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Evaluation of Thyroid Hormones and Some Biochemical Variables in Patients with Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is a permanent loss of kidney function which is diagnosed when the glomerular filtration rate (GFR) is under 60 ml\min\1.73m2 for more than three months. The present study was conducted at Kidney Transplant and Dialysis Center in the Medical City in Baghdad from October 2018 to April 2019. Sixty CKD patients with an age ranged of 40 to 65 years and 25 healthy subjects were involved in this study. Blood samples were collected to evaluate the levels of kidney function parameters and thyroid hormones. The levels of urea, creatinine and uric acid showed highly significant ($p \leq 0.01$) increases in CKD patient in comparison with the control group, while the values of GFR and creatinine clearance showed highly significant ($p \leq 0.01$) decreases. The results of thyroid hormones showed highly significant ($p < 0.01$) decreases in the levels of T3 and T4 along with a highly significant ($p < 0.01$) increase in the level of TSH in the patients.

Keywords: CKD, Thyroid Gland, Urea, Creatinine, Uric Acid

تقييم مستويات هرمونات الغده الدرقيه وبعض متغيرات الكيمياء الحياتيه في المصابين بلمراض الكلى المزمنه

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الخلاصه

مرض الكلى المزمن هو الخساره الدائميه لوظائف الكلى ويتم تشخيصه عندما يكون معدل الترشيح الكبيبي اقل من 60 مل في الدقيقه الواحده لاكثر من ثلاثة شهور .تمت هذه الدراسه في مركز زراعة وغسل الكلى في مدينة الطب في بغداد للمدة من تشرين الثاني 2018 الى نيسان 2019 .ستون مريضا من المصابين بامراض الكلى المزمنه تراوحت اعماهم بين (40-65) سنه وخمس وعشرون من الاشخاص الاصحاء تم شمولهم في هذه الدراسة.جمعت عينات الدم لغرض تقييم مستوى فحوصات وظائف الكلى ومستوى هورمونات الغدة الدرقية .اظهرت النتائج وجود ارتفاع عالي المعنويه في مستويات اليوريا والكرياتنين وحامض اليورك في المرضى مقارنة بالاصحاء , بينما اظهر معدل الترشيح الكبيبي ومعدل تصفيه الكرياتنين انخفاض عالي المعنوية.اظهرت نتائج هورمونات الغدة الدرقية حصول انخفاض معنوي عالي في مستوى هورمونات ال T3,T4 وارتفاع عالي المعنوية في مستوى الهورمون المحفز للدرقية قي مرضى الكلى مقارنة بالاصحاء.

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Introduction

Chronic kidney disease is described as an irreversible permanent renal damage that is diagnosed when
the glomerular filtration rate is under 60 ml\min\1.73m2 for more than three months. CKD is divided into 5 stages based on GFR level [1]. According to the national kidney foundation, Stage I is when GFR level is normal (more than 60 ml\min\1.73m2) with no symptoms or signs of the disease, while some indications of kidney dysfunction are manifested by abnormalities in some tests such as proteinuria . In stage II, GFR decreases to 60-89 mL/min with evidence of kidney damage. Some patients in this stage show occasional symptoms (uremia, anemia, fluid retention), while others may have no symptoms. In stage III, CKD patients show a decrease in the GFR value to 30-59 mL/min. Individuals could have manifestations of kidney damage or not at all, but the most prevalent sign in this stage is hypertension which is present in most of the patients. In stage IV, the GFR is highly decreased to 15-29 mL/min and patients may have abnormal elevation in creatinine and urea levels. Symptoms of this stage include anorexia, edema, impaired memory, and decreased cognitive function. The last stage (V) in CKD is classified as End Stage Renal Disease with a GFR of less than 15 mL/min. [2].

CKD has been a serious public health concern in the last years, due to its high prevalence among the population worldwide and the possible mortality. The disease also leads to recurrent hospitalizations and high socioeconomic burden [3]. GFR is the amount of plasma that filtrate in the kidney in one minute [4]. GFR is an important indicator to evaluate the renal function and health. GFR is also used to determine the dose of medication and monitor the progression of disease [5]. Urea is primarily derived from dietary protein intake and the turnover of tissue protein. In the gut, protein absorption is performed by the small intestine [6, 7]. The muscle metabolism results in the production of creatinine as an end product from creatinine phosphate it excretes by kidney. Creatinine is the most current parameter for kidney function. Another test is creatinine clearance test which measures the effectiveness of the kidneys to remove creatinine from the blood. The test compares, in a specified time which is usually 24 hours, serum creatinine with the amount of creatinine excreted [8].

Uric acid is the end product of purine metabolism. Its production and metabolism involve the liver, whereas its homeostasis is controlled by the kidney which, along with the intestine, is mainly responsible for its excretion. Serum uric acid is usually increased in patients with CKD. The common relation between hyperuricemia and CKD refers to the retention of uric acid in patients. Other factors involved in the elevation of uric acid hyperuricemia include genetic and familial factors. Uric acid is also raised due to high diet intake, reduced excretion, fasting and quick weight loss, hereditary reasons and the presence of kidney stones [9, 10]. Thyroid hormones include Triiodothyronine (T3) and thyroxine (T4), with the former having many important roles related to the metabolism, heart rate, digestion, muscle control, function and development of brain, and bone maintenance. T3 forms twenty percent of the thyroid hormones [11, 12].

Thyroxin is one of the thyroid hormones that represent 80 percent of the thyroid production. Thyroxin is also called tetraiodothyronine because it contains four iodine atoms. When the hormone travels to organs such as the kidney, liver and others to exert its action, it is converted into triiodothyronin as the active form [13, 14]. The activity T3 is four times more powerful than that of T4 [12]. Thyroid stimulating hormone (TSH) is produced from the anterior pituitary gland and promotes the stimulation and inhibition of thyroid hormones' secretion from the thyroid. The production of TSH is controlled by a hypothalamic hormone called thyrotropin (TRH), depending on environmental, developmental, and circadian stimuli [15]. The control of the thyroid hormones secretion occurs through feedback inhibition by the hypothalamic-pituitary-thyroid axis (HPT). At first, the hypothalamus produces the thyrotropin releasing hormone (TRH) which travels to the anterior pituitary and induces its production of thyroid stimulating hormone (TSH) [16]. Dysfunctions of thyroid hormones, including hypothyroidism and hyperthyroidism, affect renal blood flow, GFR, tubular function, electrolyte homeostasis, and structure of kidney. The effect of thyroid dysfunction on kidney disease patients is direct, such as in acute kidney injury, CKD with or without dialysis, kidney transplantation and severe glomerulonephritis [17].

Materials and methods

This study involved 60 patients (male and female, age range 40-65 years) with CKD and 25 healthy persons and was conducted at the Dialysis and Kidney Transplant Center of Al-Jerahat hospital at the medical city in Baghdad from October 2018 to April of 2019. All the patients were in stage IV of the disease and never had dialysis. Venous blood was obtained after diagnosis of CKD by a specialist doctor. Serum was separated by centrifugation at 3000 rpm for 10 minutes. The samples were stored at -20°C before analysis. The kits used in urea and uric acid determination were based on colorimetric change, while creatinine test was based on reading the absorbance in a fixed time. GFR was calculated using the epidemiology equation and creatinine clearance was determined by Cockcroft-Gault equation [18]. The ELISA kits used for T3 and T4 measurement was based on competitive enzyme immunoassay principle, while that for TSH measurement was based on immune-enzymometric principle. For the statistical analysis, SAS software (Version 9.1th ed. SAS. Inst. Inc. Cary. N.C. USA) was used.

Results and discussion

Kidney function parameters

Figure-1 demonstrates that the serum level of urea showed highly significant ($p \leq 0.01$) increase in patients with chronic kidney disease (131.91 ± 7.94 mg\dl) compared with the control group (25.40 ± 1.16 mg\dl), while the standard normal range is 7-37 mg\dl.

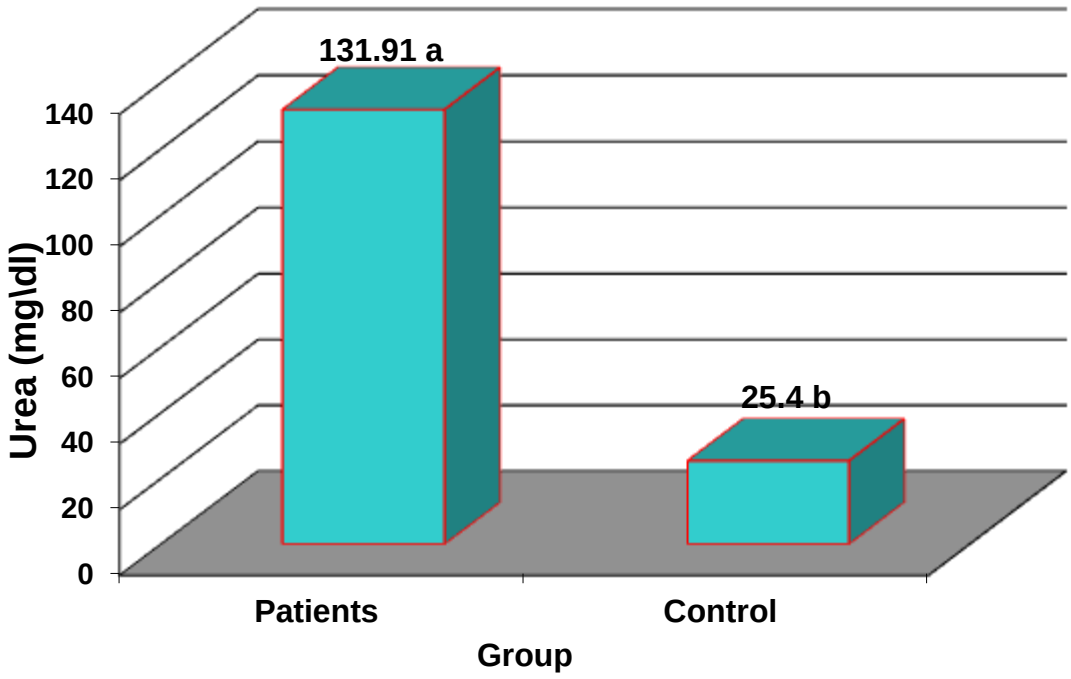

Figure 1-Level of Urea in patients and control.

Creatinine level showed a highly significant increase ($p \leq 0.01$) in patients with CKD (5.38 ± 0.40 mg/dl) in comparison with the control group (0.678 ± 0.03 mg/dl), whereas the normal rang is 0.5-1.2, as show in Figure-2.

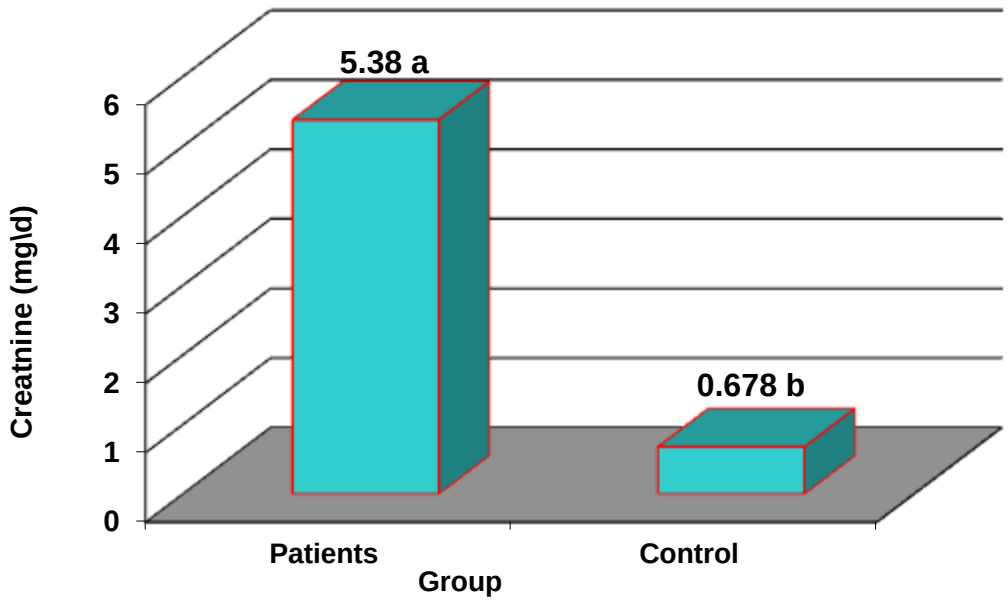

Figure 2-Level of Creatinine in patients and control.

Levels of uric acid in this study showed a highly significant ($p \leq 0.01$) increase (8.08 ± 0.31 mg/dl) in CKD patients in comparison with the control group (4.17 ± 0.24 mg/dl), with the normal range being 2.4-6 mg\dl, as show in Figure-3.

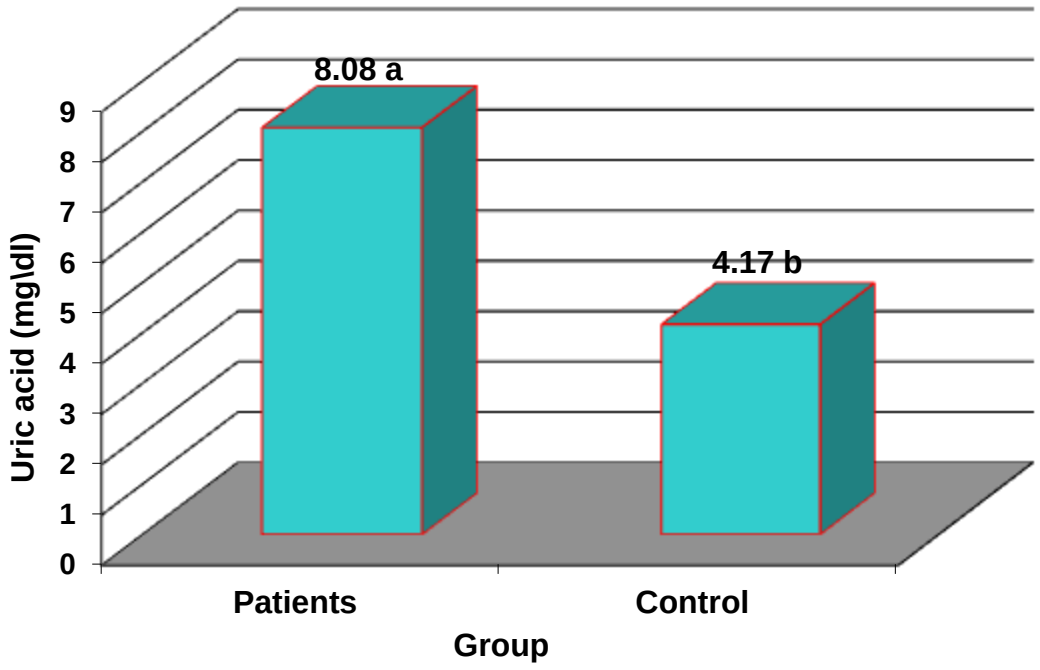

Figure 3-Level of Uric acid in patients and control.

As demonstrated in Figure-4 the level of glomerular filtration rate showed a highly significant ($p \leq 0.01$) decrease (16.03 ± 1.71 ml\min\1.73m2)) in CKD patient as compared with the control group (102.04 ± 3.30 ml\min\1.73m2), while the normal range is 90-120 ml\min\1.73m2.

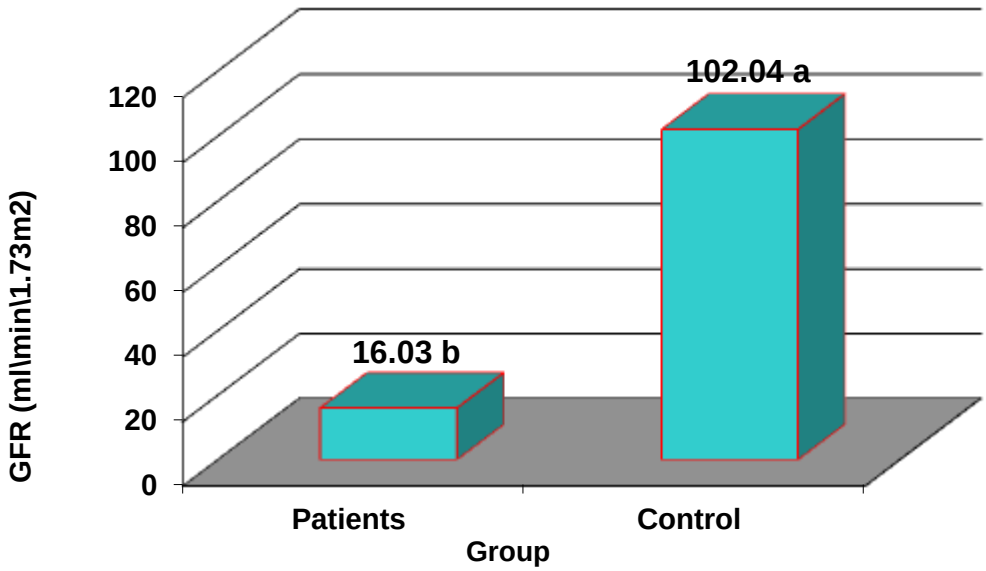

Figure 4-Level of GFR in patients and control.

Creatinine clearance level demonstrated a highly significant ($p \leq 0.01$) decrease (20.54 ± 1.80 ml/min) in patients with CKD in comparison with the control group (141.60 ± 7.13 ml/min), as show in Figure-5, whereas the normal range is 88-128 ml/min.

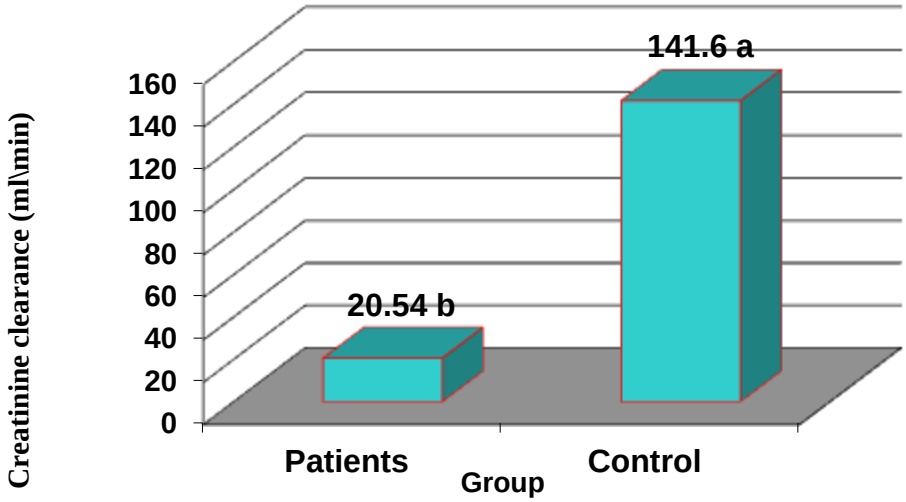

Figure 5-Level of Creatinine clearance in patients and control.

Urea nitrogen in blood is directly associated with the excretory function of the kidney. During CKD, the kidney is unable to excrete urea, which becomes concentrated in the blood [19]. This inability of urea excretion is due to damage in the kidney itself, resulting in tubular necrosis and loss of the ability of filtering. Medications may also lead to kidney damage. The dehydration caused by CKD can also raise the level of urea because of low rate of renal excretion [8]. Renal excretion, tubular secretion and creatinine degradation are declined in CKD patients, causing creatinine level elevation. Also, meat intake and protein supplement lead to an increase in serum creatinine. Another reason of high level of creatinine is the medications that inhibit tubular creatinine secretion and decrease the breakdown of creatinase by the gut [20].

A uric acid level is a consequence of CKD, while it is also a sign of other factors that also lead to kidney disease. This elevation results in reduction of GFR and tubular secretion, which lead renal insufficiency [21]. The decline in GFR represents the irreversible nephron loss and this parameter

determines even the earlier asymptomatic stages of CKD that is. It reflects the rate of clearance of exogenous substances from the plasma to the urine.

The most important marker of GFR is creatinine since it is eliminated through the glomerular filtration. GFR is decreased as a result of limitation in tubular excretion [22]. Determination of creatinine clearance was shown to have many limitations, as it is dependent on muscular mass and weight of patients, and it decreases with age [23].

Thyroid hormone level

The levels of thyroid hormones showed a highly significant ($p \leq 0.01$) decrease for T3 (1.761 ± 0.12 nmol\l) and T4 (140.39 ± 6.49 nmol\l) in patient with CKD in comparison with those of the control group (3.360 ± 0.19 nmol\l and 237.27 ± 9.03 nmol\l, respectively) as shown in Figures- 6 and 7. The normal range for T3 is 1.59-5.88nmol\l and for T4 is 121-325nmol\l. While, the level of TSH showed a highly significant ($p \leq 0.01$) increase (2.766 ± 0.15 µIU\ml) in patients with CKD as compared to the control group (1.991 ± 0.14 µIU\ml), while the normal range is 0.39-6.1 µIU\ml.

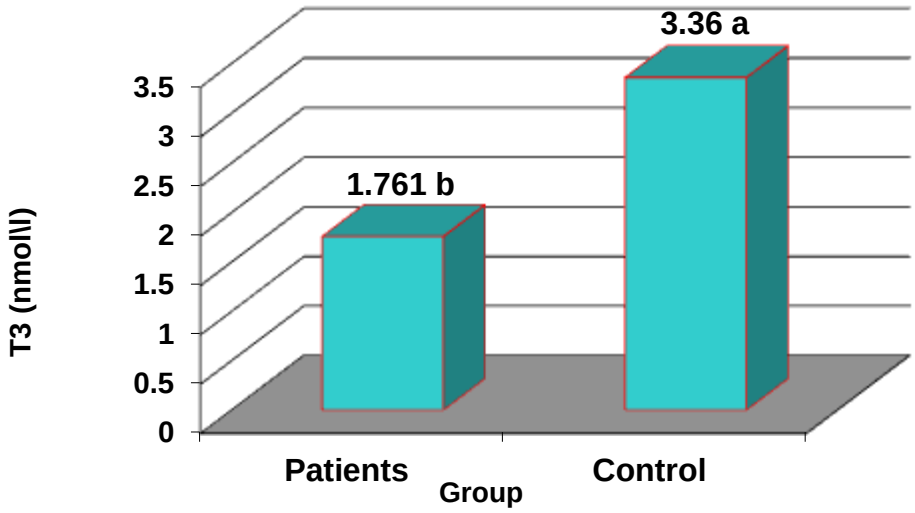

Figure 6-Level of T3 in patients and control.

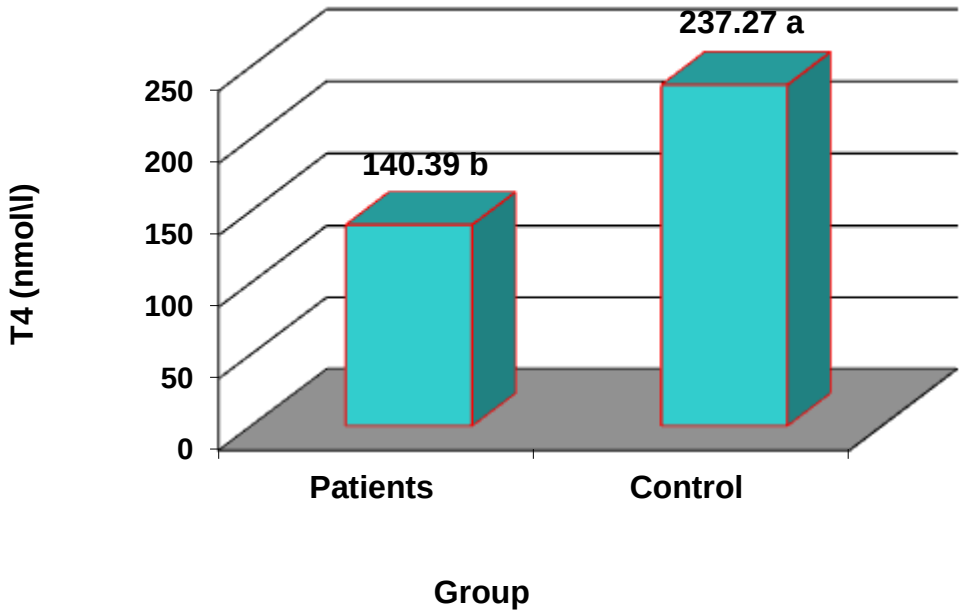

Figure 7- Level of T4 in patients and control

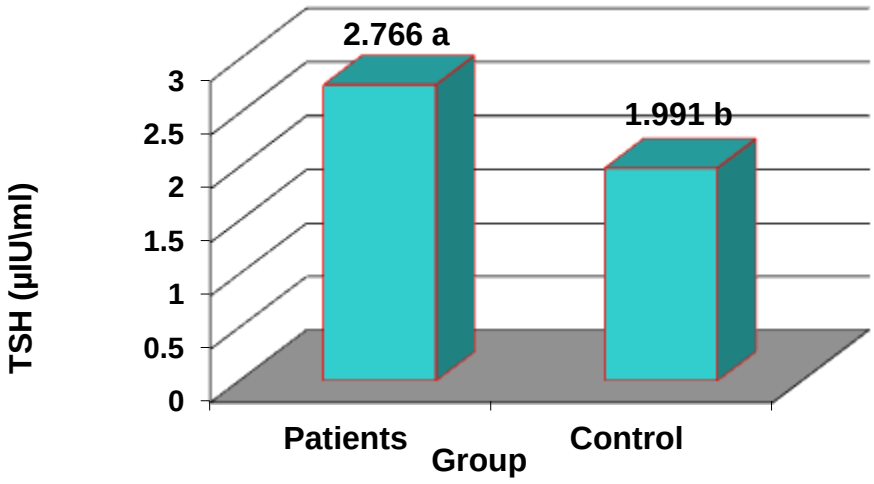

Figure 8-Level of TSH in patients and control.

Chronic kidney disease has an effect on the pituitary-thyroid axis which is the main control axis of thyroid hormones and metabolism of thyroid hormones. Primary hypothyroidism is common in CKD patients who have decline in estimated GFR. Low T3 syndrome is the most common thyroid dysfunction in patients with CKD. However, T4 levels are also affected because of impaired protein binding of T4 [24]. Several factors are associated with T3 reduction in patients with CKD, such as systemic acidosis, endothelial damage markers, and inflammation. 1 5′-deiodinase enzyme is responsible for the conversion of T4 into T3 during inflammation. Some cytokines inhibit the expression of this enzyme, such as tumor necrosis factor (TNF) and interleukin (IL)-1 [25]. Low T3 level is common in CKD patient due to the decreased peripheral deiodinase conversion of T4 to T3. This effect takes place due to metabolic acidosis and protein malnutrition, both are found in CKD [26].

In response to feedback inhibition of T3 and T4, the pituitary gland produces TSH, the levels of which are reduced in CKD patients due to blunted TSH response, blunted responses to thyrotropin releasing hormone (TRH), low renal clearance of TSH, and lower response of TRH. This can also take place due to non-thyroidal illness (NTI) which returns to normal after resolution from CKD [27] **.** Reduction in the levels of thyroid hormones in CKD patients occurs regardless of age and sex. Many factors such as iodine metabolism defects and autoimmune thyroditis contribute to the clinical or subclinical hypothyroidism effects on physical function, cognitive function, quality of life, and development of depression in patients with CKD [28].

Studies on subclinical hypothyroidism and CKD patients showed high decline in GFR rate in those who did not take thyroid hormone. Thyroid hormone therapy could delay reaching the end-stage renal disease because it lowers the decline rate of GFR in kidney disease patients with subclinical hypothyroidism [29, 30]. .

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