

The Effect of Low FT3 Level on Kidney Disease Progression and Potassium Levels in Euthyroid Adult Patients with Solitary Kidney

Tek Böbrekli Erişkin Hastalarda Düşük Serbest T3 Seviyesinin Böbrek Hastalığı İlerlemesine ve Potasyum Seviyesine Etkisi

ABSTRACT

OBJECTIVE: The aim of this study was to investigate the effect of low FT3 levels on CKD progression and hyperkalemia in euthyroid patients with solitary kidney.

MATERIAL and METHODS: Seventy-six solitary kidney outpatients were enrolled in the study. Patients with a preexisting thyroid disease were excluded. The baseline and final laboratory parameters were evaluated. Serum Thyroid hormones (TSH, FT3 and FT4) were measured at baseline.

RESULTS: The mean age of the patients was 50.4 ± 13.8 years and mean follow-up was 43 ± 29 months. Of the patients, 24% had progressive CKD and 19.7% developed hyperkalemia. Patients with a progressive course had lower FT3 levels (2.71 ± 0.34 vs. 3.17 ± 0.47 ; $p < 0.001$). Similarly hyperkalemic patients had lower FT3 values (2.77 ± 0.34 vs. 3.13 ± 0.49 ; $p = 0.011$). FT3 levels were negatively correlated with, age, history of hypertension and serum potassium level and positively correlated with serum albumin and eGFR levels. In multivariate regression analysis, FT3 levels were independently associated with progression of CKD. Low eGFR and RAS-blocker use was independently associated with the development of hyperkalemia.

CONCLUSION: In patients with solitary kidney, low FT3 level is associated with the progression of CKD. In addition, development of hyperkalemia is common in CKD patients with low FT3 levels.

KEY WORDS: Chronic kidney disease, Hyperkalemia, Low T3 syndrome, Solitary kidney, Thyroid hormones

ÖZ

AMAÇ: Çalışmanın amacı ötiroid soliter böbrekli hastalarda düşük serbest T3 seviyelerinin, KBH ilerlemesi ve hiperkalemi üzerine etkilerini incelemektir.

GEREÇ ve YÖNTEMLER: Poliklinikte izlenen 76 tek böbrekli erişkin hasta çalışmaya dahil edildi. Tiroid hastalığı olanlar çalışma dışı bırakıldı. Başlangıç ve son kontrol laboratuvar sonuçları değerlendirildi. Tiroid hormon testlerine (TSH, sT4 ve sT3) başlangıçta bakıldı.

BULGULAR: Hastaların yaş ortalamaları $50,4 \pm 13,8$ yıl ve ortalama takip süresi 43 ± 29 aydı. Hastaların %24'ünde KBH'da ilerleme ve %19,7'de hiperkalemi gelişti. KBH'da ilerleme gösteren hastalarda sT3 seviyeleri daha düşüktü ($2,71 \pm 0,34$ vs. $3,17 \pm 0,47$; $p < 0,001$). Benzer şekilde hiperkalemi gelişen hastalarda sT3 seviyeleri daha düşüktü ($2,77 \pm 0,34$ vs. $3,13 \pm 0,49$; $p = 0,011$). sT3 seviyesi yaş, hipertansiyon öyküsü ve potasyum düzeyi ile negatif, serum albümin ve GFH ile pozitif koreleydi. Çoklu analizde; sT3 düzeyi KBH progresyonu ile, hiperkalemi gelişimi ise düşük GFH ve RAS bloker kullanımıyla bağımsız ilişkiliydi.

SONUÇ: Soliter böbrekli hastalarda düşük serbest T3 seviyeleri KBH ilerlemesi ile ilişkilidir. Düşük sT3 seviyeli KBH hastalarında hiperkalemi gelişimi sıktır.

ANAHTAR SÖZCÜKLER: Kronik böbrek hastalığı, Hiperkalemi, Düşük T3 sendromu, Tek böbrek, Tiroid hormonları

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INTRODUCTION

Compared to the general population, hypothyroidism and low triiodothyronine (T3) syndrome is more common in chronic kidney disease (CKD) patients (1-5). According to various studies, the low T3 syndrome is closely related to the stage of CKD. It is observed in 10% of the patients with stage 1 and in 80% of those with stage 5 disease (4,5). Low T3 levels in this group are associated with poor clinical outcomes such as cardiovascular morbidity and mortality (6-8). In addition; T3 causes hemodynamic changes by directly acting on lipid profile-cardiac contractility- peripheral and systemic vascular resistance and blood pressure, and it changes electrolyte homeostasis by affecting glomerular and tubular function (1,6).

Today, advances in radiodiagnostic imaging modalities have improved diagnosis of renal masses, stones and infections in the general population and increased the number of nephrectomies due to these disorders. Also, living donor renal transplantation (donor nephrectomy) has surpassed cadaveric kidney transplantation in many countries, thus; these events increased the frequency of adult solitary kidney patients (9,10).

Progression of CKD in adults with solitary kidney is an important issue. In these patients; hypertension, proteinuria, obesity and metabolic syndrome are major risk factors for CKD progression and electrolyte abnormalities including hyperkalemia are common (9,11). However, the impact of thyroid dysfunction on CKD progression is not clear. In the general population, thyroid dysfunction can lead to changes in sodium, potassium and calcium-phosphorus metabolism (12-14). Several studies have presented an association between hypothyroidism and hyponatremia and / or hyperkalemia (12-15). The aim of this study was to examine the effects of low T3 levels on the development and progression of CKD and hyperkalemia in euthyroid patients with solitary kidney.

MATERIALS and METHODS

Study Subjects

This longitudinal observational study included 145 solitary kidney patients with stable function who were followed at the outpatient clinics of nephrology and transplantation of a tertiary care hospital between January 2007 and December 2012. Twenty-three patients with less than six months follow-up, twenty-four cases without thyroid function test results, six patients with a history of preexisting thyroid disease, fifteen with a diagnosis of hypothyroidism and one patient with hyperthyroidism were excluded from the study. Thus, seventy-six patients were allocated into the study protocol. Progression to kidney failure that was defined as a 25% or greater decline in baseline eGFR (16) and development of hyperkalemia that implies potassium levels > 5.5mmol/L during follow-up or requirement of potassium-lowering treatment was determined as the primary endpoint of the study.

The physical and laboratory examinations of patients were kept regularly in confidential files. The initial, first and third year and final laboratory parameters were evaluated. Estimated GFR (eGFR) was calculated by the MDRD formula. Δ eGFR was calculated as the difference between the baseline eGFR and eGFR of the last visit. Proteinuria of the patients was calculated from 24-hour urine specimen.

Thyroid Function Tests

Serum TSH, freeT4 (FT4), and free T3 (FT3) were measured by chemiluminescent immunoassay. Normal ranges for TSH, FT3 and FT4 were 0.41-4.24 mIU/mL, 2.5-3.9 pg/mL, and 0.61-1.06 ng/dL respectively. Thyroid function tests were evaluated at baseline. Patients were divided into 2 groups according to the median FT3 level. Group 1 includes patients with FT3 level \leq 3.03 pg / mL and Group 2 signifies those with a FT3 level >3.03 pg / mL.

Hyperkalemic patients were divided into 4 groups in terms of additional potential risk factors. Group 1 included patients older than 50 years (according to the median age) Group 2 includes Group 1 plus those with an eGFR of less than 56 mL / min / 1.73m² (with respect to the median eGFR.), Group 3 involves Group 2 plus those regularly taking renin-angiotensin system (RAS) blockers and Group 4 is Group 3 plus those with FT3 levels lower than the cumulative average.

STATISTICS

All analyzes were performed using SPSS 15.0 for Windows statistical program package. Mean and standard deviation of the values (mean \pm SD) was calculated. Pearson test was used in the correlation analysis. The difference between the two groups was assessed by student's t-test and by chi-square test where appropriate. The amount of proteinuria is not normally distributed. Therefore, log conversion value of proteinuria was used in univariate and multivariate analysis. The forward stepwise Cox-regression analysis was used to determine the independent predictors of CKD progression and the development of hyperkalemia. P < 0.05 was considered statistically significant.

RESULTS

The mean age of patients was 50.4 \pm 13.8 (range:22-84 years) and 56% were male. Average follow-up was 43 \pm 29 (6.3-119) months. The cause of nephrectomy was stone disease in fourteen (18.4%), pyelonephritis in nine (11.8%), renal mass in eight (10.6%), atrophied non-functioning kidney in five patients (6.6%) and living donation in forty cases (52.6%). Hypertension was present in 42%, diabetes in 13% and a history of coronary artery disease was obtained in 4% of the patients. All thirty-three hypertensive patients were using antihypertensive medication. Nineteen patients were using RAS-blockers (ACE inhibitors and / or angiotensin-receptor blockers ARB), 3 patients had ACE-inhibitor and ARB combination, 13 patients were using calcium channel blockers, 6 patients were treated with beta-blocker and

18 patients with diuretics. Twenty-four patients (72%) were receiving two or more antihypertensive medication.

The average baseline serum creatinine of the patients was 1.48 ± 0.84 mg / dL, and eGFR was 56 ± 23 mL / min / 1.73m^2 . Average 24-hour urinary protein value was 2.21 ± 0.55 g/d and average potassium level was 4.3 ± 0.7 mmol/L. Seven of patients were in stage 1, 25 of patients were in stage 2, 37 were in stage 3 and 7 of patients were in stage 4 CKD. At the final visit; the mean serum creatinine, eGFR and potassium levels of the patients were 1.73 ± 1.55 mg / dL, 56 ± 27 mL / min / 1.73m^2 and 4.6 ± 0.5 mmol/L, respectively. During the follow-up, eighteen patients (24%) had a progressive course and fifteen (19.7%) developed hyperkalemia. In addition, five patients (6.5%) required renal replacement therapy and 4 patients (5.2%) died. These results are given in Table I.

Patients with a progressive course were older (56.6 ± 13.3 vs. 48.50 ± 13.5 ; $P = 0.03$), hypertensive (72% vs. 33%, $p = 0.003$), having lower baseline eGFR (44 ± 32 vs. 60 ± 16 ; $p = 0.06$) and had high levels of proteinuria (2.76 ± 0.65 vs. 2.05 ± 0.39 ; $p = 0.001$), and potassium values (4.8 ± 0.8 mmol/L vs. 4.1 ± 0.6 mmol/L, $p < 0.001$), but were having lower baseline serum sodium (136 ± 3.6 mmol/L vs. 139 ± 3.3 mmol/L; $p = 0.026$) concentration. In addition; the progressors had lower FT3 levels (2.71 ± 0.34 pg / mL vs. 3.17 ± 0.47 pg / mL; $p < 0.001$) but the TSH (1.20 ± 0.80 mIU/L vs. 1.52 ± 0.69 mIU/L; $p = 0.09$) and FT4 levels (0.88 ± 0.19 ng/dL vs. 0.93 ± 0.27 ng/dL; $p = 0.553$) were not different from non-progressors.

Patients with hyperkalemia were older (57.6 ± 9.9 vs. 48.60 ± 14.2 ; $p = 0.02$), hypertensive (93% vs. 30%, $p < 0.001$), were frequently using RAS blockers (52% vs. 8.7%; $p < 0.001$), had lower baseline eGFR (36 ± 14 vs. 61 ± 22 ; $p < 0.001$) and were more proteinuric (2.90 ± 0.55 vs. 2.12 ± 0.48 ; $p = 0.001$), and having high potassium levels (5.3 ± 0.6 mmol/L vs. 4.0 ± 0.5 mmol/L;

$p < 0.001$) but lower baseline serum sodium (136 ± 3.5 mmol/L vs. 139 ± 3.2 mmol/L; $p < 0.01$) concentration. Hyperkalemic patients had low FT3 levels (2.77 ± 0.34 pg / mL vs. 3.13 ± 0.49 pg / mL; $p = 0.011$). However, no difference was observed between serum TSH (1.22 ± 0.64 mIU/L vs. 1.50 ± 0.73 mIU/L; $p = 0.175$) and FT4 levels (0.94 ± 0.25 ng/dL vs. 0.91 ± 0.26 ng/dL; $p = 0.673$) of hyper- and normokalemic cases. The incidence of hyperkalemia was higher in patients with the use of RAS-blockers (52.6% vs. 8.7%, $p < 0.001$).

Free-Triiodothyronine and Related Outcomes

TSH, FT3 and FT4 levels of the patients were given in Table I. FT3 levels were negatively correlated with age, hypertension and systolic blood pressure and positively correlated with hemoglobin, serum albumin and potassium levels and with eGFR (Table I). The relation between FT3 and eGFR with FT3 and serum potassium levels were depicted in Figure 1 and Figure 2, respectively.

When patients were divided into 2 groups according to the median FT3; those with low FT3 were older, hypertensive and were having lower levels of eGFR, serum albumin and hemoglobin. In terms of clinical outcomes, patients with low levels of FT3 were likely to exhibit progressive kidney disease (36% vs. 9%; $p = 0.005$), required renal replacement therapy (10% vs. 0%; $p = 0.044$), had increased mortality (10% vs. 0%; $p = 0.044$) and were often hyperkalemic (28%, 9%; $p = 0.031$) (Table I). FT3 levels independently predicted kidney disease progression (Table II).

In Group 2 (FT3 > 3:03 pg / mL), 3 patients with progressive kidney disease had an average FT3 level of 3.19 pg / mL (range: 3:13 to 3:25).

When subgroups of patients with hyperkalemia compared, patients in group 4 had 12.8-fold increased risk of developing hyperkalemia. These findings are presented in Figure 3.

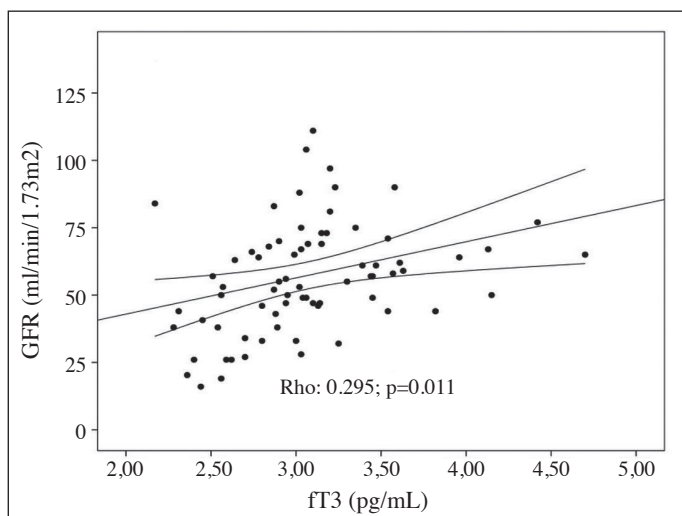


Figure 1: Relation between FT3 and eGFR.

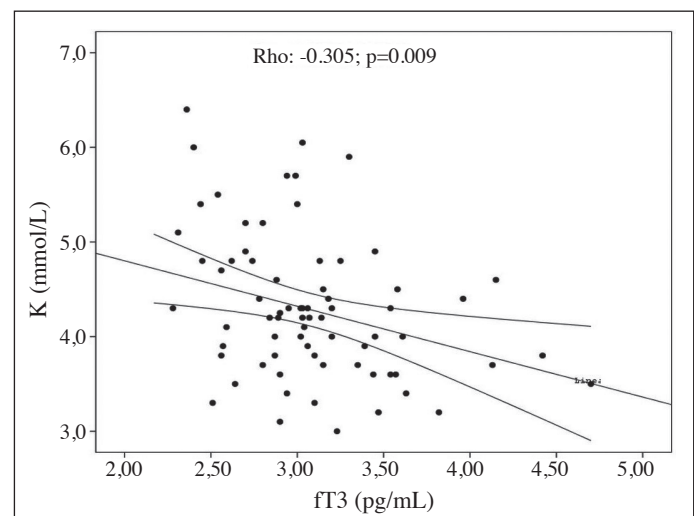


Figure 2: Relation between FT3 and serum potassium levels.

Table I: Baseline demographic, clinical, and biochemical data of the patients.

| Characteristic | FT3 Groups | | | | FT3 Versus Variables | |
|------------------------------------|---------------------|-----------------------------|-----------------------------|------------------|----------------------|------------------|
| | All patients (n:76) | Group 1 (n:40; ≤3.03 pg/mL) | Group 2 (n:36; >3.03 pg/mL) | P value | Rho Value | P value |
| Age (yr) | 50.4±13.8 | 55.3±13.5 | 44.7±12.1 | 0.001 | -0.414 | <0.001 |
| Men (%) | 56 | 44 | 65 | 0.073 | 0.110 | 0.356 |
| Hypertension (%) | 42 | 49 | 29 | 0.093 | -0.255 | 0.029 |
| Diabetes(%) | 13 | 15 | 6 | 0.188 | -0.132 | 0.266 |
| Systolic blood pressure (mmHg) | 125±18 | 129±18 | 121±17 | 0.059 | -0.333 | 0.004 |
| Diastolic blood pressure (mmHg) | 77±10 | 78±10 | 76±9.9 | 0.420 | -0.134 | 0.260 |
| Laboratory findings | | | | | | |
| FT3 (pg/mL) | 3.06±0.49 | 2.73±0.24 | 3.45±0.40 | <0.001 | 1 | - |
| FT4 (ng/dL) | 0.92±0.25 | 0.86±0.23 | 0.98±0.27 | 0.049 | 0.243 | 0.038 |
| TSH (mIU/L) | 1.45±0.72 | 1.48±0.79 | 1.37±0.62 | 0.518 | 0.109 | 0.360 |
| Hemoglobin (g/dl) | 13.5±1.8 | 12.9±1.85 | 14.3±1.21 | <0.001 | 0.283 | 0.015 |
| Albumin (g/dl) | 4.2±0.4 | 4.16±0.42 | 4.32±0.39 | 0.087 | 0.238 | 0.042 |
| GFR(Basal) (mL/min/1.73m2) | 56±22 | 51±23 | 65±18 | 0.007 | 0.295 | 0.011 |
| Proteinuria | 2.21±0.55 | 2.29±0.59 | 2.15±0.51 | 0.299 | -0.165 | 0.192 |
| Serum Sodium (Basal) (mmol/L) | 137±3.6 | 137±3.3 | 136±3.8 | 0.258 | -0.108 | 0.364 |
| Clinical Outcomes | | | | | | |
| Development of Hyperkalemia n, (%) | 15(19.7) | 12 (28) | 3 (9) | 0.031 | -0.295 | 0.011 |
| Progressive status n, (%) | 18(24) | 15(36) | 3 (9) | 0.005 | -0.405 | <0.001 |
| Renal Replacement Therapy n, (%) | 5(6.5) | 5(10) | 0(0) | 0.044 | -0.226 | 0.055 |
| Mortality n, (%) | 4(5.2) | 4(10) | 0(0) | 0.044 | -0.233 | 0.047 |

Table II: Cox regression analysis for predictors of renal progression.

| Predictors | Unadjusted | | Model 1 | | Model 2 | |
|----------------------|---------------------|---------|---------------------|---------|---------------------|---------|
| | HR (95 % CI) | p value | HR (95 % CI) | p value | HR (95 % CI) | p value |
| FT3 (per 1 pg/ml) | 0.38 (0.05-0.27) | 0.001 | 0.61 (0.08-0.49) | <0.01 | 0.18 (0.03-0.39) | 0.01 |
| Age (per 1 year) | 1.047 (1.003-1.092) | 0.034 | 1.012 (0.959-1.068) | 0.661 | 1.078 (0.970-1.202) | 0.15 |
| Hypertension (+/-) | 5.337 (1.660-17.16) | 0.005 | 3.566 (0.880-14.44) | 0.075 | 1.280 (0.98-16.78) | 0.84 |
| Proteinuria (gr/day) | 1.004(1.001-1.007) | 0.001 | - | - | 1.002 (1.001-1.003) | 0.01 |
| GFR(mL/min/1.73m2) | 0.962 (0.933-0.991) | 0.012 | - | - | 1.046 (0.994-1.102) | 0.07 |

All Variables: Age, History of Hypertension, proteinuria and Glomerular filtration Rate (GFR), Free T3.

Model 1: Free T3, Age, History of Hypertension.

Model 2: Model 1 and Proteinuria and Glomerular filtration Rate.

Table III: Cox regression analysis for predictors of hyperkalemia.

| Predictors | Unadjusted | | Model 1 | | Model 2 | |
|--------------------|------------------------|---------|------------------------|---------|-------------------------|---------|
| | HR (95 %CI) | p value | HR (95 %CI) | p value | HR (95 %CI) | p value |
| ftT3 (per 1 pg/ml) | 0.116 (0.20-0.65) | 0.02 | 0.417 (0.058-2.985) | 0.40 | 0.788 (0.102-6.103) | 0.82 |
| Age (per 1 year) | 1.052 (1.005-1.102) | 0.03 | 0.987 (0.931-1.047) | 0.69 | 0.988 (0.926-1.054) | 0.71 |
| GFR(mL/min/1.73m2) | 0.926 (0.887-0.967) | 0.001 | 0.920 (0.870-0.975) | 0.005 | 0.913 (0.862-0.0980) | 0.01 |
| RAS blockers(+/-) | 11.55 (3.194-41.80) | <0.001 | | | 7.920 (1.660-37.46) | 0.009 |

All Variables: Free T3, Age, Use of RAS blockers, and Glomerular filtration Rate(GFR).

Model 1: Free T3, Age, Glomerular filtration Rate.

Model 2: Model 1 and Use of RAS blockers.

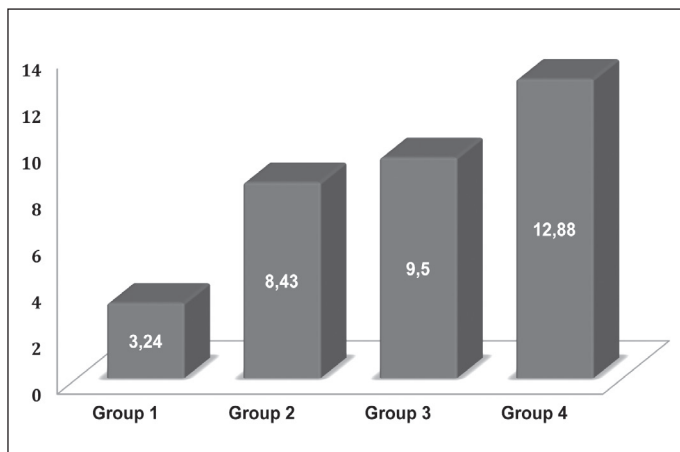


Figure 3: The risk of hyperkalemia in 4 subgroups.

Group 1 includes patients older than 50 years Group 2 includes Group 1 plus those with an eGFR of less than 56 mL / min / 1.73m2, Group 3 involves Group 2 plus those regularly taking the RAS blockers and Group 4 is Group 3 plus those with FT3 levels lower than the cumulative average.

The decrease in eGFR and treatment with RAS blockers were independent predictors of hyperkalemia development in multivariate analysis (Table III).

DISCUSSION

In this study, low levels of FT3 in adult patients with a solitary kidney was found to be an important parameter predicting CKD progression. Additionally, presence of low free-T3 significantly increased the risk for the development of hyperkalemia especially in patients harboring the risk factors as older age, stage 3 CKD and RAS- blocker use.

In the course of CKD, a compensatory increase in potassium excretion from kidneys occurs up to the development of end-stage renal failure (17,18). Here; angiotensin- renin-aldosterone

cascade plays an important role and hyperkalemia in the early stages of CKD, is often attributed to the use of RAS blockers and / or aldosterone antagonist (18). Despite an average eGFR of 56 mL / min / 1.73m2, 20% of our patients developed hyperkalemia. In these patients, low eGFR and treatment with RAS-blockers were independent risk factors for hyperkalemia and low free -T3 levels further increased this risk .

There are very few studies about the interaction of hypothyroidism and serum potassium levels in the literature (12-14). Schwarz and colleagues conducted a study on 9012 patients who admitted to the emergency department and hyperkalemia was 1.75 times higher in patients with hypothyroidism compared with euthyroid patients (7% vs. 4%) (13). Similarly, patients with thyroid carcinoma who were older than 60 years and receiving RAS-blocker drugs, significantly had higher risk of developing hyperkalemia following bilateral total thyroidectomy induced hypothyroidism (14). Different mechanisms may be responsible for the relationship between hyperkalemia and low FT3 (19-21). In the presence of overt hypothyroidism, angiotensin and angiotensin-converting enzyme level decreases and renin increases and / or decreases. In addition, intrarenal RAS system is inhibited, AT1 receptor expression might decrease and AT2 receptor activation is enhanced (19-21). However, in the course of renal failure but without overt hypothyroidism, low T3 levels may cause RAS system inhibition and / or may lead to differences in receptor levels and this process may increase the risk of hyperkalemia. In many studies, low levels of FT3 is associated with hypervolemia and this could secondarily inhibit RAS system which would eventually lead to hyperkalemia (22-24). In our study, we found significant correlation between FT3 levels and hypertension, particularly systolic blood pressure elevation. This may suggest that patients with low FT3 levels are hypervolemic and through secondary inhibition of the RAS system, they are prone to be hyperkalemic.

Nephrectomy is a risk factor for CKD development and even in healthy individuals with donor nephrectomy, progression to end-stage renal disease (ESRD) is possible both after indication and donor nephrectomy; basically the renal residual volume but also age, obesity and the presence of co-morbid conditions such as diabetes and hypertension are important for predicting the progression of renal disease (9-11, 25). However, in these patients, the effect of thyroid function on renal outcome is unknown. In CKD, there is a negative association between eGFR and hypothyroidism (overt or subclinic) and low T3 levels (2-4). Large-scale cohort studies showed that the prevalence of low-T3 syndrome was 8.2 %, 10.9%, 20.8%, 60.6% and 78.6 % at stages 1 to 5 of CKD, respectively and in hemodialysis patients, it reached 90 % (4,5). Active T3 can be reduced through an adaptive process to minimize the energy expenditure due to poor clinical outcomes as malnutrition and inflammation during the course of CKD. Also, with renal failure, T4-5'-deiodinase enzyme of kidney, which is almost entirely responsible for the synthesis of the active form of triiodothyronine substantially decreases and these two factors may cause low-T3 syndrome (1,5,6). In patients with CKD, this process is directly related to cardiovascular morbidity and mortality (6-8). In our study, there was an inverse relationship between FT3 levels and eGFR in patients with solitary kidney and those with low T3 levels exhibited approximately 4-fold increase in terms of renal disease progression. In the CKD population, there is no study investigating the relationship between low-FT3 levels and renal outcomes. However, the available data indicates poor renal outcome of patients with subclinical and clinical hypothyroidism and notifies the probability of a better outcome with thyroid replacement therapy (26-28).

Our study has some drawbacks. First of all, it includes limited number of patients and thyroid hormone tests were performed once. Therefore, we could not follow the variability in thyroid hormone levels that could happen in the course of CKD. Moreover, we do not have a second arm in patients with low FT3 level of whom receiving hormone substitution to elucidate whether such an intervention could resolve electrolyte disorder and prevent kidney disease progression. Finally, this study consisted patients with a solitary kidney due to nephrectomy, thus it could not reflect all solitary kidney patients (i.e. congenital solitary kidney patients).

In conclusion, free T3 levels in patients with a solitary kidney are associated with the progression of renal disease. In this population, development of hyperkalemia is common in patients with low FT3 levels particularly for those with low eGFR and receiving RAS blocker drugs.

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Conflict of interest: declare no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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