# Serum Triiodothyronine (T*3*) hormone evaluation in patients with Chronic Kidney Disease and its value as an inflammatory marker

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**Abstract: Background:** End-stage renal disease (ESRD) alters the hypothalamic-pituitary-thyroid hormone axis as well as the peripheral thyroid hormone metabolism. **Aim of the study:** The aim of this work is to study the serum triiodothyronine (T3) hormone level in patients with CKD and its value as an inflammatory marker in relation to CRP and IL-6. **Patients and methods:** This study was done at Al- Azhar university Hospital New Damietta, in the period from May 2013 to February 2014.This study was done on sixty male patients who were selected from outpatient clinic of Internal Medicine Department and Hemodialysis Unit. These patients were divided according to presence or absence of Renal Replacement Therapy (RRT) into two groups **Group A** thirty patients with CKD on RRT (Regular Hemodialysis) and **Group B** thirty patients with CKD without RRT (conservative treatment).All patients were subjected to full history taking, clinical examination and laboratory investigations with specific interest for CRP, IL-6 and thyroid function tests. **Results:** Hypertension and diabetes mellitus are the most common causes of CKD and prevalence of hypertension was 83.3% in group A, 60% group B, the inflammatory markers IL-6 and CRP was higher in group A. In addition, serum fT3 had low values in these group than patients in-group B There was positive correlation between creatinine clearance and (albumin, FT3 and FT4), and there was negative correlation between creatinine clearance and (IL-6, CRP, TSH and urea). Serum levels of lipids are higher in-group A There was positive correlation between IL-6 and (CRP, S. uric acid. S.creatinine, urea and TSH) There was negative correlation between IL-6 and (albumin, creatinine clearance, FT3 and FT4), There was highly significant predictive value between IL-6 and (CRP, TSH, FT3 and FT4). There was positive correlation between CRP and (IL-6, uric acid, S. creatinine, urea and TSH). **Conclusion:** The low T3 levels in CKD patients have been correlated with higher levels of markers of inflammation [highly sensitive C-reactive protein, and IL-6]; freeT3 could be used as an inflammatory marker and may be used as prognostic factor for cardiovascular morbidity in CKD Patients.
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**Keywords:** Triiodothyronine, end stage renal disease, inflammation.
**Abbreviations:** CKD: Chronic Kidney Disease RRT:Renal Replacement Therapy GFR: Glomerular filtration rate CRP: C-reactive protein IL-6: Interleukin 6 HD : Hemodialysis

## 1. Introduction

End-stage renal disease (ESRD) alters the hypothalamic-pituitary-thyroid hormone axis as well as the peripheral thyroid hormone metabolism. Triiodothyronine ($T_3$) is the most metabolically active thyroid hormone which may be reduced in ESRD patients even with a normal TSH level in spite of its normal thyroid production and normal or even decreased clearance rates **(Song *et al.,* 2009). Iervasi *et al.,* (2003)** suggested that low T3 was an independent predictor of survival in various illness states. And proposed that biomarkers of inflammation were associated with low T3 levels in hemodialysis and peritoneal dialysis patients and the thyroid dysfunction may be implicated in the pathogenic pathway, which link microinflammation to survival in dialysis patients. **Christ-Crain *et al.,* (2003)** showed that CRP levels are overtly elevated in patients with subclinical or clinical hypothyroidism and revealed consistent and intriguing links between biomarkers of inflammation and thyroid hormones in patients with hypothyroidism and in the general population **Zoccali *et al.,* (2005)** showed that consistent and independent inverse associations between IL-6 and CRP as an indicator of endothelial activation/dysfunction and fT3 in patients with chronic kidney disease (CKD) and found that fT3 was reduced to an important extent during intercurrent inflammatory processes, this alteration resolved as inflammation faded away. In addition, the inflammation acutely interferes with thyroid function in patients with chronic kidney disease (CKD) and this interference is fully reversible

and independent of the glomerular filtration rate (GFR).

ESRD patients have low serum T3 levels irrespective of serum TSH levels. The explanation is that thyroid abnormalities can occur within hours of acute illness, and the magnitude of these alterations correlates with severity of the disease and survivals **(Bruckert *et al.*, 2009). Bruckert *et al.*, (2009)** found that low free T3 hormone is an independent predictor of mortality in hemodialysis patients, so ESRD patients with relatively higher serum free T3 had a lower mortality risk than patients with lower serum-free T3. In addition, they suggested that low T3 was associated with inflammation and cardiovascular morbidity in ESRD patients. **Song *et al.*, (2009)** suggested that low T3 could be a marker of prognosis in persons with renal problems

**Aim of the work**

The aim of this work was to study the serum triiodothyronine ($T_3$) hormone level in patients with CKD and its value as an inflammatory marker in relation to CRP and IL-6.

## 2. Patients and Methods

This study was done at Al-Azhar university Hospital New Damietta, in the period from May 2013 to February 2014.This study was done on sixty male patients who were selected from outpatient clinic of Internal Medicine Department and Hemodialysis Unit. These patients were divided according to presence or absence of Renal Replacement Therapy (RRT) into two groups **Group A** thirty patients with CKD on RRT (Regular Hemodialysis, HD was performed for 4 hours, three times weekly using conventional heparin. Blood access was through arterio-venous fistula. Blood flow rate was usually 300–350ml/min with a dialysate flow rate of 500 ml/min. Ultrafiltration varied according to patient's actual weight. The membrane used was biocompatible with surface area suitable for each patient. Bicarbonate was the buffer) and **Group B** thirty patients with CKD without RRT (conservative treatment).

**Inclusion Criteria:** History of (CKD) is not less than six months; duration of dialysis is not less than six months.

**Exclusion criteria:** Patients suffering from previous thyroid dysfunctions, Patients with clinical findings of thyroid diseases, Patients on medications that affect the study outcome as (Thionamides, Lithium, amiodarone, interferon), Patients under treatment of thyroid disorders by L-thyroxin or antithyroid drugs such as carbimazole or thiouracils; Patients with diseases or conditions that interfere with CRP, IL-6 or thyroid profile as (Fever, infections of arterio-venous fistula, Drugs, UTI, Malignancies ,TB or Collagen diseases).

All studied patients were subjected to full history taking, complete clinical examination and laboratory investigations that included CBC, fasting blood glucose, liver function tests (ALT, AST, albumin, and bilirubin), kidney function tests (creatinine, urea, uric acid, creatinine clearance, estimated GFR and urine analysis), high sensitive CRP, lipid profile (cholesterol, triglycerides, HDL and LDL), and estimation of serum thyroid hormones (TSH, FT3 and FT4) and IL- 6.

Thyroid hormones (TSH, FT3 and FT4) were measured by chemiluminescence with Immulite (1000) with kit (Diagnostic Products Corporation; Los Angeles, CA, USA).

Human IL-6 was measured by ELISA Kit (Assaypro) according to manufacturer instructions. This assay employs a quantitative sandwich enzyme immunoassay technique. IL-6 in standards and samples was sandwiched by the immobilized antibody and a biotinylated polyclonal antibody specific for human IL-6, which was recognized by a streptavidin-peroxidase conjugate. All unbound material was then washed away and a peroxidase enzyme substrate was added. The color development was stopped and the intensity of the color was measured by microplate ELISA reader (Model: Sunrise-Basic Tecan, Austria).

Abdominal ultrasound by A real time scanning device Ultrasonic Version 6.03 with convex probe, 3.5-5 MHz, was used for estimation of kidney size, criteria suggestive of CKD and presence of ascites (mild, moderate, severe) **(Bates *et al.*, 2006).**

**Statistical analysis of data:** The data were processed and analyzed using the statistical package for social sciences (SPSS) program. Description of quantitative variables in the form of Mean and Standard Deviation (mean ±SD). Description of qualitative variables by frequency and percentage. Chi-square test was used to compare qualitative variables between groups. Unpaired t-test was used to compare quantitative variables, in parametric data (SD<50% mean). Positive Predictive Value (PPV) = true positive/ true positive plus false positive; Negative Predictive Value (NPV) = true negative/true negative plus false negative and overall accuracy = true positive +true negative/total. $P$ value < 0.05 was considered significant.

## 3. Results

Hypertension and diabetes mellitus were the most common causes of CKD and prevalence of hypertension was 83.3% in-group A, 60% group B. There was significant increase of cholesterol and LDL and significant decrease of HDL in-group A when compared to group B. Furthermore, there was significant increase of C-reactive protein and interleukin-6 in-group A when compared to group B

(1.02±0.37, 106.30±42.57 vs 0.52±0.18, 44.13±16.55 respectively). In addition, there was significant increase of TSH and significant decrease of fT3 and fT4 in-group A when compared to group B (4.50±1.71, 1.0±0.17, 7.53±1.87 vs 3.22±0.61, 1.21±3.52 and 10.83±3.52 respectively). **(Table1)**.

In studied groups, there was positive correlation between creatinine clearance and (albumin, FT3 and FT4) and negative correlation between creatinine clearance and (IL-6, CRP, TSH and urea), There was highly significant predictive value between creatinine clearance and (IL-6, FT3 and FT4). In addition, there was significant predictive value between creatinine clearance and (CRP, TSH). There was non-significant predictive value between creatinine clearance and (albumin, uric acid, s.creatinine and bl. urea). There is positive correlation between IL-6 and (CRP, s. uric acid. s.creatinine, bl. urea and TSH). **(Table2)**.

As regard to correlation in group A; there was significant positive correlation between IL-6 from one side; and each of CRP and TSH; while there was significant, inverse correlation between IL-6 from one side and each of albumin, creatinine clearance, fT3 and fT4. In addition, there was significant negative correlation between CRP from one side and each of albumin, creatinine clearance fT3 and fT4 while the correlation between CRP and TSH was positive correlation. In addition, albumin significantly and positively correlated with TSH, fT3 and fT4. Furthermore, creatinine clearance had significant negative correlation with TSH and positive correlation with fT3 and fT4 **(Table 3)**.

In-group B, there was positive significant correlation between IL-6 and each of CRP and TSH, while there was significant negative correlation between IL6 and each of albumin, creatinine clearance, fT3 and fT4. In addition, there was significant positive correlation between CRP and each of urea and TSH, while the correlation was negative between CRP and each of albumin, fT3 and fT4. Furthermore, there was significant negative correlation between albumin and urea; while the correlation between albumin and each of TSH, fT3 and fT4 was significant positive correlation. There was positive correlation between creatinine clearance and each of fT3 and fT4.

In studied groups there was negative correlation between IL-6 and (albumin, creatinine clearance, FT3 and FT4) in addition; There was highly significant predictive value between IL-6 and (CRP, TSH, FT3 and FT4), and significant predictive value between IL-6 and S. albumin **(Figure 1, (Figure 2).**

In studied groups, there was positive correlation between CRP and (IL-6, uric acid, S.creatinine, bl.urea and TSH). There was negative correlation between CRP and (albumin, creatinine clearance, FT3 and FT4); in addition, there was highly significant predictive value between CRP and (IL-6, TSH, FT3 and FT4), and significant predictive value between CRP and (albumin, creatinine clearance) **(Table 4).**

**Table (1): Comparison between studied groups as regard to age, DM, Hypertension, and laboratory investigations**

| Variable | | Group A | Group B | Test | P |
|---|---|---|---|---|---|
| Age (years) | | 49.4±4.9 | 47.3±4.0 | 1.78 | 0.08(NS) |
| Diabetes No. (%) | | 18(60.0%) | 18(60.0%) | 0.001 | 1.0(NS) |
| Hypertension No. (%) | | 25(83.3%) | 18(60.0%) | 4.02 | 0.045* |
| Disease duration (years) | | 2.7±1.2 | 2.1±0.96 | 2.04 | 0.046* |
| Kidney function tests | Urea (mg/dl) | 79.5± 14.7 | 36.3 ± 9.6 | 13.48 | 0.001 * |
| | Creatinine (mg/dl) | 7.4 ± 1 | 3.6 ± 0.8 | 16.07 | 0.001 * |
| | Uric acid (mg/dl) | 14.6 ± 6.2 | 7.55 ± 2.1 | 5.89 | 0.001 * |
| | Creatinine clearance ml/min | 11.9 ± 7.1 | 63.7 ± 17 | 15.42 | 0.001 * |
| | e.GFR ml/min | 17.00 ± 4.7 | 63.7 ± 17 | 14.52 | 0.001 * |
| Lipid profile | Cholesterol (mg/dl) | 188.67±46.89 | 135.57 ±16.89 | 5.83 | 0.001 * |
| | Triglycerides (mg/dl) | 114.33±29.00 | 101.67± 26.76 | 1.75 | 0.08(NS) |
| | LDL (mg/dl) | 118.70±49.98 | 57.63 ± 15.12 | 6.40 | <0.001 * |
| | HDL (mg/dl) | 48.30 ± 17.94 | 60.33 ± 7.10 | 3.41 | 0.002 * |
| Fasting blood glucose (mg/dl) | | 129 ±39 | 146 ± 52 | 1.37 | 0.18(NS) |
| Highly sensitive C-reactive protein (mg/L) | | 1.02±0.37 | 0.52±0.18 | 6.79 | <0.001* |
| Interleukin-6 (ng/ml) | | 106.30±42.57 | 44.13±16.55 | 7.45 | <0.001* |
| Thyroid function | TSH MIU/L | 4.50±1.71 | 3.22±0.61 | 3.87 | 0.001* |
| | fT3 Pg/ml | 1.0±0.17 | 1.21±0.10 | 6.01 | <0.001* |
| | fT4 ng/dl | 7.53±1.87 | 10.83±3.52 | 4.53 | <0.001* |

**Table (2): Correlation between creatinine clearance and other parameters in studied groups**

| | Creatinine clearance | | |
|---|---|---|---|
| | R | P | ** |
| IL6 | -0.470 | 0.009 | * |
| CRP | -0.416 | 0.022 | |
| Albumin | 0.037 | 0.847 | |
| Uric Acid | 0.205 | 0.277 | |
| TSH | -0.380 | 0.038 | * |
| FT3 | 0.504 | 0.004 | ** |
| FT4 | 0.473 | 0.008 | ** |

*: significant
**: Highly significant
- : negative correlation

**Table (3): Correlation between IL-6 and other parameters in group A**

| | IL6 | | |
|---|---|---|---|
| | R | P | |
| CRP | 0.975 | 0.000 | ** |
| Albumin | -0.437 | 0.016 | * |
| Creatinine clearance | -0.470 | 0.009 | ** |
| Uric Acid | 0.264 | 0.159 | |
| Creatinine | 0.051 | 0.789 | |
| Urea | 0.215 | 0.254 | |
| TSH | 0.810 | 0.000 | ** |
| FT3 | -0.946 | 0.000 | ** |
| FT4 | -0.651 | 0.000 | ** |

*: significant
**: Highly significant
- : negative correlation

**Table (4): Correlation between CRP and other parameters in studied groups**

| | CRP | | |
|---|---|---|---|
| | R | P | |
| IL-6 | 0.975 | 0.000 | ** |
| Albumin | -0.418 | 0.022 | * |
| Creat_clearance | -0.416 | 0.022 | * |
| Uric Acid | 0.270 | 0.148 | |
| Creatinine | 0.086 | 0.653 | |
| Urea | 0.204 | 0.279 | |
| TSH | 0.821 | 0.000 | ** |
| FT3 | -0.913 | 0.000 | ** |
| FT4 | -0.634 | 0.000 | ** |

*: significant
**: Highly significant
- : negative correlation

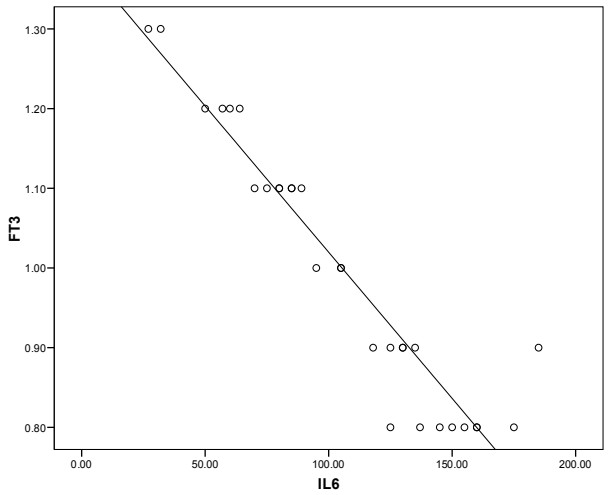


**Figure 1: Correlation between FT3 and IL6 In studied groups**

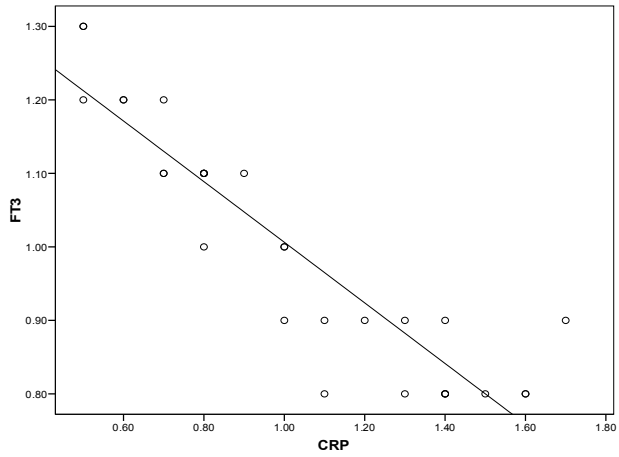


**Figure 2: Correlation between FT3 and CRP In studied groups**

## 4. Discussion

End-stage renal disease (ESRD) alters the hypothalamic-pituitary-thyroid hormone axis in addition to the peripheral thyroid hormone metabolism. Among thyroid hormones, T3 is the most metabolically active thyroid hormone and may be reduced in ESRD patients even with a normal TSH level. In general, reduced T3 levels in ESRD patients are due to the decreased peripheral tissue conversion of T4 into T3, while thyroid gland production of T3 is normal and T3 clearance rates are normal or decreased, as in other non-thyroidal illnesses **(Kumar *et al.*, 2009). Lim *et al.*, (2009)** reported that uremic patients have a variety of non-renal, non-thyroidal disorders that affect thyroid hormone metabolism, such as diabetes, infections, and malnutrition, and they are often treated by drugs that interfere with thyroid function.

In this study, we evaluated serum free T3 in patients with chronic kidney disease by measurement of thyroid hormones and their comparison with the most reliable inflammatory markers (IL-6 and CRP).

We observed that values of serum free Tri-iodothyronine were less in-group A (1.00±0.17) than in group B (1.21±0.10). In addition, this finding was present in each group by variable degrees according to severity, stage of chronic kidney disease and duration of dialysis. This is in agreement with **Lo *et al.,* (2010)** who reported that a variety of alterations in thyroid hormone levels and metabolism have been reported in patients with chronic renal failure and low T3 has been consistently found to be the most common disturbance.

In both groups, we observed that fT3 was positively correlated with eGFR (creatinine clearance). This is in accordance with **Lo *et al.,* (2010)** who reported that fT3 positively correlated with eGFR

In this study, we found that fT4 has a positive relation to creatinine clearance (eGFR). Therefore, a decrease in creatinine clearance that was observed with more advanced CKD stages was associated with a decrease in fT4. Another study reported by **Kaptein (2007)** found that fT4 and TSH are of no significant value to predict outcome in patients with non-thyroidal illness including CKD.

We found that fT3 values were less in-group A (1.00 ± 0.17) than in-group B (1.21± 0.10).These findings are in agreement with **Boelen *et al.,* (2005)** who found that those with relatively lower plasma fT3 levels were older, included a greater proportion of individuals with previous cardiovascular events and of diabetics, and displayed lower hemoglobin and serum albumin and higher serum interleukin-6 (IL-6) and C-reactive protein (CRP) when compared to those with higher fT3. In addition, **Diez and Iglesias (2009)** suggested that thyroid hormones, especially T3, could be considered as a marker for survival in patients with kidney disease.

In-group A we observed that fT3 was reduced according to duration of dialysis. In group B, we observed that fT3 was reduced according to duration of disease and according to stage of chronic kidney disease. This is in agreement with **Lo *et al.* (2010)** who reported that fT3 was reduced by variable degrees according to stage of CKD described by estimated GFR .In the present study IL-6 values were higher in group A (106.30 ± 42.57), who were on hemodialysis, than in group B (44.13 ± 16.55) who were on conservative treatment.

In this study, we observed that plasma free triiodothyronine fT3 in CKD was highly correlated with inflammatory markers IL-6 and CRP, thus we suggested that fT3 is considered as a good inflammatory marker and strong predictors of mortality, This is in agreement with **Tripepi *et al.,* (2005)** who reported the similar result in their study.

In both groups, fT3 was negatively correlated to IL-6, i.e. fT3 was reduced by variable degrees according to stage of chronic kidney disease while IL-6 was elevated by variable degrees. These findings were also present in fT4, which has a negative correlation to IL-6 and CRP. In both groups, we observed that CRP was elevated by variable degrees according to stage of chronic kidney disease but without the same degree as IL-6. IL-6 and CRP are inflammatory markers that elevated in patients with chronic kidney disease. In both groups, CRP values were elevated but more in group A (1.02 ± 0.37) than in (group B) (0.52 ± 0.18). In both groups, IL-6 values were elevated but more in group A (106.30 ± 42.57) than in (group B) (44.13 ± 16.55). On the other hand, fT3 values were less in-group A (1.00 ± 0.17) than in-group B (1.21 ± 0.10). This is in accordance with **Stenvinkel *et al.,* (2006)** who demonstrated increased levels of various acute phase reactants such as C-reactive protein (CRP).

We showed strong negative correlation between fT3 and IL-6 ($P$<0.001) and C-reactive protein, ($P$<0.001) in both groups. This is in accordance with **Bartalena *et al.,* (2004)** who reported that serum IL-6 is often elevated in non-thyroidal illness including chronic kidney disease and the plasma concentration of this cytokine was negatively correlated to that of fT3. IL-6 was found to be a potential risk factor that could predict the observed lower circulating level of T3

The malnutrition-inflammation complex is a major clinical problem in patients with ESRD. in our study we observed that serum albumin values were less in **group A** (3.16±0.48) than in **group B** (3.40±0.47) who are on conservative treatment. In both groups, we observed that fT3 was in positive correlation to serum albumin. In both groups, we also observed that there is a negative correlation between IL-6 and albumin. On the other hand, albumin was considered as an established inverse acute-phase reactant, which reflects also the nutritional status. This is in accordance with **Stenvinkel *et al.,* (2009)** who reported that albumin is a hallmark of a negative protein-energy balance in uremic patients.

There was negative correlation between IL-6 and severity or staging of chronic kidney disease. In addition, IL-6 values were more increased in **group A** (106.30 ± 42.57) than in **group B** (44.13 ± 16.55). These suggest that more inflammatory condition and morbidity is expected in **group A** than **group B**

We also observed that values of serum cholesterol, triglycerides and low density lipoproteins (LDL) were higher in group A than in (group B). On the other hand, the protective and more benefit high

density lipoproteins (HDL) was less values in group A (48.30 ± 17.94) than in (group B) (60.33 ± 7.10). This means that cardiovascular morbidity and mortality were expected to be higher in group A than in (group B). These findings were more observed with low fT3 values, which were found in group A than in group B. This is in accordance with **Zoccali *et al.*, (2005)** who reported that low T3 was associated with inflammation and cardiovascular morbidity in ESRD patients. These observations suggest that low T3 may be used as a marker of prognosis in persons with CKD. In addition, a study by **Bruckert *et al.*, (2002)** who found that there was a risk factor for subclinical atherosclerosis in euthyroid hyperlipidemia patients. **Pingitore *et al.*, (2005)** suggested that the cardiovascular system is very sensitive to thyroid hormone and not only clinical and subclinical hypothyroidism but also a low T3 syndrome is associated with changes in myocardial performance and death in patients with heart failure.

**Conclusion:**

The low T3 levels in CKD patients have been correlated with higher levels of markers of inflammation; highly sensitive C-reactive protein and IL-6, free T3 could be used as an inflammatory marker and may be used as a prognostic factor for cardiovascular morbidity and mortality in CKD Patients.

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