Original Article

Correlation of Fibroblast Growth Factor-23 with Thyroid Disorder in Patients with Chronic Kidney Disease

Abdullah Adil Raoof[1], Ali Jasim Hashim Al-Saedi[2], Dina Nabil[3]

[1]Department of Medicine, College of Medicine, University of Kirkuk, Kirkuk, [2]Baghdad Teaching Hospital, Baghdad, Iraq, [3]Baghdad—Medical City, Kidney Transplantation Center, Kirkuk, Iraq

Abstract

Background: Various thyroid functional test abnormalities are commonly observed in chronic kidney disease (CKD) due to alterations in thyroid hormone synthesis, metabolism, and regulation. **Objectives:** The objectives of this study were to detect the levels of thyroid hormones at various stage of CKD and find a correlation of thyroid hormones with fibroblast growth factor-23 (FGF23). **Materials and Methods:** A cross-sectional study was conducted at an outpatient clinic (patient with chronic renal failure). Eighty patients reported chronic renal failure in an outpatient clinic from June 2020 to February 2021. Experimental work was carried out at private laboratories in Kirkuk, Iraq. **Results:** According to the findings of this study, the age group with the highest risk of renal failure was 61–70 years, with a rate of 25%. The highest age group of patients with renal failure was 51–60 years with 23.8%, whereas the lowest age group of patients with renal failure was 31–40 years with 6.3%. FGF23 levels in the end stage increased significantly ($P \leq 0.05$) as compared with other CKD stages. About thyroid hormones, T3 and T4 levels in the end stage were significantly lower ($P < 0.05$) than in other CKD stages. However, thyroid-stimulating hormone (TSH) levels in the end stage increased significantly ($P < 0.05$) compared with other CKD stages. The findings of this study revealed an inverse association between FGF23 and T3, with increased levels of FGF23 resulting in lower levels of T3, and the levels of correlation were $R^2 = 0.5931$, also increased levels of FGF23 resulting in lower levels of T4, and the levels of correlation were $R^2 = 0.6356$. Finally, the increase in levels of FGF23 lead to an increase in levels of TSH and the levels of correlation were $R^2 = 0.7106$. **Conclusions:** Based on the results of this study, the study showed that there is a strong association between thyroid hormones and chronic renal failure. There is a decrease in thyroid hormone levels with an increase in fibroblast growth factor 23 levels.

Keywords: Chronic kidney disease, fibroblast growth factor-23, thyroid hormones

Introduction

Chronic kidney disease (CKD) is defined as kidney impairment that lasts for more than 3 months and is indicated by atypical albumin excretion or decreased kidney function as measured or approximated by the glomerular filtration rate (GFR).[1-5] Multiple endocrine disorders (e.g., insulin resistance and secondary hyperparathyroidism) have been identified as extrarenal complications of CKD as well as potential predictors of morbidity and mortality in this population.[6] It has long been known that there are associations between kidney and thyroid functions. Different kidney disorders have been linked to different thyroid dysfunctions.[7] The human body synthesizes thyroid hormones (TH) precisely in accordance with the shift in energy that it demands.[8] THs are necessary for healthy kidney growth and development. On the contrary, the kidney serves as a target tissue for certain iodothyronines functions in addition to being a metabolic and TH-removing organ.[9] In addition to the hypothalamus–pituitary–thyroid axis, CKD affects peripheral metabolism.[10] The 32-kDa peptide known as fibroblast growth factor-23 (FGF23) regulates calcium–phosphate balance. As the illness worsens, FGF23 levels increase.[11] In early CKD, this first physiological

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Address for correspondence: Dr. Abdullah Adil Raoof, Department of Medicine, College of Medicine, University of Kirkuk, Iraq.
E-mail: dr.abdullahkopurlu@uokirkuk.edu.iq

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adaption is essential for maintaining phosphate balance, but in advanced CKD, prolonged exposure and high concentrations can be detrimental, especially to the cardiovascular system. Retrospective studies have demonstrated a substantial correlation between high levels of FGF23 and unfavorable outcomes in all stages of CKD.[12-16] As a result, the study's goals were to measure TH levels at various stages of chronic renal disease and determine whether they were correlated with FGF23. The National Kidney Foundation developed criteria as part of its Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) to stratify CKD patients:

Stage 1: normal eGFR R 90 mL/min per 1.73 m^2 and persistent albuminuria
Stage 2: eGFR between 60 and 89 mL/min per 1.73 m^2
Stage 3: eGFR between 30 and 59 mL/min per 1.73 m^2
Stage 4: eGFR between 15 and 29 mL/min per 1.73 m^2
Stage 5: eGFR 15 mL/min per 1.73 m^2 or end-stage renal disease (ESRD)[17]

Materials and Methods

Study design

A cross-sectional research was done on 80 patients with chronic renal failure from June 2020 to February 2021 at Kirkuk outpatient clinic in Iraq.

Target population

The target population consists of patients with chronic renal disease of both sexes (48 men and 32 women) between the ages of 20 and 71 who attend an outpatient clinic in Kirkuk, Iraq.

Biochemical tests

The human FGF23 and TH enzyme-linked immunosorbent assay (ELISA) kits are a solid-phase sandwich ELISA designed to detect and quantify the levels of human FGF23 and TH in plasma, and serum.

Ethical approval

The study was carried out in conformity with the ethical standards set forth in the Helsinki Declaration. Before a sample was taken, it was done with the patient's verbal and analytical consent. This approval was obtained on April 2, 2020.

Statistical analysis

Under the SPSS and Microsoft Excel XP systems, data were statistically analyzed using the Minitab statistical tool. The minimum and maximum values, as well as the mean and standard deviation (SD), were used to present the data.

Duncan's multiple range test was used to compare data means using the analysis of variance test.

Results

The ages

According to the findings of this study, the age group with the highest risk of renal failure was 61–70 years, with a rate of 25%. The highest age group of patients with renal failure was 51–60 years, with 23.8%, whereas the lowest age group of patients with renal failure was 31–40 years, with 6.3%, as seen in Table 1.

Fibroblast growth factor 23

Findings of this study revealed substantial variations between CKD levels. In contrast, FGF23 levels in the end stage (192.15 ± 13.71) increased significantly ($P \leq 0.05$) as compared to other CKD stages. In stage 1, the lowest level of FGF23 (5.63 ± 0.29) was found, as seen in Table 2.

Thyroid hormones

Triiodothyronine

The current research found that CKD stages differed significantly. Triiodothyronine (T3) levels in the end stage were 5.17 ± 0.14; on the other hand, they were somewhat lower ($P \leq 0.05$) than in other CKD stages, although the highest level of T3 was in stage 1 (6.34 ± 0.28), as seen in Table 3.

Thyroxine

This study found major variations between CKD levels. Thyroxine (T4) levels in the end stage (7.17 ± 0.14) were significantly lower ($P = 0.05$) than in other CKD stages. The highest degree of T4 was found in stage 1 (10.44 ± 0.31), as seen in Table 4.

Table 1: Age groups of in present study

Age (years)	Gender		Total
	Male	Female	
20–30	8 (16.7%)	4 (12.5%)	12 (15%)
31–40	3 (6.3%)	2 (6.2%)	5 (6.3%)
41–50	5 (10.4%)	2 (6.2%)	7 (8.7%)
51–60	9 (18.8%)	10 (31.3%)	19 (23.8%)
61–70	12 (25%)	8 (25%)	20 (25%)
≤71	11 (22.9%)	6 (14.3%)	17 (21.2%)
Total	48 (58%)	32 (18.8%)	80 (100.0%)

Table 2: FGF23 level in studied groups

Gender Parameter	FGF23	*P* value
Stage 1	5.63 ± 0.29 e	0.000*
Stage 2	27.34 ± 1.28 d	
Stage 3	58.39 ± 4.62 c	
Stage 4	128.31 ± 11.92 b	
Stage 5	192.15 ± 13.71 a	

Similar letters mean no significant differences, while different letters mean significant ($P<0.05$) differences

*means there are significant ($P<0.05$) differences

Table 3: T3 level in studied groups

Gender Parameter	T3	P value
Stage 1	6.34 ± 0.28 a	0.000*
Stage 2	5.85 ± 0.14 c	
Stage 3	5.61 ± 0.19 c	
Stage 4	5.29 ± 0.23 b	
Stage 4	5.17 ± 0.14 b	

Similar letters mean no significant differences, while different letters mean significant (P<0.05) differences

*means there are significant (P<0.05) differences

Table 4: T4 level in studied groups

Gender Parameter	T4	*P* value
Stage 1	10.44 ± 0.31 a	0.000*
Stage 2	9.42 ± 0.09 c	
Stage 3	8.41 ± 0.22 c	
Stage 4	7.31 ± 0.18 b	
Stage 4	7.17 ± 0.14 b	

Similar letters mean no significant differences, while different letters mean significant (P<0.05) differences

*means there are significant (P<0.05) differences

Table 5: TSH level in studied groups

Gender parameter	TSH	*P* value
Stage 1	1.614 ± 0.161 c	0.000*
Stage 2	1.904 ± 0.127 b	
Stage 3	1.92 ± 0.118 b	
Stage 4	2.237 ± 0.134 a	
Stage 4	2.415 ± 0.146 a	

Similar letters mean no significant differences, while different letters mean significant (P<0.05) differences

*means there are significant (P<0.05) differences

Thyroid-stimulating hormone

This study found major variations between CKD levels. Thyroid-stimulating hormone (TSH) levels in the end stage (2.415 ± 0.146) increased significantly ($P < 0.05$) compared to other CKD stages. In contrast, the lowest degree of TSH was in stage 1 (1.614 ± 0.161), as seen in Table 5.

Correlations

Correlation between FGF23 and T3

The findings of this study revealed an inverse association between FGF23 and T3, with increased levels of FGF23 resulting in lower levels of T3, and the levels of correlation were $R^2 = 0.5931$, as seen in Figure 1.

Correlation between FGF23 and T4

Findings of this study illustrated an inverse association between FGF23 and T4, with increased levels of FGF23 resulting in lower levels of T4, and the levels of correlation were $R^2 = 0.6356$, as seen in Figure 2.

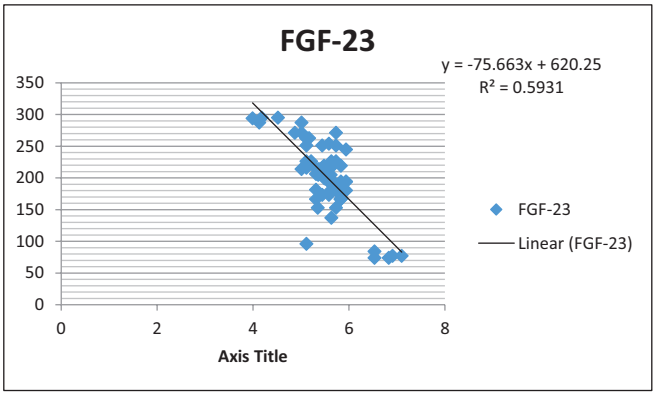

Figure 1: Correlation between FGF23 and T3

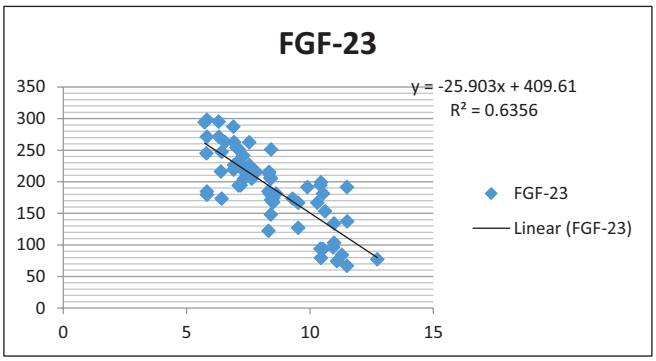

Figure 2: Correlation between FGF23 and T4

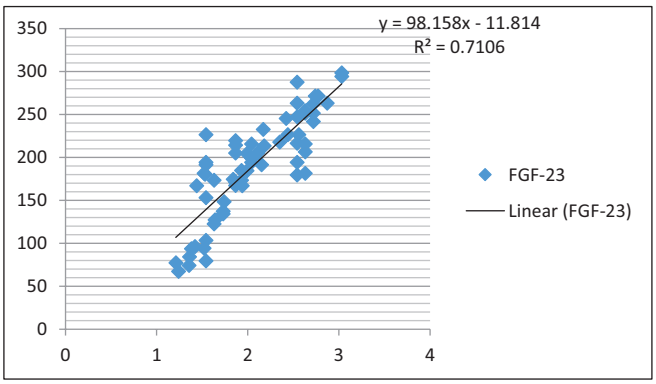

Figure 3: Correlation between FGF23 and TSH

Correlation between FGF23 and TSH

The results of this study showed a positive correlation between FGF23 and TSH, as it was observed that the increased in levels of FGF23 lead to an increase in the levels of TSH, and the levels of correlation were $R^2 = 0.7106$, as shown in Figure 3.

Discussion

A recent study discovered considerable variations in CKD stages. The levels of FGF23 in the end stage of CKD

significantly increased ($P < 0.05$) when compared to the other phases of the disease. FGF23 was linked in a dose–response manner to the probability of death or ESRD.[18] Athab *et al.*'s[19] prior results from Iraq report that 52.07% of patients had a drop in calcium, 1.33% had a rise in calcium, and 46.6% had normal serum calcium levels along with an increase in FGF23 level. According to Portales-Castillo *et al.*,[20] patients with CKD had higher levels of FGF23, while their serum calcium levels were still below acceptable limits.

The relationship between CKD and decreased GFR, decreased phosphorous excretion, and elevated serum FGF23 levels is well understood.[21,22] CKD and ESRD calcification and increased FGF23 have been linked in several studies.[23,24]

TSH is produced by the pituitary gland in response to feedback inhibition of T3 and T4, and levels of TSH are decreased in CKD patients as a result of muted TSH responses, blunted responses to thyrotropin-releasing hormone (TRH) responses, low renal clearance of TSH, and lower responses of TRH. This may also occur as a result of a nonthyroidal disease, which returns to normal once CKD is resolved.[25] Regardless of age or gender, TH levels decrease in CKD patients. The effects of clinical or subclinical hypothyroidism on physical function, cognitive function, quality of life, and the onset of depression in patients with CKD are caused by a variety of factors, including defects in iodine metabolism and autoimmune thyroiditis.[26]

Studies on people with CKD and subclinical hypothyroidism revealed that people who did not take TH experienced a rapid decline in GFR. Because TH therapy slows the rate at which GFR declines in kidney disease patients with subclinical hypothyroidism, it may prevent the development of ESRD.[27,28]

While TSH levels were typically average or raised and THs (T3 and T4) were somewhat reduced in patients with CKD, these findings were in line with those of Kaneko[29] and Singh *et al.*[10] Patients with CKD have persistently high levels of FGF23, which continue to grow as renal function declines. When patients reach ESRD, FGF23 concentrations are frequently 100–1000 times above average.[30]

The results of this study demonstrated a negative correlation between T3 and FGF23, and as has been shown in other research, chronic kidney illness lowers TH levels while raising FGF23 levels. This study draws the conclusion that decreased TH levels are associated with elevated levels of chronic renal disease (T3 and T4). Iodothyronine deiodinase is activated by fasting, chronic metabolic acidosis, and chronic protein insufficiency, which all contribute to low T3 levels in CKD (which aids in T3 synthesis from T4). Certain factors have an impact on proteins that bind to T3.[31,32]

Conclusions

Based on the results of this study, the study showed that there is a strong association between THs and chronic renal failure. There is a decrease in TH levels with an increase in FGF23 levels.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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