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# Relationship between Thyroid Functions and Estimated Glomerular Filtration Rate in Patients with Chronic Kidney Disease

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## ABSTRACT

**Background:** Chronic kidney disease (CKD) stands for a gradual decline in renal function occurring over months or years. Thyroid hormones exert specific influences on cellular differentiation as well as growth. The interaction between the thyroid and kidney in their respective functions has been recognized for several years. Thyroid dysfunction influences renal development as well as physiology, while kidney diseases may lead to thyroid dysfunction.

**Objective:** Our research was carried out to assess the correlation between thyroid function and estimated GFR among CKD cases.

**Patients and methods:** Our team designed a cross-sectional study including 117 cases developing CKD of varying etiology but not undergoing hemodialysis. Participants underwent a categorization based on GFR, measured by the " CKD Epi Formula" that fell between 15.1 and 58.2 ml/min/1.73 $m^2$ into, group 1 involved cases developing CKD stage 3a, GFR (45-59), group 2 involved cases developing CKD stage 3b, GFR (30-44) and group 3 involved cases developing CKD stage 4, GFR (15-29).

**Results:** TSH exhibited a significant increase within group 3 as opposed to (group 1 and group 2). Anti TPO and anti-thyroglobulin showed an insignificant variation among the three stages of GFR classification and no significant association was seen between GFR and (anti TPO and anti-thyroglobulin). A significant positive association was observed between TSH and (ACR and GFR). Free T3 and free T4 showed an insignificant variation among the three levels of ACR. A significant positive association was also documented between (anti TPO, anti-thyroglobulin) and ACR. No association was observed between GFR and (FT3, FT4, anti TBO, anti-thyroglobulin).

**Conclusion:** In CKD cases of varying etiology but not undergoing hemodialysis, a significant positive association was reported between TSH and (serum urea, creatinine, ACR) and between ACR and (anti TPO and anti-thyroglobulin). A significant negative association was documented between TSH and GFR.

**Keywords:** Thyroid Functions, TSH, CKD, Hypothyroidism, eGFR.

## INTRODUCTION

CKD stands for a gradual decline in renal function occurring over months or years. Individuals developing a GFR below 60 mL/min/1.73 $m^2$ for three months or more are categorized as CKD cases[(1)].

A worldwide rise in the CKD incidence has been documented, resulting in its recognition as a public health issue [(2)].

Thyroid hormones (TH) exert specific influences on cellular differentiation as well as growth. They also regulate critical physiological activities in almost all human tissues. TH level changes have been noted among individuals developing CKD. Additionally, thyroid dysfunction has risen with the CKD progression[(3)].

The interaction between the thyroid and kidney in their respective functions has been recognized for several years. Thyroid dysfunction influences renal development as well as physiology, while kidney diseases may lead to thyroid dysfunction. Thyroid and renal disorders may coexist due to similar etiologies[(4)].

Clinically, thyroid gland disorders like hypothyroidism as well as euthyroid sick syndrome (ESS), have been identified among CKD cases, particularly in stage 5 CKD. Individuals developing hypothyroidism may exhibit significant decreases as regards estimated eGFR, which may be enhanced with TH replacement therapy. Hypothyroidism may also result in hyperlipidemia as well as atherosclerosis in coronary and peripheral arteries. Similar to hypothyroidism, ESS was linked to endothelial dysfunction among cases developing stage 3 or 4 CKD, along with elevated mortality risks in CKD stage 5[(5)].

This study aimed at assessing the association between thyroid function and estimated GFR among CKD cases.

## PATIENTS AND METHODS

Our team designed a cross-sectional study at the Internal Medicine Department of Tanta University Hospital and the National Institute of Nephrology and Urology, including 117 cases developing CKD within the timeframe between May 2022 and May 2023.

Our team included cases, with the age of 18 years or more of both genders. They developed CKD (eGFR of below 60 mL/min/1.73 $m^2$ for 3 months or more). They were not dialysis dependent. We excluded those on anti-thyroid medications, cases developing congenital thyroid anomaly, cases who previously presented with thyroid conditions or underwent any thyroid surgical procedures, cases developing DM, with cardiac disease or having malignancies or mental disorders.



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**Ethical consideration:**

**Before we started our research, Tanta University Institutional Review Board approved the protocol and all related documentation for ethical and research permission (approval code: 35493/5/22). The study adhered to the Helsinki Declaration throughout its execution. Our team gathered a signed informed consent from all participants including the research's aim as well as all the steps conducted. We endured data confidentiality, with data only utilized in research. Each participant had a specific code number within a special folder. The research's findings were only utilized in scientific publishing. Our team adhered to full aseptic approaches while conducting the procedures. Proper healthful disposal was employed.**

## METHODS

Our team gathered a comprehensive medical history from all participants, including age, gender, smoking status, as well as comorbidities that involved smoking history, hypertension, DM, dyslipidemia, hepatic diseases, asthma, cardiovascular disorders, thyroid medication, and others. We then conducted a thorough physical examination including the evaluation of the overall condition as well as vital signs, like systolic and diastolic blood pressure, heart rate, as well as temperature. Standard laboratory assessments encompassed CBC, C-reactive protein (CRP), fasting blood glucose, 2-hour postprandial blood glucose, as well as HbA1c, along with kidney function testing (blood urea and serum creatinine) and albumin-creatinine ratio, categorized as normal or mildly increased (<30 mg/g), moderately increased albuminuria (30-300 mg/g), as well as severely increased albuminuria (>300 mg/g). We also conducted imaging examinations including ultrasonography of both kidneys.

According to the KDIGO recommendations, CKD cases underwent categorization into five grades based on GFR: grade 1 (eGFR above 90 ml/min/1.73 $m^2$), grade 2 ( between 60 and 89 ml/min/1.73 $m^2$), grade 3a (between 45 and 59 ml/min/1.73 $m^2$), grade 3b (between 30 and 44 ml/min/1.73 $m^2$), grade 4 (between 15 and 29 ml/min/1.73 $m^2$), as well as grade 5 (eGFR below 15 ml/min/1.73 $m^2$).

Particular laboratory assessments involved anti-thyroid peroxidase (with a normal range of 34 IU/mL), anti-thyroglobulin (with a normal range of up to 115 IU/mL), TSH (with a normal range between 0.27 and 5 µIU/mL), free T3 (with a normal range between 2.3 and 4.5 pg/mL), as well as free T4 (with a normal range between 0.93 and 1.7 ng/dL).

**Blood sampling and processing:**

Our team collected a 10-ml venous blood sample within plain vacutainer tubes after an 8-10 hour fasting period, in accordance with quality control and safety protocols for sample collection. Two milliliters were incorporated into EDTA for complete blood count. The serum was isolated from the other vacutainer for routine and specialized laboratory analysis employing fine centrifugation at 3000 rpm for fifteen minutes. Serum samples were sent to the laboratory within two hours following collection for examination. Blood urea and serum creatinine were analyzed employing a fully automated chemistry analyzer (Konelab Thermoscientific Prime 60, USA). Serum electrolytes (sodium, potassium, and ionized calcium) were assessed with the Diestro RS232 Electrolyte Analyzer.

**Calculation of eGFR by CKD-EPI equation:**

The CKD-EPI equation, formulated as a singular expression, was GFR = 141 × min (Scr/κ, 1) α × max (Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black].

Scr denotes serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for men, min represents the lesser of Scr/κ or 1, and max signifies the greater of Scr/κ or 1.

***Statistical analysis***

The statistical software IBM SPSS version 25.0 was used for all statistical computations. When appropriate, data were described using frequencies (number of instances), percentages, median and interquartile range, and mean± SD. For regularly distributed data, one-way ANOVA was used to compare the numerical variables between study groups; for non-normally distributed data, the Mann-Whitney U test and Kruskal Wallis test were used. The $X^2$-test was used for categorical data comparisons. The Spearman correlation test was used. Statistical significance was established for two-sided p values that were less than or equal to 0.05

## RESULTS

Our cross-sectional study was performed on 117 patients suffering from CKD of varying etiology but not undergoing hemodialysis who have been considered for the study after fulfilling the inclusion criteria. The studied cases were then divided according to their GFR using the EPI CKD equation into the following three groups, group 1 involved cases developing Stage 3a (GFR45-59 ml/min/1.73$m^2$), group 2 involved cases developing Stage 3b (GFR30-44 ml/min/1.73$m^2$) and group 3 involved cases developing Stage 4 (GFR15-29 ml/min/1.73$m^2$).

G1 had 20 patients, men represented 15 patients (75%), while the remaining portion was occupied by women (25%). G2 had 24 patients, men as well as women represented 50%. G3 had 73 patients, men represented 35 patients (47.9%), while women were 38 patients (52.1%). Age exhibited a significant variance between G3 and stage G2 and between stage G1 and G2(P=0.001) (**Table 1**).

**Table (1):** Sex and Age of the patients

**Table (1):** Sex and Age of the patients

| **Sex** | | **Group 1** | **Group 2** | **Group 3** | **Total** | **Test** | **P value** |
|---|---|---|---|---|---|---|---|
| **Male** | **N** | 15 | 12 | 35 | 62 | **Chi-square** | P=0.094 |
| | **%** | 75.0% | 50.0% | 47.9% | 53.0% | $X^2$=4.721 | |
| **Female** | **N** | 5 | 12 | 38 | 55 | | |
| | **%** | 25.0% | 50.0% | 52.1% | 47.0% | | |
| **Total** | **N** | 20 | 24 | 73 | 117 | | |
| | **%** | 100.0% | 100.0% | 100.0% | 100.0% | | |
| **Age (years)** | | | | | | | |
| Range | | 19 – 50 | 25 – 76 | 19 – 80 | | | 0.001* (1) |
| Mean | | 33.15 | 51.29 | 46.07 | | | |
| Pairwise comparison (3) | | P1: 0.001*, P2: 0.138, P3:0.001* | | | | | |

*: significant. (1) One way ANOVA test, (3) Post hook test (Bonferoni test).

P1: P value between G1 and G2. P2: P value between G2 and G3. P3: P value between G1 and G3.

Regarding CBC parameters, hemoglobin had a median value of 9.8 gm/dl, while total leucocytic count indicated a median value of 6.7. Moreover, platelet count indicated a median value of 211. The analysis of the diabetic profile revealed that fasting and 2 hours post prandial blood glucose levels had median values of 89 and 119 respectively. Additionally, HbA1c ranged between 3.5 and 5.7% (**Table 2**).

**Table (2):** Routine Laboratory investigation of the studied patients

| **Parameters** | **Min - Max**<br>**Median (IQR)** |
|---|---|
| **HB (gm/dl)** | 6.5-14<br>9.8(2.4) |
| **WBCs ($10^3$/fl)** | 3.6-16<br>6.7(3.3) |
| **Platelet ($10^3$/fl)** | 100-427<br>211(82.5) |
| **FBG (mg/dl)** | 70-112<br>89(18.5) |
| **2 hours postprandial glucose (mg/dl)** | 88-139<br>119(25) |
| **HbA1c (%)** | 3.5-5.7<br>4.6(3.85) |
| **CRP (mg/dl)** | 1-50<br>8(10.5) |

Rang, median and IQR: Non-parametric test.

Urea exhibited a significant increase as regards G2 as opposed to G1 and a significant increase within G3 as opposed to stage G1. Creatinine showed a significant increase within G3 as opposed to (stage G1 and G2), and ACR showed a significant increase within G3 than stage G1. TSH exhibited a significant increase within G3 as opposed to G1 and G2. Free T3 and free T4 exhibited statistically non-significant decline among the three stages of GFR classification (**Table 3**).

**Table (3):** Renal functions of the studied patients

| **Studied variables** | | **GFR ((ml/min/1.73 m$^2$)** | | | **Total** | **P value** |
|---|---|---|---|---|---|---|
| | | **Group 1 (1)** | **Group 2 (2)** | **Group 3 (3)** | | |
| | Mean ± SD | 71.94 ±13.6 | 98.2 ±5.1 | 103.9 ±25.5 | 97.7 ±26.39 | <0.001*(1) |
| | Pairwise comparison (3) | P1= 0.001* P2=0.950 P3<0.001* | | | | |
| **Creatinine** (mg/dl) | Min- Max | 1.3-2 | 1.5-2.45 | 1.8-5.42 | 1.3-5.42 | <0.001*(2) |
| | Median (IQR) | 1.65 (0.3) | 1.9 (0.3) | 3 (1) | 2.5 (1.13) | |
| | Median (IQR) | 30 (143.2) | 35 (95) | 90 (251.5) | 40 (187.25) | |
| | Pairwise comparison | P1= 0.827, P2=0.386, P3=0.022* | | | | |
| **TSH** (uiu/ml) | Min- Max | 0.59 -9.3 | 0.05-9.5 | 0.04-20.96 | 0.04-20.96 | 0.049*(2) |
| | Median (IQR) | 3.7 (5.3) | 4.1 (3.8) | 5.2 (5.3) | 4.9 (5.2) | |
| Pairwise comparison | P1=0.04* P2=0.046* P3=0.044* | | | | | |
| **Free T3** (pg/dl) | Min- Max | 1.9-3.8 | 0.57-4.9 | 0.2-4.9 | 0.2-4.9 | 0.638(2) |
| | Median (IQR) | 2.45 (0.95) | 2.48 (1) | 2.1 (1.95) | 2.25 (1.23) | |
| **Free T4** (ng/dl) | Min- Max | 0.8-1.6 | 0.05-2.4 | 0.01-3.73 | 0.01-3.73 | 0.270(2) |
| | Median (IQR) | 1.1 (0.47) | 0.91 (0.51) | 0.99 (0.79) | 1 (0.65) | |

Rang, median and IQR: Non-parametric test.
P1 (1-2) P2 (2-3) p3 (1-3) *: statistically significant (P ≤ 0.05)
(1)One way ANOVA test, (2)Kruskal Wallis test, (3)Post hook test (Bonferoni test)
GFR: Glomerular filtration rate. ACR: Urine albumin to creatinine ratio
P1: P value between G1 and G2. P2: P value between G2 and G3. P3: P value between G1 and G3.

Anti TPO and anti-thyroglobulin were insignificantly different among the three stages of GFR classification (**Table 4**).

**Table (4):** Thyroid antibodies of the studied patients

| **Studied variables** | | **GFR (ml/min/1.73 m$^3$)** | | | **Total** | **P value** |
|---|---|---|---|---|---|---|
| | | **Group 1** | **Group 2** | **Group 3** | | |
| **Anti TPO** | Negative | 13 | 13 | 35 | 61 | 0.391 |
| | | 65.0% | 54.2% | 47.9% | 52.1% | |
| | Positive | 7 | 11 | 38 | 56 | |
| | | 35.0% | 45.8% | 52.1% | 47.9% | |
| **Anti Thyroglobulin** | Negative | 14 | 15 | 44 | 73 | 0.440 |
| | | 70.0% | 62.5% | 60.3% | 62.4% | |
| | Positive | 6 | 9 | 29 | 44 | |
| | | 30.0% | 37.5% | 39.7% | 37.6% | |

*: significant, Chi square test, Anti TPO: Anti-thyroid peroxidase

TSH exhibited a significant increase in severely-elevated albuminuria as opposed to (normal and moderately-elevated albuminuria) and in moderately increased albuminuria than normal. Free T3 and free T4 showed an insignificant variation among the three stages of GFR classification (**Table 5**).

**Table (5):** Thyroid functions of the studied patients according to level of ACR

| Studied variables | | Level of ACR | | | P value |
|---|---|---|---|---|---|
| | | Normal (1) | Moderately increased albuminuria (2) | Severely increased albuminuria (3) | |
| **TSH** (uiu/ml) | Min- Max | 0.04-8.1 | 0.5-12.5 | 1.34-20.96 | <0.001* |
| | Median (IQR) | 3.48 (2.98) | 6.2 (5.49) | 8 (8.13) | |
| | **Pairwise comparison** | | P1=0.010* P2=0.050* P3<0.001* | | |
| **Free T3** (pg/dl) | Min- Max | 0.8-4.9 | 0.3-4.4 | 0.2-4.9 | 0.085 |
| | Median (IQR) | 2.5(1.36) | 2.2(1.15) | 1.8(1.46) | |
| **Free T4** (ng/dl) | Min- Max | 0.60-3.73 | 0.01-3.01 | 0.26-2.5 | 0.096 |
| | Median (IQR) | 1.1(0.6) | 0.93(0.79) | 0.75(0.53 | |

Rang, median and IQR: Non-parametric test.
P1(1-2), P2(2-3), P3(1-3). *: significant, Kruskal-Wallis test
P1: P value between normal and moderately increased albuminuria.
P2: P value between moderately increased albuminuria and severely increased albuminuria.
P3: P value between normal and severely increased albuminuria.

Anti TPO and anti-thyroglobulin was significantly different among normal, moderately increased albuminuria and severely increased albuminuria groups (**Table 6**).

**Table (6):** Thyroid antibodies of the studied patients according to level of ACR

| Studied variables | | ACR (mg/g) | | | P value |
|---|---|---|---|---|---|
| | | Normal | Moderately increased albuminuria | Severely increased albuminuria | |
| **Anti TPO** | Negative | 36 | 23 | 2 | <0.001* |
| | | 73.5% | 44.2% | 12.5% | |
| | Positive | 13 | 29 | 14 | |
| | | 26.5% | 55.8% | 87.5% | |
| **Anti-Thyroglobulin** | Negative | 41 | 42 | 7 | 0.002* |
| | | 83.7% | 80.8% | 43.75% | |
| | Positive | 8 | 9 | 9 | |
| | | 16.3% | 23.7% | 56.25% | |

*: Significant.
A significant positive association was documented between (TSH and anti TPO) and ACR, between anti-thyroglobulin and ACR, between TSH and blood urea, and between TSH and serum creatinine. A significant negative association was observed between TSH and GFR. No association was observed between GFR and ACR, between free T3 and (urea and creatinine), between free T4 and (urea and creatinine), and between GFR and (FT3, fT4, anti TBO, anti-thyroglobulin) (**Table 7**).

**Table (7):** Correlation between (TSH, Anti TPO, Anti Thyroglobulin, GFR) with ACR and thyroid functions with kidney functions

| | ACR (mg/g) | | Blood urea (mg/dl) | | Serum Creatinine (mg/dl) | | GFR (ml/min/1.73 $m^2$) | |
|---|---|---|---|---|---|---|---|---|
| | rs | P | rs | P | rs | P | rs | P |
| **TSH** (uIU/ml) | 0.585* | <0.001* | 0.218 | 0.018* | 0.180 | 0.038* | -0.442 | 0.029* |
| **Anti TPO** | 0.448 | <0.001* | | | | | -0.162 | 0.082 |
| **Anti Thyroglobulin** | 0.202 | 0.029* | | | | | -0.108 | 0.246 |
| **Free T3** (pg/dl) | | | -0.099 | 0.288 | -0.127 | 0.095 | 0.004 | 0.969 |
| **Free T4** (ng/dl) | | | 0.075 | 0.423 | -0.140 | 0.132 | 0.010 | 0.916 |

rs Spearman correlation, *: Significant.

## DISCUSSION

In Egypt, CKD is a serious health issue. Approximately 13% of Egyptian adults have CKD, which contributes significantly to morbidity, mortality, and medical costs [6]. It has been known for a number of years that thyroid and renal function are related. Renal growth and development, GFR, renal transport systems, and salt and water balance are all directly impacted by TH [4,7].

It has been determined that thyroid disorders increase the likelihood of developing CKD, and vice versa[8,9]. Furthermore, modifications in TH could arise in CKD cases without a preexisting intrinsic thyroid problem, referred to as nonthyroidal sickness syndrome[10]. The correlation between renal and thyroid functioning is being investigated in Egyptian cases, which motivated us to do the current research.

Our research was carried out at the Internal Medicine Department of Tanta University Hospital and the National Institute of Nephrology and Urology to investigate the correlation between thyroid function and estimated GFR among CKD cases. This cross-sectional study included 117 cases suffering from CKD of varying etiology but not undergoing hemodialysis from May 2022 to May 2023.

Participants underwent categorization based on GFR, measured by the " CKD Epi Formula" that ranged between 15.1 and 58.2 ml/hr/1.73m$^2$ into the following groups, group 1 involved cases developing CKD stage 3a, GFR (45-59 ml/min/1.73 m$^2$), group 2 involved cases developing CKD stage 3b, GFR (30-44 ml/min/1.73 m$^2$) and group 3 involved cases developing CKD stage 4, GFR (15-29 ml/min/1.73 m$^2$). Our team gathered a comprehensive medical history from all participants, the conducted a thorough physical examination, laboratory investigations, thyroid ultrasound, as well as echocardiography.

In our research, TSH exhibited a significant increase within stage 4 as opposed to stage 3a and 3b. A significant negative association was documented between TSH and GFR (r= -0.442, p=0.029).

Numerous epidemiological studies mostly undertaken in European cohorts have shown an inverse relationship between eGFR and serum TSH levels and/or hypothyroidism risks [9]. **Rhee et al.**[11] stated that a 10 mL/min/1.73 m$^2$ lower eGFR exhibited a correlation with a 0.11-mIU/L greater serum TSH (95% CI 0.10–0.11 mIU/L greater serum TSH, P < 0.001).

Additionally, **Meuwese and his colleagues**[12] reported that eGFR was reduced among participants having greater TSH concentrations (P = 0.021). **Kamal and his colleagues**[9] reported a significant negative association between GFR and TSH among their CKD cases (r = - 0.656 – p < 0.001). Nonetheless, that significance faded in their CKD patients receiving hemodialysis (p = 0.77). A prior cohort research indicated that TH replacement among subclinically hypothyroid individuals developing CKD is linked to enhanced preservation of kidney function as opposed to non-treatment, indicating that hypothyroid-induced disturbances in kidney function could be changeable[13].

In our research, free T4 as well as FT3 exhibited an insignificant variance among the three stages of GFR classification. Additionally, no significant association was documented between GFR and (FT3 and FT4). Similarly, **Kamal and his colleagues**[9] observed no significant association between free T4 and eGFR among their included CKD cases receiving hemodialysis (p = 0.993). However, the same study revealed a significant positive association between the same two parameters among CKD cases not receiving hemodialysis (r = 0.552, p < 0.001).

In contrast to our research, According to a study conducted by **Kim and his colleagues**[14], a correlation was documented between thyroid function and kidney function. The performed data analysis from the Korea National Health and Nutrition Examination Survey between 2013 and 2015, addressing that a 1 µg/dL rise of free thyroxine (fT4) exhibited a correlation with reduced eGFR on multivariate linear regression analysis. However, such a correlation was reversed following age adjustment.

**Kamal and his colleagues**[9] reported a significant positive association between eGFR and the estimated free T3 levels (r = 0.554 – p < 0.001) among CKD cases.

As regards our research, a significant positive association was documented between TSH and urea (r=0.218, p value=0.018). Additionally, a significant positive association was documented between TSH and serum creatinine (r= 0.180, p=0.038). Regarding urea, produced in the liver during amino acids and other nitrogenous metabolites' catabolism, undergoes a normal excretion into the urine via kidneys as fast being produced. During renal function impairment, elevated blood urea concentrations steadily accumulate[15]. Creatinine stands as a metabolic by-product of creatine phosphate in muscle, generated by the body at a consistent pace. Creatinine is mostly eliminated from the bloodstream through kidneys. Reduced renal clearance induces elevated blood creatinine levels[16].

Our results did not address association between free T3 and freeT4 and (urea and creatinine). **Fawzy and his colleagues**[17] reported that serum creatinine had a mean value of 3.26 mg/dl (range, 1.4 – 5.7mg/dl) in their included 80 CKD patients. They reported no significant correlations between free T3 and either serum urea or creatinine (p = 0.214 and 0.074, respectively).

According to our results, anti TPO and anti-thyroglobulin were insignificantly different among the three stages of GFR classification. **Zhao and his colleagues**[18] conducted retrospective study utilizing the medical records of 246 nephropathy cases, 82 of whom developed concurrent autoimmune thyroid disease (AITD). They addressed that the TPO-Ab and TG-Ab levels were more common in the kidneys of cases developing nephropathy and AITD.

Our research addressed significant positive association between anti TPO and ACR (P value<0.001), and between anti-Thyroglobulin and ACR. Anti TPO and anti-Thyroglobulin exhibited a significant variance among (normal, moderately elevated albuminuria and severely elevated albuminuria) indicating P < 0.001 and 0.015 respectively. **Zhu and his colleagues**[19] included one hundred twenty newly diagnosed T2DM cases developing Hashimoto's thyroiditis as well as euthyroidism, along with fifty sex and age-matched T2DM with non-Hashimoto's and other thyroid disease. UACR exhibited a correlation with TPO-Ab ($r = 0.349$, $P < 0.05$).

**Gilles and his colleagues**[20] investigated 159 TPO antibody-negative cases within early CKD stages (serum creatinine 0.92–1.51 mg/dl) with ages of a median 52 years and developing median daily proteinuria of 6.6 g/10 mmol creatinine. Additionally, they addressed that median TSH showed a significant increase among cases as opposed to the controls (1.81 mU/l vs 1.34 mU/l, p.<0.001). Cases developing proteinuria exhibited increased TSH levels, along with urinary TH loss.

Our research indicated that TSH exhibited a significant increase in severely-elevated albuminuria as opposed to normal and moderately-elevated albuminuria as well as in moderately-elevated albuminuria as opposed to normal (P < 0.05). Additionally, a significant positive association was documented between TSH and ACR. Free T3 as well as Free T4 exhibited an insignificant variance among the three ACR levels.

**Wheatley and his colleagues**[21] investigated 9 female cases having normal serum total thyroxine (T4) as well as triiodothyronine (T3) yet increased TSH concentrations. Six cases exhibited generalised oedema linked to maximal diurnal weight gains beyond 1.4 kg. Under forced water diuresis conditions, prior to- and during physiological 1-thyroxine replacement, the supine transcapillary escape rate of albumin (TERA) was estimated. Among the six cases developing edema and excessive diurnal weight gains, the salt and water retention on tilting showed lower values utilizing thyroxine treatment. The albumin transcapillary escape rate in subclinical hypothyroid condition was elevated.

Conversely, **Du and his colleagues**[22] evaluated 581 cases of developing albuminuria. Their cases underwent categorization into subgroups with <30 mg/g (n = 269), 30–300 mg/g (n = 196), and >300 mg/g (n = 116) of albuminuria. Interestingly, they addressed that TT4 as well as FT4 exhibited significant variance among three ACR groups that (both $P < 0.001$). They also detected a positive association between albuminuria and increased serum T4 and fT4 values. Conversely, TT3, FT3 as well as TSH showed no correlation with albuminuria.

In agreement with our findings, **Das and his colleagues**[23] addressed that TSH levels exhibited a correlation with increased microalbuminuria prevalence (adjusted odds ratio 2.06 [95% CI: 1.14–3.72]; $P = 0.02$), when performing a comparison between the highest and the lowest quartile of TSH. Multiple linear regression analysis exhibited an independent correlation between serum TSH and urine albumin creatinine ratio ($\beta = 0.007$, $t = 2.03$ and $P = 0.04$).

Similarly, **Wu and his colleagues**[24] addressed an inverse correlation between serum FT3 levels and diabetic nephropathy among euthyroid cases developing T2DM, being independent of conventional risk factors. Additionally, they addressed a correlation between subclinical hypothyroidism and microalbuminuria among prediabetic cases and T2DM cases where subclinical hypothyroidism exhibited an independent correlation with microalbuminuria prevalence along with increased diabetic nephropathy risks[25].

In disagreement with our findings, a research by **Reinhardt and his colleagues**[26] prospectively studied the correlation between kidney and thyroid function among thyroid antibody-negative cases throughout all CKD stages. rT3 levels negatively linked to albuminuria ($r = -0.286$, $p < 0.001$) and showed a significant reduction among severe albuminuria cases as opposed to those developing mild or moderate albuminuria (ACR3: 0.28 vs. ACR2: 0.32 vs. ACR1: 0.36 nmol/l, $p < 0.001$). The albuminuria severity did not have an influence on TSH, fT4, T3, fT3, and TBG. The variations could be partly due to the fact that their cohort only involved thyroid antibody-negative cases. Furthermore, their cases were older while developing more progressive CKD stages as opposed to other cohorts.

## CONCLUSIONS

In CKD patients of varying etiology but not undergoing hemodialysis, a significant positive association was documented between TSH and (serum urea, creatinine, ACR) and between ACR and (anti TPO and anti-thyroglobulin). Additionally, a significant negative association was observed between TSH and GFR.

## LIMITATIONS

The sample size was relatively small. Our study didn't evaluate the thyroid dysfunction treatment influence on renal function parameters in CKD patients. More prospective multicenter studies with a large sample size are necessary.

## CONCLUSION

This study showed the inverse relationship between TSH and eGFR, so we recommend application of thyroid hormones in routine lab in CKD patients for earlier detection of hypothyroidism. Additional research is essential to detect the thyroid hormones role in the pathogenesis of CKD and as adjunctive therapy to control CKD progression.

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