatinine, albumin, phosphorus, and calcium, alkaline phosphatase, a single determination of the albumin/creatinine ratio (ACR) in a spot urine sample, and fasting lipid profile], clinical parameters (systolic and diastolic blood pressure, and body mass index) were obtained from all study participants. Thyroid functions were evaluated for all patients. TSH was measured using Roche Elecsys modular analytics E 170 with electrochemiluminescence immunoassay (ECLIA method). The analytical sensitivity of TSH is 0.005 μIU/ml and of FT_4 it is 0.023 ng/dl. High serum TSH (>4.5 μIU/ml; normal range: 0.27–4.5 μIU/m) and normal FT_4 levels (normal range: 0.93–1.7 ng/dl) were required for the diagnosis of SCH. Patients with high TSH (>4.5 μIU/ml) and low FT_4 levels (<0.93 ng/dl) were classified as being overt hypothyroid irrespective of whether they had symptoms of hypothyroidism or not. Informed consent was obtained from all the study participants, and the ethics committees of both tertiary-care hospitals approved the study.

Statistical Analysis

Baseline characteristics of the study participants were expressed as means ± SD and percentages. Prevalence of SCH was also determined (n/%). Comparisons between both groups, namely patients with SCH and patients with normal TSH, were done using Student's t test (for continuous variables) and the χ^2

Table 1. Baseline characteristics of the study participants

Patient characteristics	All participants (n = 137)	Patients with SCH (n = 34)	Patients with normal TSH (n = 103)
Age, years	43 ± 13.3	39 ± 9.3	41 ± 11.2
Males, n (%)	107 (78.1%)	25 (73.5%)	82 (79.6%)
Diabetics, n (%)	45 (32.8%)	17 (50.0%)	28 (27.2%)
Smokers, n (%)	38 (27.7%)	14 (41.2%)	24 (23.3%)
Duration of dialysis, years	5.6 ± 2.2	5.5 ± 2.1	5.6 ± 2.5
Hemoglobin, g/dl	8.5 ± 1.5	9.1 ± 0.8	8.5 ± 1.0
Body mass index	21.5 ± 3.4	22.1 ± 3.1	22.7 ± 2.9
Systolic blood pressure, mm Hg	142 ± 10.7	139 ± 12.5	141 ± 11.9
Diastolic blood pressure, mm Hg	86.3 ± 9.2	84.9 ± 11.2	87.3 ± 8.7
Blood urea nitrogen, mg/dl	119.8 ± 67.1	91.0 ± 40.2	121.0 ± 32.9
Creatinine, mg/dl	9.0 ± 4.0	9.2 ± 3.0	10.0 ± 1.9
Serum calcium, mg/dl	8.4 ± 1.4	8.5 ± 1.2	8.9 ± 1.1
Serum phosphate, mg/dl	5.5 ± 1.8	5.2 ± 1.4	5.4 ± 1.3
Serum albumin, g/dl	3.7 ± 0.5	2.5 ± 0.8*	3.8 ± 0.4
Alkaline phosphatase, IU	162.4 ± 147.9	161.0 ± 103.5	174.0 ± 78.9
FT_4, ng/dl	1.2 ± 0.2	1.1 ± 0.2	1.2 ± 0.2
TSH, μIU/ml	4.2 ± 2.5	5.1 ± 3.1	3.2 ± 0.6
HbA_{1C}, %	8.7 ± 0.7	8.9 ± 0.5	9.1 ± 0.3
ACR, mg/g	1,573.6 ± 523.1	1,476.0 ± 356.5	1,640.1 ± 580.8
Total cholesterol, mg/dl	193.4 ± 31.2	193 ± 36.5	192.7 ± 35.2
HDL cholesterol, mg/dl	46.5 ± 5.76	44.2 ± 7.9	47.2 ± 8.3
LDL cholesterol, mg/dl	116.3 ± 33.9	115 ± 37.4	114.8 ± 33.8
Triglycerides, mg/dl	130.6 ± 67.2	128.9 ± 72.8	130 ± 68.3

* $p = 0.012$. All other comparisons were nonsignificant. All values are mean levels measured before dialysis.

test (for categorical variables), as appropriate. Associations between patient characteristics [age, gender, glycosylated hemoglobin (HbA_{1C}), serum albumin and urinary albumin excretion (measured by ACR)] and SCH were assessed using simple and multiple logistic regression analysis. Variables such as age, gender, HbA_{1C}, serum albumin, and ACR were selected to be adjusted in the logistic regression model by virtue of them being confounders in the association between SCH and ESRD or by a process of forward selection of variables where variables that had significant association with SCH in unadjusted analysis were included in the adjusted model. Variables that were neither confounders nor had a significant association with SCH in the unadjusted model were not included in the adjusted model. Logistic regression analysis, expressed as odds ratio, gave us a measure of the association between selected variables and SCH. Subsequently, multiple linear regression analysis was used to assess the association between SCH and serum albumin after adjusting for other variables: age, gender, HbA_{1C}, and ACR. Here, again, variable selection was similar to what has been described for logistic regression analysis. The multiple linear regression analysis gave us a numerical association between selected variables and SCH. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS for Windows (version 15.0; SPSS, Chicago, Ill., USA).

Results

Of the 137 ESRD patients (mean age: 43 ± 13.38 years), 107 were males (78.1%), 45 diabetics (32.8%; all had type 2 diabetes mellitus and none type 1 diabetes mellitus), 127 hypertensives (92.7%), and 38 were smokers (27.7%). Baseline characteristics are listed in table 1.

Table 2. Association between patient characteristics and SCH

Patient characteristics	Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	β (95% CI)	p value
Age	1.11 (0.96–1.19)	0.211	1.03 (0.91–1.16)	0.183	0.34 (–0.21 to 0.48)	0.531
Gender	0.99 (0.89–1.05)	0.174	1.03 (0.91–1.15)	0.117	–0.21 (–0.55 to 0.35)	0.233
HbA_{1C}	1.02 (0.91–1.14)	0.076	1.06 (0.82–1.28)	0.423	0.36 (–0.12 to 0.78)	0.078
Serum albumin	3.37 (1.91–5.21)	0.012	3.11 (2.15–4.98)	0.036	–4.61 (–2.75 to –5.92)	0.026
ACR	1.14 (0.85–1.44)	0.354	1.18 (0.88–1.47)	0.276	0.91 (–0.10 to 1.34)	0.122

Model 1: unadjusted logistic regression analysis; model 2: multiple logistic regression analysis; model 3: multiple linear regression analysis. β = β coefficient. The dependent variable in this model is TSH.

SCH prevalence was 24.8% (34 patients). Mean ACR was 1,573.6 ± 523.1 mg/g, with no patient having nephrotic-range proteinuria. Patients with SCH had significantly lower serum albumin levels compared to patients with normal serum TSH levels (table 1). Serum albumin was significantly associated with SCH in both unadjusted (OR: 3.37, 95% CI: 1.91–5.21, p = 0.012) and adjusted (OR: 3.11, 95% CI: 2.15–4.98, p = 0.036) logistic regression analysis (table 2). All other variables did not have a significant association. Multiple linear regression analysis identified that for every 1 g/dl drop in serum albumin TSH increased by 4.61 μIU/ml (95% CI: 2.75–5.92, p = 0.026).

Discussion

Our study has shown a high prevalence of SCH (24.8%) in ESRD patients. Our results are concordant with similar studies in other populations linking renal impairment with thyroid disease. In a study by Lim [12], the prevalence of goiter in ESRD was 0–58% and of SCH 0–9.5%. In the patients studied by Kaptein et al. [13] in 1988, the prevalence of goiter was as high as 43% compared to only 6.7% in the control group. In another report, the prevalence of goiter in ESRD was 58% [14]. Lo et al. [10] had correlated hypothyroidism with different levels of estimated GFR according to National Kidney Foundation CKD staging and concluded that reduced kidney function was associated with an increase in the prevalence of SCH and overt hypothyroidism. In agreement with our study, in their study prevalence of hypothyroidism (combining overt hypothyroidism and SCH) amounted to 23.1% in CKD patients with an estimated GFR <30 ml/min/1.73 m^2. Similarly, Chonchol et al. [9] observed an 18% prevalence of SCH in CKD patients not requiring dialysis. Kang et al. [15] reported that SCH was common among ESRD patients who were receiving continuous ambulatory peritoneal dialysis and that it may be associated with cardiac dysfunction.

In CKD patients, thyroid hormone physiology is known to be altered. Baseline TSH becomes elevated, reaching sometimes levels >20 μIU/ml, response to exogenous thyrotropin-releasing hormone (TRH) gets blunted, diurnal rhythm of TRH gets disturbed, and there is an observed reduction in serum T_4 levels [13]. The Wolff-Chaikoff effect or increase in total-body inorganic iodide can block thyroid hormone production and hence may explain the higher frequency of goiter and hypothyroidism in CKD patients [13]. Further, chronic metabolic acidosis may cause hypothyroidism in these patients. The possible mechanisms were demonstrated by Brungger et al. [16] in their experimental model. They showed that meta-

bolic acidosis significantly decreased serum T_3 and T_4 levels, with a corresponding increase in serum TSH levels thereby resulting in hypothyroidism.

Our study has shown a decreased level of serum albumin to be a risk factor for SCH in ESRD patients. Our patients with SCH had significantly lower serum albumin levels compared to patients with normal TSH (table 1). Contrary to our observation, Kang et al. [15] reported that in their study cohort comprising 51 ESRD patients on continuous ambulatory peritoneal dialysis, patients with SCH had significantly higher serum albumin levels compared to patients with normal serum TSH levels. The reason for this difference is not clear. However, the important differences between our study and their study are that they included patients on continuous ambulatory peritoneal dialysis while our study involved hemodialysis patients; further, their study cohort was relatively small compared to ours. Details about urinary albumin loss in their study cohort are not known. These differences render it difficult to arrive at a conclusion.

Gilles et al. [17] made the interesting observation that patients with proteinuria had higher TSH levels, which can be explained by the possible loss of thyroid hormones in the urine. Evidence has not favored the association between hypoalbuminemia and other endocrine abnormalities in CKD [18]. However, hypoalbuminemia in patients with CKD is an independent risk factor for cardiovascular mortality [19]. There have been controversies as to whether SCH in ESRD warrants thyroxine supplementation. Depressed thyroid function can be considered as an adaptation to minimize protein catabolism in ESRD patients. Hence, attempts to correct this might be detrimental to the patient. Proof to this statement comes from the observation that ESRD patients who received thyroxin replacement were observed to have a negative nitrogen balance and an increased leucine flux [20]. However, the cardiovascular risk among patients with a combination of ESRD, SCH, and hypoalbuminemia is yet to be determined. The effect of thyroxine replacement in this subgroup has to be answered by future randomized trials.

Limitations

The cross-sectional study design prevented us from understanding the temporality in the association between SCH, serum albumin, and ESRD. The small sample size was a second limitation that prevented us from estimating effect modification due to gender, age, and diabetes status. Single measurements of all laboratory values create doubts regarding the precision of these estimates. Also, a search for etiology of SCH or a measure of anti-thyroid antibodies was not performed in our study which limits us from understanding if the SCH observed in our patients was related to decreased GFR or to a primary thyroid pathology.

Conclusions

In conclusion, our study has shown a 24.8% prevalence of SCH among a cohort of ESRD patients. Hence, it may be a good practice to routinely monitor thyroid functions in all ESRD patients. SCH is associated with serum albumin in ESRD patients. Further larger randomized trials and longitudinal follow-up may be needed to answer the controversies regarding thyroxin replacement in ESRD patients with SCH, especially when associated with hypoalbuminemia.

Disclosure Statement

The authors have no conflict of interest to disclose.

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