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Original Research Article

Effects of Thyroid Dysfunction in Chronic Kidney Disease Patients

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Abstract

The interactions between thyroid and kidney functions are well determined thyroid hormones affect renal development and physiology and kidney is required in the regulation of thyroid hormones metabolism.

The goal of the current study was to evaluate the prevalence of thyroid dysfunction in patients with chronic kidney diseases (CKD). The study included (50) hemodialysis patients. All subjects were investigated with laboratory tests to estimate thyroid function, including: serum free tri iodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH). Results were compared with the same measurements in (50) control groups. The incidence of CKD detected among those both with subclinical hypothyroidism (40.0%) and overt subclinical hyperthyroidism (34.0%) and low FT3 in H.D patients (5.6976±1.85334) in comparison with control groups. In conclusion. We observed high of thyroid function disorders in CKD patients. Low FT3 syndrome and high subclinical hypothyroidism are the frequently thyroid function disorders in CKD patients.

Key Words: Chronic kidney disease, hyperthyroidism, hypothyroidism, renal function, thyroid disorder.

الخلاصة

التفاعلات بين وظائف الغدة الدرقية والكلى تم تحديدها بشكل جيد: هرمونات الدرقية تؤثر على نمو وفسيولوجية الكليتين وان الكلى ضرورية في تنظيم العمليات الايضية لهرمونات الغدة الدرقية. الهدف من الدراسة الحالية هو تقييم نسبة حدوث الخلل في الغدة الدرقية لدى المرضى الذين يعانون من أمراض الكلى المزمنة. وتضمنت الدراسة (٥٠) مريضا في مرحلة الغسيل الكلوي. وقد تم التحقيق من الفحوص المخبرية لتقدير وظيفة الغدة الدرقية، بما في ذلك: تريودوثيرونين الحر من المصل (FT3)، هرمون الغدة الدرقية الحر (FT4) والهرمون تحفيز الغدة الدرقية (TSH). تمت مقارنة النتائج مع نفس القياسات في (٥٠) مجموعة سيطرة. تم الكشف عن انتشار المرض الكلوي المزمن بين أولئك الذين يعانون من اعراض قصور الغدة الدرقية تحت السريري (٤٠٪) وفرط نشاط الغدة الدرقية دون السريري (٣٤٪) وانخفاض FT3 في مرضى الديلزة (٥,٦٩٧٦ ± ١,٨٥٣٣٤) بالمقارنة مع مجموعات السيطرة. وكخلاصة لاحظنا ارتفاع اضطرابات وظائف الغدة الدرقية في مرضى الكلى المزمن. انخفاض متلازمة FT3 وارتفاع اعراض نقص الغدة الدرقية تحت السريري في كثير من الأحيان في المرضى الكلى المزمن.

الكلمات المفتاحية: الديلزة، نقص الغدة الدرقية، هرمونات الدرقية، تريودوثيرونين الحر.

Introduction

Kidney disease (CKD) is defined as the presence of kidney damage or decreased kidney function for at least 3 months [glomerular filtration rate (GFR) < 60 ml/min/1.73 m2] due to renal parenchymal damage. CKD is divided into five stages according to GFR and the presence or absence of kidney damage. The interplay between thyroid and the kidney in each other's functions is known for many years [1]. Disorders of the thyroid and kidney may co-exist with common etiological factors.

Thyroid dysfunction affects renal physiology, development, protein synthesis and cell growth, whereas kidney disease could result in thyroid dysfunction. Thyroid hormone status affects the functioning renal mass (measured as the kidney to body mass ratio), with hypothyroidism reducing this ratio and hyperthyroidism increasing it [2].

Thyroid hormones affect renal function by both pre-renal and direct renal effect. Pre-renal effects are mediated by the influence of thyroid hormones on the cardiovascular system and the renal blood flow (RBF).

The direct renal effects are mediated by the effect of thyroid hormones on.

Glomerular filtration rate (GFR) tubular secretory and re-absorptive processes, as well as the tubular secretory and re-absorptive processes, as well as the hormonal influences on renal tubular physiology. Thyroid hormones affect renal clearance of water load by their effects on the GFR [3].

Patients on hemodialysis (HD) due to CKD have low thyroid hormone levels and elevated TSH. Though the total T4 levels are low, heparin inhibits T4 binding to protein, thereby increasing free T4 fraction in CKD patients after heparin dialysis [4].

Hyperthyroidism results in increased RBF and GFR [5]. The effect of thyroid hormones on RBF and GFR occurs at multiple levels.

GFR is the best parameter to evaluate renal function, which is assessed via perdition equations based on serum creatinine (medical biochemistry).

Serum creatinine, an inverse marker of GFR, is significantly decreased in hyperthyroid patients, not only due to an increase in GFR but also due to the reduction in overall muscle mass [6]. Urea is a major nitrogenous end product of protein and amino acid catabolism, produced by liver and distributed throughout intracellular and extracellular fluid. In kidneys, urea is filtered out of blood by glomerular and is partially being reabsorbed with water [7]. The most frequently determined clinical indices for estimating renal function depends upon concentration of urea in the serum. It is useful in differential diagnosis of acute renal failure and pre renal condition where blood urea nitrogen-creatinine ratio is increased [8].

Recently studies have proposed that Cystatin C, a cysteine protease inhibitor constitutively secreted by all nucleated cells, is a new marker of renal function and can function as a predictor of GFR [9]. It can be used as an endogenous marker for CKD in general population including those receiving dialysis and transplantation [10]. Serum cystatin C has been observed superior to serum creatinine in estimating GFR in the range 60-90 mL/min/1.73m2. on the contrary to creatinine, serum cystatin C is not affected by sex, race, muscle mass and diet. In addition, it has been observed superior to creatinine in determining GFR in transplantation patient.

The current study was undertaken to examine thyroid hormones level and determine the status of the biochemical parameters cystatine C, creatinine, and urea in CKR patients. In addition, the relationship between thyroid dysfunction and CKD were investigated.

Materials and Methods:

This study was carried out at AL-Kut Hospital and AL-Zahra Hospital for the period from November 2016 to February 2017. Patients with CKD were individuals diagnosed of the disease having estimated GFR of < 60 ml/min/1.73m2 and stages 4 and 5 of National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) stages. The study included (50) hemodialysis patients (30 male and 20 female) were diagnosed as having E.S.R.D based on previous medical reports and clinical examination by consultant nephrologists. The age range was (40-70 years) with a mean of age (39.15±68.18 years). A control group comprised (50) healthy volunteers who had no history of kidney disease. The study purpose was explained to each participant and

investigation carried out following written consent.

Minividas Instrument was used for evaluation of thyroid function test. The assay principle combines an enzyme immunoassay competition method with a final fluorescent detection (ELFA). Venous Blood (5ml) sample was collected from each patient and control using sterile disposable syringes. The Blood sample was left to clot at room temperature, and then separated by centrifugation at (3000) rpm for 10 minutes to collect serum. Serum was divided into 3 aliquots and kept deep freeze (-20) until used. Serum Cystatin C was estimated using human Cystatin C ELISA kit (Elabscience Biotechnology, Wuhan, China) via ELISA. Creatinine in the sample reacts with picrate in alkaline medium forming a colored complex. The complex formation rate is measured in a short period to avoid interferences. Urea concentration was measured using clinical chemistry auto analyzer (Architect plus, C4000, Abbott, USA).

Statistical analysis were performed using SPSS, version 24 (IBM Inc., Chicago, IL). Descriptive analysis was used to show the mean and standard deviation of variable. The significance of difference between mean values was estimated by Student t-test. The probability $P<0.05$ was regarded as significant. ANOVA was used to determine difference between group variables.

Results:

Table (1) showed the demographic characteristics of participants which showed that the majority of patient with CKD was male 30 (60%) & less than female 20 (40)% between (40-49) years with 21 (42%) for patient groups against 15 (30%) for control groups.

Table (1): Demographic characteristics of the participants.

Age groups(year)	**Patients**		**Control**	
	No.	**%**	**No.**	**%**
(40-49)	21	42.0	15	30.0
(50-59)	14	28.0	14	28.0
(60->70)	15	30.0	21	42.0
Total	50	100.0	50	100.0
Gender	**Patients**		**Control**	
	No.	%	No.	%
Male	30	60.0	29	58.0
Female	20	40.0	21	42.0
Total	50	100.0	50	100.0

The hormonal data of patients and controls are listed in Table 2.

FT3 in H.D patients (5.6976±1.85334) showed lower level in comparison with control groups (6.0600±1.38946) but not reach the level of significance ($p>0.05$).

While, FT4 level was significantly higher ($P<0.05$) (13.5704±2.85563) than that of control groups (10.3520±8.91770). Serum TSH level was highly significant ($p< 0.01$) in patients (4.9566±1.71565) in comparison with control groups (2.7300±0.91702).

Table (2): Hormonal data in all participants.

	Mean± SD.	t	P-Value	C.S.
FT3 (pnm/1)/Patients	5.6976±1.85334	1.228	.225	P>0.05 (NS)
FT3(pnm/l)/Control	6.0600±1.38946			
FT4(pnm/l)/Patients	13.5704±2.85563	2.366	.022	P<0.05 (S)
FT4(pnm/l)/Control	10.3520±8.91770			
TSH(MIU/ml)/Patients	4.9566±1.71565	7.763	.000	P<0.01 (HS)
TSH(MIU/ml)/Control	2.7300±0.91702			

Table 3 shows the prevalence of CKD among participants by sub types of thyroid dysfunction. Prevalence of CKD was unlike among the various subtypes of thyroid dysfunction, with a higher prevalence of CKD detected among those both with subclinical hypothyroidism (40.0%) and overt subclinical hyperthyroidism (34.0%). While less prevalence of CKD was observed in both overt subclinical hypothyroidism (18.0%) & subclinical hyperthyroidism (8.0%).

Table (3): Relationship between GFR and Thyroid disorder stags.

Thyroid disorder Stags		Glomerular filtration Rate		Total
		Severe	Kidney failure	
Subclinical Hypothyroidism	No.	5	15	20
	%	10.0%	30.0%	40.0%
Overt Subclinical Hypothyroidism	No.	1	8	9
	%	2.0%	16.0%	18.0%
Subclinical Hyperthyroidism	No.	1	3	4
	%	2.0%	6.0%	8.0%
Overt Subclinical Hyperthyroidism	No.	1	16	17
	%	2.0%	32.0%	34.0%
Total	No.	8	42	50
	%	16.0%	84.0%	100.0%

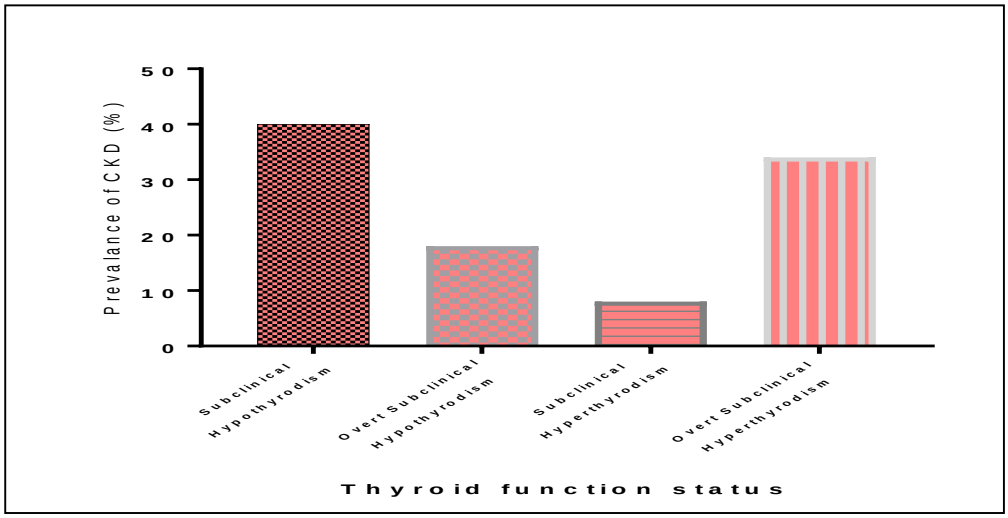

Figure (1): The prevalence of CKD among participants.

Table-4 data explained that there were highly significant difference (P<0.01) in urea, creatinine & cystatine Concentration of H.D. patients compared to controls respectively. Table (5) Results showed that the levels of urea, creatinine, cystatine CFT3 & TSH by using student t-test was highly significant (P<0.01) as compared with GFR, while level of FT4 was only significant (P≤0.05).

Table (4): Clinical characteristics of patients andcontrol groups.

	Mean± SD.	T	P-Value	C.S.
Urea(mg/dl)/Patients	118.460±31.885	19.740	.000	P<0.01 (HS)
Urea(mg/dl)/Control	30.060±5.449			
Creatinine (mg/dL)/Patients	5.355±1.813	17.938	.000	P<0.01 (HS)
Creatinine(mg/dL)/ Control	0.881±0.223			
Cystatine C(mg/l)/ Patient	1.899±0.660	11.821	.000	P<0.01 (HS)
Cystatine C(mg/l)/ Control	0.785±0.158			

Table 5: T- Test between GFR and urea, creatinine, cystatine C and thyroid hormonal status for Patient groups

	T	P-Value	(C.S.)
GFR *Vs*Urea	22.986	.000	P<0.01 (HS)
GFR*Vs*Creatinine	6.694	.000	P<0.01 (HS)
GFR *Vs*CystatineC	13.401	.000	P<0.01 (HS)
GFR*Vs* FT3	8.039	.000	P<0.01 (HS)
GFR *Vs*FT4	1.986	.050	P≤0.05 (S)
GFR*Vs*TSH	8.898	.000	P<0.01 (HS)

Discussion:

The current study was performed on ESRD patients underwent hemodialysis to consider the effect of HD on FT3, FT4 and TSH. Thyroid hormones play a vital role in various metabolic pathways within the human biochemical reactions. Any alteration in the amount of serum thyroid hormones directly cause metabolic disorders in various organs and modify the normal metabolic pathway of various organs, including kidney [11]. On the other hands, CKD causes thyroid dysfunction in multiple ways, including low circulating thyroid hormone concentration, changed peripheral hormone metabolism, disturbed binding to carrier proteins, decrease tissue thyroid hormone content, and increased iodine stock in thyroid glands. We observed decreasing trend for free T3 levels (though the decrease were not significant), and increasing trend for free T4 level (significant rise) which may be due to a decrease in the peripheral synthesis of T3 from T4 or due to chronic metabolic acidosis. Other study reported that The decreased FT3 concentration can also be attributed to the increase in excretion of bound and FT4 in urine of CKD patients [12]. Our results showed a high significant for TSH across CKD stages patients which suggest that TSH level increases with the progression of renal impairment (which is indicated by a decrease in GFR). These results are in agreement with [13].

Hypothyroidism may be either subclinical or overt. Subclinical hypothyroidism is described by a serum TSH above the higher

reference limit in combination with a normal free thyroxin, serum T3 and T4 concentrations are at the lesser end of the reference range [14]. While overt hypothyroidism is accompanied by low serum T4 and T3 or T4 chiefly and free T4 is decreased [15].

Detection of CKD in early stages is important. Currently, both parameters serum creatinine and GFR are being used to diagnose, determine prognosis and monitor the response to treatment. Low cost, easy to estimate and specificity makes serum creatinine a better parameter to depend on. However, serum creatinine has certain limitations. In the current study, an alternative marker, serum cystatin C has been studied and related with serum creatinine.

The measurement in plasma of indirect markers of GFR, blood urea and serum creatinine is routinely used to evaluate GFR. Nevertheless, they are influenced by muscle mass, age, feeding status, sex, and individual variation. In addition, tubular secretion of creatinine occurs in humans, which leads to an overestimation of GFR based on serum creatinine in patients with a moderate to severe diminishes in GFR. Urea is reabsorbed from the tubules, and this happens to a superior extent at slow tubular flow rates. Thus, blood urea is not a reliable indicator of GFR. Moreover, production and excretion of urea is not constant. Serum creatinine frequently is used as a more dependable measure of GFR than blood urea in CKD patient [16].

Studies revealed that serum cystatin C is superior to serum creatinine in the estimation of the GFR injuries [17, 18].

Nevertheless, most studies of cystatin C have focused on fields where the problems of serum creatinine are most clear, including specific population groups with starvation, extensive decreased body surface area, particularly low body mass. These results lead to the conclusion that serum cystatin C is much better as an examination test for decreased GFR and for monitoring changes in established kidney disease [19].

Conclusion:

There are numerous mechanisms of collaboration between kidney and thyroid functions in the disease states of each other organ. There are not only functional alterations but also structural correlates of these interaction.

Patients with CKD had a dysfunction in their thyroid gland (hypothyroidism). The severity of renal dysfunction is more obvious in subclinical hypothyroidism than in the overt subclinical hypothyroidism patients.

It can be observed that FT3 is not significant but FT4 is significant and TSH is highly significant. However, serum cystatin C assays are more expensive than serum creatinine assays, serum cystatin C evaluation can still be used as an adjunct to monitor patients when serum creatinine level is inconclusive in particular in patients with long duration, poorly controlled diabetes mellitus or hypertension. As subclinical hypothyroidism has been increased in CKD patients, thyroid function should be assessed in patients with deteriorating renal function, and following the patients with severe subclinical hypothyroidism and renal dysfunction to assess the evolution to overt hypothyroidism.

Conflict of Interest

The authors have declared that there is no conflict of interest.

References:

1- Kaptein EM,2002. Thyroid function in renal failure. Contrib Nephrol.,50:64–72

2- Vargas F, Moreno JM, Rodriguez-Gomez I, Wangensteen R, Osuna A, Alvarez-Guerra M, et al , 2006. Vascular and renal function in experimental thyroid disorders. Eur J Endocrinol. 154:197–212.

3- Silverberg DS, Ulan RA, Fawcett DM, Dossetor JB, Grace M, Bettcher K,26009. Effects of chronic hemodialysis on thyroid function in chronic renal failure. Can Med Assoc J.109:282–6.

4- Emmanouel DS, Lindheimer MD, Katz AI,1974. Mechanism of impaired water excretion in the hypothyroid rat. J Clin Invest. 54:926–34.

5- Den Hollander JG, Wulkan RW, Mantel MJ, Berghout A,2005. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol (Oxf) .62:483–7.

6- Manetti L, Pardini E, Genovesi M, Campomori A, Grasso L, Morselli LL, et al,52005. Thyroid

function differently affects serum cystatin C and creatinine concentrations. J Endocrinol Invest, 28:346–9.

7- Azar, A.T., 2013. Measurement of Renal Function. In Modelling and Control of Dialysis Systems (pp. 45-98). Springer Berlin Heidelberg.

8- Mitchell HR and Kline W., 2006.Renal function testing. Amer J Kidney Dis., 47(1),:174-173.

9- Arpegård, J., Viktorin, A., Chang, Z., de Faire, U., Magnusson, P.K. and Svensson, P., 2015. Comparison of heritability of cystatin C-and creatinine-based estimates of kidney function and their relation to heritability of cardiovascular disease. J Amer Heart Assoc, 4(1):e001367.

10- Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey J and Gansevoort RT a.,28013. CKD Prognosis Consortium. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 369(10):932-43.

11- Mansourian, A.R., 2010. A review on post-puberty Hypothyroidism: A glance at myxedema. Pak J Biol Sci., 13(18), p.866.

12- Mohapatra D., Panda P., Behera M and Priyadarsini N.,2016. Study of correlation between chronic renal failure and thyroid hormones. 5.(2277-8179):14-15

13- Song SH, Kwak, IS, Lee DW, Kang, YH, Seong, EY, Park JS. The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone. Nephrology Dialysis Transplantation, 2008; 24(5):1534-1527.28

14- J.Larry Jameson, Anthony P.W. ,2010. Disorders of the thyroid gland . 550 pages

15- David Haarburges, MB Bch, MMed, Fcpath. Thyroid disease: thyroid function tests and interpretation; CME: Your SA Journal of CPD, 2012; 30(7):239-243.

16- Fricker M., aWiesli P., Brandle M., Schwegler B. and Schmid C.,12003 Impact of thyroid dysfunction on serum cystatin C. Kidney International.63: 1943-1946.

17- Dharnidharka VR, AKwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function:a meta-analysis. Amer J Kidney Dis., 2002; 40: 221-226.

18- Roos JF., Doust J., Tett SE., and Kirkpatrick CM. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adult and children- A meta-analysis. Clin Biochem. 20017; 40:375-381.

19- DSa J., Shetty S., Bhandary R. and Ashalatha VR.,12017. Association between serum cystatin C and creatinine in chronic kidney disease subjects attending a tertiary health care centre. J Clin Diagn Res.11(4):BC09-BC112.