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RESEARCH ARTICLE OPEN ACCESS

PREDICTIVE BIOCHEMICAL MARKER SERUM FT4/FT3 RATIO IN SUBCLINICAL HYPOTHYROIDISM PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

BACKGROUND: The early stage of hypothyroidism is subclinical hypothyroidism which could developed to apparent hypothyroidism and cause adverse metabolic flaws, prevalence of hypothyroidism is high in chronic kidney disease (CKD) incidence, in inclusion to those undergoing dialysis. Various studies reveled association between functioning of thyroid and metabolic syndrome. However, association between FT3/FT4 ratio and the SCH are not elaborated. Though, this study is focused to assess the ratio FT3/FT4 in identifying ScHt in CKD patients. **METHODS:** In a prospective case control study 53 known CKD samples underwent hemodialysis and 60 normal sample were opted for the study. Both control and CKD samples contain serum creatinine a is measured and evaluation of glomerular filtration rate (GFR) is calculated to know function of kidney and thyroid parameter serum FT3, FT4and TSH were measured for determining the FT3/FT4 ratio. **RESULTS:** Thyroid stimulating hormone levels were remarkable enhanced in patients without undergoing dialysis and with CKD in comparison to control groups (P<0.034). FreeT3 level was significantly less (P<0.001) and FT4/FT3 ratio was significant higher (p< 0.001) in patients of CKD without undergoing dialysis in comparison of controls. The area under the curve (AUC) of ROC curve for the steady variables of serum FT4/FT3 ratio was 0.914 with CI: 0.832 to 0.997. **CONCLUSIONS:** Solely FT3, FT4 had very minute sensitivity in detection of subclinical hypothyroidism in chronic kidney disease. In this study we demonstrated that the FT4/FT3 ratio establishment was advantageous step in detection of sub clinical hypothyroidism in patients with chronic kidney disease.

KEY WORDS: Sub clinical hypothyroidism, FT4/FT3 ratio, chronic kidney disease.

INTRODUCTION

Sub Clinical Hypothyroidism is a medical constrain with least symptoms or not any symptoms of hypothyroidism. [1] ScHt is an enhanced serum thyroid-stimulating hormone level accompanying a normal free FT4 and FT3 amount. [2] ScHt prevalence was found 11.3% and is more leading in women.[3] Females with greater degree of antiTPO antibodies contains greater number of cases of ScHt.[4] According to National Health and Nutrition Examination Survey (NHANES) the criteria to recognizing ScHt was increased in TSH level between 5-10 µIU/mL and with normal free T4 without any clinical manifestation. The incidence of ScHt enhanced with age.[5] and with increased intake of dietary iodine.[4] As SCH is inversely proportional with Glomerular filtration rate (GFR) as SCH elevates steadily GFR get decreased. Several studies revealed the association of ScHt and chronic kidney disease (CKD) it includes chronic inflammation,[6] altered iodine metabolism, reduced sensitivity to hormones and autoimmune thyroiditis.[7] CKD may known as less GFR of <60 mL/min/1.73m2 for greater than three months, with or without recognizable damage of kidney.[8]

Less blood flow in renal because of abnormality in left ventricle, elevated vasoconstriction, intrarenal vasoconstriction and decreased renal expression of endothelium dependent vasodilators like VEGF, IGF are responsible for diminish GFR in hypothyroidism.[9-11] Epidemiological associated information implies predialysis incidence with CKD have higher risk of hypothyroidism.[12] ScHt is prevailing in CKD incidence not acquiring treatment for chronic dialysis.[13] TSH is analyzed to enhanced in CKD with thyrotropin by uremic effect.[14]

Literature had revealed an elevated prevalence of ScHt in CKD patients compared to normal controls. [15-17] ScHt had been identified as a indicator of all reasons of mortality in chronic dialysis and as risk factor for assisting the development and progression of nephropathy and cardiovascular incidents in type 2 diabetic patients. [18-19]

Few studies reported the association between thyroid function and metabolic syndrome, [20-22] However, association between the FT3/FT4 ratio and the ScHt is not understood. Consequently, the present study aims to investigate the fT3/fT4 ratio in identifying the ScHt in CKD patients. The purpose of the present study was to find better biochemical marker to recognize the ScHt in CKD patients who have not undergone to dialysis, it is essential for determine better biochemical marker to identify the ScHt in CKD patients who have not undergone on dialysis, it is essential for the clinicians initial detection, intervention and optimal management of patients.

METHODS

A comparative case control study for nine months of time on patients attended Chettinad hospital and research institute, Chennai. The total number of healthy 60 samples and controls 53 suffering from CKD of distinct etiology but not underwent hemodialysis were added in this study after fulfilling the inclusion criteria.

The study was approved by Institutional Ethics Committee, Chettinad Academy of Research and Education. An informed consent was taken from all the cases before their inclusion into the study.

INCLUSION CRITERIA

1. Patients of CKD above 18 years of age does not need long-lasting dialysis with TSH levels> 5.5 mIU/L. CKD was detected on the basis of history and investigations.
2. Also patients with more than three months duration of kidney disease.
3. Aberration of urea and creatinine results.

EXCLUSION CRITERIA

1. Pregnant women.
2. Patients less than 18 years of age group.
3. Past history of any medication for thyroid disease and family history of thyroid.

The sample of fasting blood was taken and FT3, FT4 and TSH serum were analyzed by chemiluminesence Immuno assay (CLIA) method according to protocol of manufactures.

Serum creatinine was identified by Jaffes Kinetic technique.

Estimated GFR is calculated by Modification of Diet in Renal Disease formula to assess kidney function, estimated GFR=175.0 × (serum creatinine−1.154) × (age−0.203) × 1.212 (if black) × 0.742 (if female).

Functional sensitivities of FT3 = 0.88 pg/mL, FT4 = 0.25ng/dL, TSH = 0.015 uIU/mL and creatinine=0.15 mg/dL was provided by manufacturer.

Reference values in our laboratory were FT3=2.5–3.9 pg/mL, FT4 = 0.58–1.64 ng/dl, TSH = 0.34–4.5 uIU/mL. Creatinine=0.7–1.3 mg/dL for male and 0.6 –1.0 mg/dL for female.

Statistical Analysis

The statistical analysis was done through SPSS software and version was 21. Normality of continual variables was detected and data expressed as mean± SD. Continuous and categorical variables were contrasted with independent t- test. Receivers employed characteristics (ROC) curves for FT4/FT3 ratio were formed. The area under ROC curve was calculated by trapezoidal rule. The independent relationship between dependent and independent variables were tested through canonical distinguish functional observation. The two tailed P values < 0.05 were observed to be statistically significant.

RESULTS

The mean of age was calculated in between men and women in control groups 38.46±8.8 and the subjects were clinically euthyroid; and in between men and woman in case group the mean age was57.7±13. Mean±SD values of creatinine, estimated GFR, TSH, FT3, FT4 and FT4/FT3 ratio were shown in Table 1.

TSH levels had been enhanced significantly in CKD patients without dialysis in contrast to control groups (P<0.034). FreeT3 level was significantly less in patients of CKD as compared to controls (P<0.001). No significant difference in serum FreeT4 level in both the case and control groups.

The FT4/FT3 serum was highly significant in patients of CKD without underwent dialysis in comparison to controls (Figure 1). In canonical distinguish functional analysis, the presence of CKD was independently involved with subclinical hypothyroidism.

The association of distinct independent variables tested through canonical distinguishable functional observation clearly revealed serum FT3 (-0.462) value had significant role in linking ScHt and CKD. Accuracy of proportion of study population was

The relationship of different independent variables tested by canonical discriminant functional analysis clearly shows, serum FT3 (-0.462) value has significant role in linking ScHt and CKD. Accuracy or the fraction of the study population was manifested precisely, associated with sensitivity and specificity of the test. The area under the curve of ROC curve for the continuous variables, serum FT4/FT3 ratio was 0.914 with CI: 0.832 to 0.997, it indicates that ration have high sensitivity and specificity, in identifying the reliability (Table-2). The outcomes of ROC graphs of our study FT4/ FT3 ratio support the relationship between ScHt and CKD (Figure 2)

DISCUSSION

The present study of FT4/FT3 ratio analyze to screen the association between ScHt and CKD, and high odds ratio (>1) explained our hypothesis. The Odds ratio for serum FT4/FT3 ratio predicted by omnibus test for model coefficients was 4.58 and corresponding confidence interval was 0.22 to 1.23. The size of interval revels large size of sample required for adequate accuracy.

Thyroid hormones could directly affect the function of kidney which could further lead to thyroid disorders. In present study elevated prevalence of ScHt (16%) is analyzed in CKD patients. Our results are consistent, with similar studies in other population connected renal abnormality with thyroid disease. This had reported that prevention of subclinical primary hypothyroidism ranges between 4% and

10% in general population [23-25] and between 7% and 26% in the elderly. [26–28]

Most participants had serum TSH results in between reference range (i.e. TSH value ranges from 0.4 to 4.5 µIU/ml with normal FreeT4 level) where as few had sub clinical hypothyroidism (i.e TSH >4. 5 µIU/ml with normal FreeT4 level. According to the National Academy of Clinical Biochemistry (NACB) recommendations the upper limit of the TSH reference range in normal population is a point of discussion recommending ~2.5 µIU/mL, rather than ~4.5 µIU/mL, i.e on account of subjects associated in study performed an initial stage of autoimmune thyroid disease. This will modify the upper limit of the TSH range and ultimately skew our data. In this study for dividing ScHt the upper limit of TSH range is very crucial.

Though, FT3 and FT4 are in between normal reference range for both control and cases. Our results reveled low FT3 level in CKD patients in contrast to controls; this will be due to affect on deiodinase (convert T4 to T3) through metabolic acidosis and protein insufficiency in CKD patients.

Considering T4 conversion to T3 is deduction in CKD, this considered higher side of T4 reference limit but in between reference interval. TSH level in CKD patients had serum TSH levels in between range but only in some cases TSH level are > 4.5 µIU/mL, with normal FT4 levels revealing subclinical hypothyroidism. Less FT3 levels have shown to be an independent indicator of mortality in hemodialysis patients.[29] The prevalence of less T3 increased CKD stage and serum T3 level is involved with seriousness of CKD.

Literature shows that less level of T3 is more common laboratory results followed by subclinical hypothyroidism.[30] The present study reveals no significant variation in serum T4 level in both case and control groups. Serum FT4 levels differ from being less to normal in CKD due to impairment protein binding of T4 in CKD.

Sl. No.	Parameter	Case (Mean±SD)	Control (Mean±SD)	p-values
1	AGE	57.7±13.350	34.33±9.444	<0.001
2	FT3	0.206±0.029	0.318±0.16	<0.001
3	FT4	0.992±0.24	0.93±0.088	NS
4	TSH	2.821±0.823	1.776±0.962	<0.034
5	FT4/FT3 ratio	5.288±2.199	3.008±0.711	<0.001
6	Creatinine	4.24±1.39	0.88±0.19	<0.001
7	eGFR	14±4.43	59.6±7.85	<0.001

Table 1. Mean and SD Values of Thyroid and Renal Profile in Control and Cases Group

Test Result Variable(s)	Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
				Lower	Upper
FT4/FT3 Ratio	0.914	0.042	< 0.001	0.832	0.997
TSH(ulu/ml)	0.643	0.072	0.056	0.501	0.785
FT3 (ng/dl)	0.068	0.036	< 0.001	0.68	0.79
FT4 (ng/dL)	0.586	0.077	0.251	0.435	0.737

The test result variable(s): TSH (ulu/mL), FT3 (ng/dL), FT4 (ng/dL) has at least one tie between the positive actual state group and the negative actual state group.

a. Under the non parametric assumption

b. Null hypothesis: true area = 0.5

Table 2. Different Variables Showing the Area Under ROC Curve

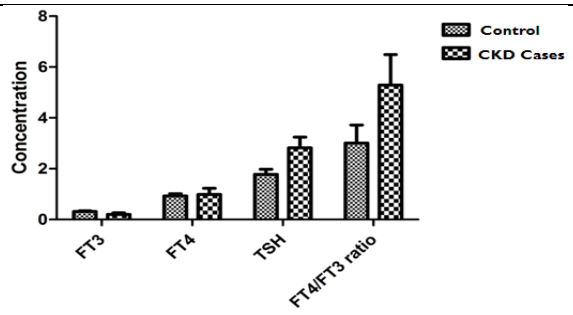

Figure 1. Comparison of Thyroid Profile FT3 – free Triiodothyronine; FT4 – Free Thyroxine; TSH – Thyroid Stimulating Hormone; FT3/FT4 Ratio in Control and CKD Cases Groups

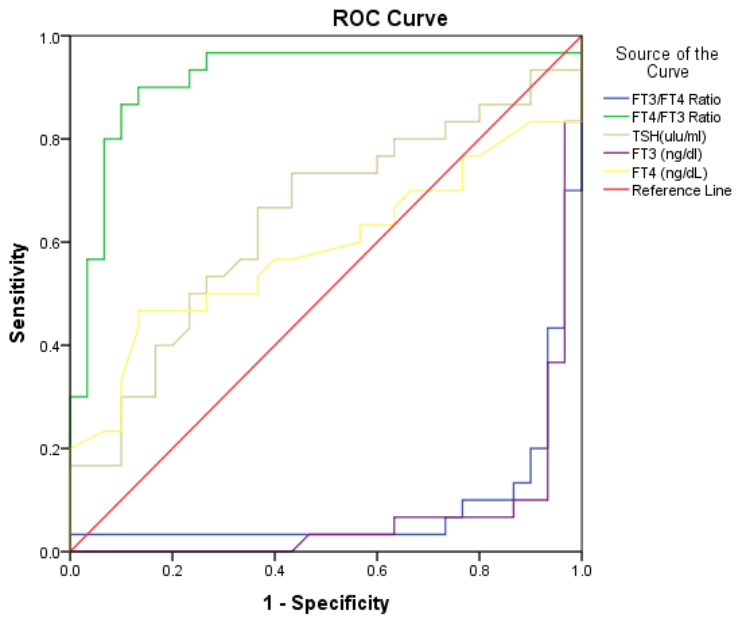

Figure 2. Receiver Operating Characteristic (ROC) Curve TSH, FT3, FT4, FT3/FT4 Ratio for the Discrimination of Healthy Controls and Patients with Chronic Kidney Disease.

CONCLUSIONS

Serum FT3 is interpreted with FT4 measurement in detection of subclinical hypothyroidism. Solely FT3 and FT4 has very minute sensitivity for detection of ScHt in CKD. Hence ratio of FT4/FT3 is fruitful to diagnose ScHt in CKD. This study shows uniform methods to collect data on serum TSH, FT4 and FT3 concentrations and ScHt was detected through widely accepted diagnostic criteria (i.e high TSH with normal FT4 levels) without any clinical manifestation. Prominent limitations in the study are low number sample size and analysis is restricted in its capability to form causal or temporal association in between subclinical hypothyroidism and CKD. Also cases and controls are not age matched; antiTPO and TBP levels were not measured. This study reveals importance of FT3/FT4 ratio establishment, further studying it in a wide number of populations validates that the FT3/FT4 ratio could be predictive marker for subclinical hypothyroidism in patients with chronic kidney disease.

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