Serum Triiodothyronine Level as an Indicator of Inflammation in Patients Undergoing Dialysis

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Introduction. It has been shown that inflammation affects thyroid function. In patients with end-stage renal disease, low plasma triiodothyronine (T3) may be an unsuspected expression of the inflammatory state of these patients. This study evaluated the correlation between T3 and high-sensitivity C-reactive protein (HSCRP) levels in patients on peritoneal dialysis (PD) and hemodialysis.

Materials and Methods. This is a cross-sectional study aiming at the correlation between T3 and HSCRP levels among 30 patients on PD, 30 patients on hemodialysis, and 20 healthy individuals. Serum levels of HSCRP, T3, thyroxine (T4), thyroid stimulating hormone, T3 resin uptake, and free T3 index (FT3I) and free T4 index (FT4I) were compared between the three groups.

Results. There were no significant differences between hemodialysis and PD patients in respect to T3, T4, FT3I, and FT4I. In PD and hemodialysis patients, T3 and FT3I were lower than in controls ($P < .001$), but there was no significant difference between PD and hemodialysis patients. T3 resin uptake and thyroid stimulating hormone differed significantly between PD and hemodialysis patients. There was a significant inverse correlation between HSCRP and T3 and FT3I among hemodialysis patients ($P = .04$); however, there was no such correlations in PD patients.

Conclusions. The relationship between T3 and HSCRP suggests that inflammation might be involved in the low T3 syndrome in hemodialysis patients, but we did not find a significant correlation between T3 and HSCRP levels in patients on peritoneal dialysis.

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INTRODUCTION

Mortality is markedly elevated in patients with end-stage renal disease (ESRD).[1] A relationship between triiodothyronine (T3) level and mortality has been documented in patients on hemodialysis and peritoneal dialysis (PD).[2] Some authors have recommended measurement of T3 levels to assess the relationship between thyroid dysfunction and risk of mortality in uremic patients.[3] Hemodialysis is associated with alterations in the concentration of circulating thyroid hormones, usually, a reduction in serum total and free T3 concentrations.[4] Primary hypothyroidism is the most common thyroid dysfunction in patients on PD. Another common alteration in thyroid function tests is the low T3 syndrome. In patients undergoing PD, significant amounts of thyroxine-binding globulin, thyroxine (T4), and T3 are lost in the peritoneal effluent.[5] The high protein loss induced by this type of dialysis could be related to an increased incidence

of thyroid dysfunction.[6]

Derangement of thyroid function in nonthyroidal illness is currently presumed as an acute-phase response produced by activation of cytokine network.[7] Cytokines may affect the hypothalamus, the pituitary, or other tissues, inhibiting synthesis of thyroid-stimulating hormone (TSH), thyroid-releasing hormone, thyroglobulin, T3, and thyroxine-binding globulins.[8] Both of the proinflammatory cytokines tumor necrosis factor and T3 have been thought to be involved in the maintenance of tissue homeostasis in the anterior pituitary gland.[9] Cytokines are also suggested to decrease the activity of type I deiodinase and to decrease the binding capacity of T3 nuclear receptors.[10] The potential deleterious effect of thyroid dysfunction on the atherosclerotic process could be confounded by the effect of inflammatory stress.[11] Increased C-reactive protein (CRP) is a strong risk factor for mortality within 1 year in patients with ESRD. Furthermore, elevated CRP levels have been identified as a risk factor for cardiovascular disease in ESRD.[12] It has become evident that inflammation plays an important role in the pathogenesis of atherosclerotic complications.[13] C-reactive protein, a major acute-phase protein and systemic marker of inflammation, predicts both all-cause and cardiovascular mortality in the dialysis population.[14] There are 2 different tests for CRP. The standard test measures a much wider range of CRP levels but is less sensitive in the lower ranges. The high-sensitivity CRP (HSCRP) test can more accurately detect lower concentrations of the protein (it is more sensitive).

Since inflammation influences thyroid function, low plasma T3 in ESRD could be an expression of the inflammatory state of these patients.[2] Most of the studies have been performed on hemodialysis patients, but with respect to PD patients, similar studies have not been done so much. In a few articles, correlation between T3 and HSCRP in PD and hemodialysis patients, simultaneously have been evaluated so far, but this area is still remained unclear. Therefore, we investigated the relationships between HSCRP and T3 in patients undergoing PD and hemodialysis.

MATERIALS AND METHODS

This case-control study included 30 patients on long-term hemodialysis (17 women and 13 men) and 30 patients on PD (14 women and 16 men) who were followed up at our Hospital. We included a control group consisted of 20 healthy persons (10 women and 10 men) recruited from hospital staff and laboratory institutions who were matched with our patients for age and sex. All hemodialysis patients were on 4-hour bicarbonate dialysis, 3 times a week, and all PD patients were on continuous ambulatory PD therapy. Informed consent was obtained from all study participants.

Patients' clinical and demographic characteristics and routine laboratory parameters were recorded at the initiation of the study, in order to exclude any significant metabolic disorder which could alter thyroid hormone metabolism. The criteria for enrolment included being on dialysis for more than 6 months; being 16 years old or older; the absence of clinical evidence of heart failure and no current acute illness; no current illnesses infectious diseases, cardiocirculatory congestion, cancer, and any other diseases requiring hospitalization; and off drugs that may affect the plasma concentration of thyroid hormones (ie, amiodarone, beta-blockers, and lithium). Patients on PD were free of peritonitis for at least 3 months at the time of enrolment. None of the patients showed clinical signs of hyperthyroidism or hypothyroidism. As heparin is known to acutely increase both total and free T4 levels in blood, the samples for thyroid hormones estimation were drawn immediately before heparin administration.

Plasma levels of T3 and T4 were measured by a commercially available radioimmunoassay kit (Radim, Aryafarmad, Tehran, Iran), and TSH measurement was performed by a sensitive immunometric assay (Biosource TSH IRMA Ref Kip 1891:96, Welland, Canada). The sensitivities were 0.08 ng/mL for T3, 1.25 ng/mL for T4, and 0.025 μIU/mL for TSH. The reference values were 0.2 μIU/mL to 5 μIU/mL for TSH, 4 μg/dL to 13 μg/dL for T4, and 60 ng/dL to 210 ng/dL for T3 levels. We selected HSCRP marker (Biosystem, Barcelona, Spain) as the inflammation marker in patients. Serum albumin measurement was performed by the bromocresol green method. Free T4 index (FT4I) was calculated by multiplying the total T4 concentration by T3 resin uptake (T3RU), and FT3I was calculated by multiplying the total T3 concentration by T3RU.

Statistical analyses were carried out using the

SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA). Comparisons between more than two groups were analyzed by 1-way analysis of variance. Within-group comparisons were analyzed by the paired *t* test in normally distributed data or by the Wilcoxon sign rank test in nonnormally distributed data. Differences in categorical variables were evaluated using the chi-square test. Relationships between continuous variables were analyzed by standard Pearson correlation coefficient test. Spearman rank correlation was used to determine correlations between thyroid hormones levels and HSCRP levels. Continuous data were expressed as a mean ± standard deviation. A *P* values less than .05 was considered significant.

RESULTS

The PD group consisted of 30 patients (17 women and 13 men) with a mean age of 51.6 ± 16.3 years, and the hemodialysis group included 30 patients (14 women and 16 men) with a mean age of 45.6 ± 16.9 years. There were 20 healthy individuals as the control group (10 women and 10 men) with a mean age of 43.9 ± 17.7 years. The Two groups of patients were comparable in terms of dialysis duration (25 months in hemodialysis group versus 39 months in the PD, *P* = .08). Primary kidney diseases were diabetic nephropathy in 11 (36.7%) and 7 (23.3%), hypertensive nephrosclerosis in 10 (33.3%) and 6 (20.0%), other causes in 6 (20.0%) and 10 (33.3%), and unknown in 3 (10.0%) and 8 (26.7%) hemodialysis and PD patients, respectively. Demographic and clinical data of participants in each group are shown in the Table.

There were no significant differences between the three groups in the HSCRP levels (*P* = .18). The hemodialysis and PD groups were comparable in plasma levels of albumin, T3, T4, FT3I, and FT4I. Serum TSH level was significantly higher in PD patients than in hemodialysis patients (*P* = .03), while T3RU was significantly lower (*P* = .009). Serum TSH level was significantly higher in PD patients in comparison with healthy individuals (*P* = .03), while serum albumin was significantly lower (*P* < .001). Plasma levels of T4 and T3RU and FT4I did not significantly differ between PD patients and healthy control participants. Plasma T3 levels and FT3I were significantly decreased in the patients on hemodialysis and PD compared to the controls. There were no statistically significant differences between PD patients and healthy subjects in respect to serum T4 levels, while T4 levels were significantly lower in hemodialysis patients than healthy subjects (*P* = .009).

In hemodialysis patients, a significant inverse correlation between serum T3 level and HSCRP level was demonstrated (r = -0.385, *P* = .04;

Demographic, Clinical, and Laboratory Data of Dialysis and Control Groups*

Characteristics	Peritoneal Dialysis	Hemodialysis	Control
Number of participants	30	30	20
Gender (%)			
Male	13 (43.3)	16 (53.3)	10 (50.0)
Female	17 (56.7)	14 (46.7)	10 (50.0)
Age, y	51.9 ± 16.3	45.6 ± 16.9	43.9 ± 17.7
Dialysis duration, m	25.28 ± 15.87	39.77 ± 18.31	…
Albumin, g/L	3.85 ± 0.46†	4.05 ± 0.40	4.41 ± 0.39
HSCRP, mg/L	3.97 ± 2.20	3.59 ± 1.98	3.28 ± 1.74
T3, ng/dL	103.83 ± 31.36†	86.05 ± 31.50†	146.55 ± 26.64
T4, µg/dL	7.43 ± 2.02	6.44 ± 2.12‡	8.51 ± 2.07
T3RU, %	28.15 ± 3.47§	31.31 ± 2.45†	28.96 ± 4.47
FT3I	29.05 ± 9.34¶	27.05 ± 10.69‖	37.14 ± 11.30
FT4I	2.08 ± 0.64	2.01 ± 0.67	2.23 ± 0.71
TSH, µIU/mL	3.21 ± 1.74†	2.31 ± 1.01#	2.50 ± 1.47

*HSCRP indicates high-sensitivity C-reactive protein; T3, triiodothyronine; T4, thyroxine; T3RU, triiodothyronine resin uptake; FT3I, free triiodothyronine index; FT4I, free thyroxine index; and TSH, thyroid releasing hormone.
†*P* < .001 compared with control
‡*P* = .004 compared with control
§*P* = .009 compared with hemodialysis
¶*P* = .04 compared with control
‖*P* = .008 Compared with control
#*P* < .001 compared with peritoneal dialysis

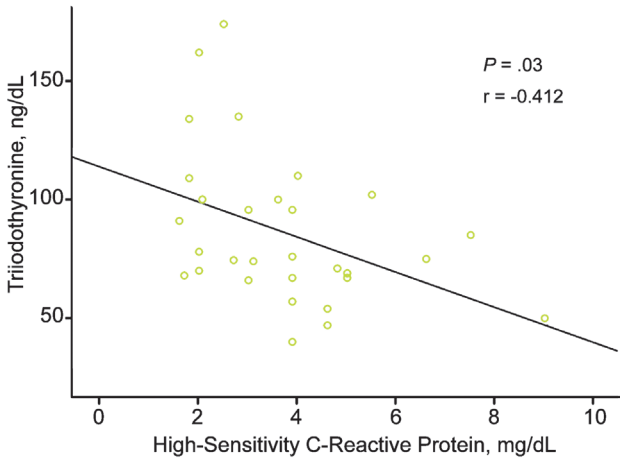

Figure 1. Relationship between plasma levels of triiodothyronine and high-sensitivity C-reactive protein in hemodialysis patients.

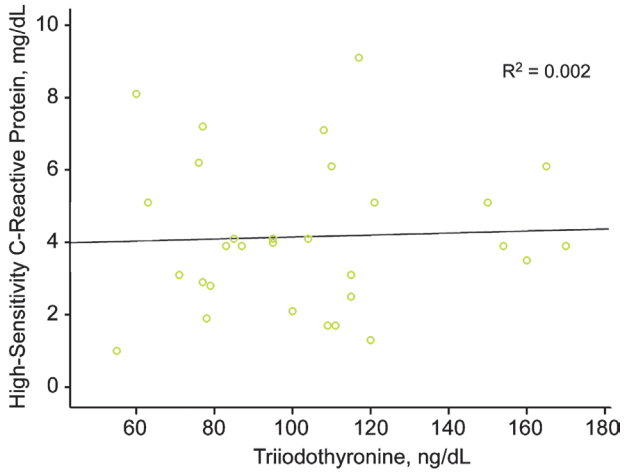

Figure 2. Relationship between plasma levels of triiodothyronine and high-sensitivity C-reactive protein in patients on peritoneal dialysis.

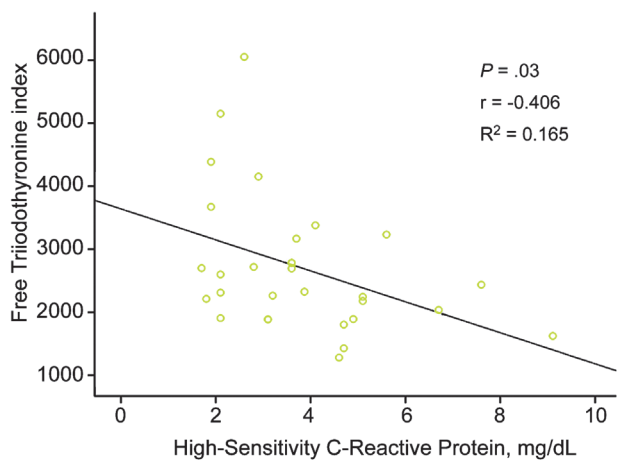

Figure 3. Relationship between free triiodothyronine index and high-sensitivity C-reactive protein in hemodialysis patients.

Figure 1), while no correlation existed between serum HSCRP level and T4, TSH, T3RU, FT3I, and FT4I. In PD patients, no correlation was observed between serum HSCRP level and T3, T4, TSH, T3RU, FT3I, and FT4I; Figure 2). A significant inverse correlation between FT3I and HSCRP level was found in hemodialysis patients (r = -0.406, *P* = .03; Figure 3). However, there was no significant inverse correlation between FT3I and HSCRP level in PD patients.

DISCUSSION

Aalterations in thyroid hormone metabolism have been reported in patients with a variety of nonthyroidal illnesses.[15] Abozena and colleagues observed that patients with CKD showed the least disturbance in levels of interleukins, despite the exhibition of lower levels of T3, T4, and TSH in a higher proportion of them compared with the patients with heart failure.[16] Uremic patients demonstrate complex thyroid dysfunction characterized by markedly depressed levels of T3 and lower (but still normal) T4 with a normal TSH. They have shown a decreased thyroid response to exogenous TSH, a blunted TSH release in response to TRH, as well as inhibited peripheral T4-to-T3 conversion.[17] Derangement of thyroid function in nonthyroidal illness is currently considered as an acute-phase response generated by activation of a cytokine network.[17] Zimmermann and colleagues[18] and Yeun and coworkers[19] found that CRP and age were the most important factors in predicting cardiovascular mortality among hemodialysis patients.

Our study, showed no statistically significant differences between the three groups with respect to HSCRP (*P* = .18). Indeed, serum CRP levels in our patients were much lower than that in other studies, although clear comparisons could not be made, and further studies are needed to be done in future. However the mean of CRP levels in the present study (3.79 mg/dL and 4.31 mg/dL in hemodialysis and PD patients, respectively) are higher than those in some previous studies for stable dialysis patients without signs of infection.[13] In the literature, a wide range of CRP levels is reported in patients undergoing dialysis.[20] The reason why the mean of the CRP is higher in the PD group most probably is that the inflammation in the PD patients can be elevated both by the

peritoneal irritation and by the decrease in the removal of the cytokines because of the decrease in the residual kidney function.[21]

In our study, circulating levels of plasma T3 in the dialysis patients were significantly lower than those in the age- and sex-matched controls. The levels of T3 were significantly lower in hemodialysis and PD patients than in controls. In the hemodialysis patients, but not in PD patients, serum T4 levels were significantly lower than T4 levels in the control group. Diminished T4 in dialysis patients has been proposed to be due to low thyroxine-binding globulin caused by protease cleavage at inflammatory sites in acute inflammatory conditions.[22] Another hypothesis for the cause of disproportionately low serum T4 concentrations in dialysis patients is the presence of abnormal serum binding due to distillation of thyroxine-binding globulin.[23] Cytokines can also elevate free T4 levels. Chopra and colleagues showed a positive correlation between free T4 and serum tumor necrosis-α in nonthyroid illness.[24] There were no significant differences in the levels of T3 according to the type of dialysis. However, PD patients presented significantly higher concentrations of TSH than that in the hemodialysis patients and control group. On the other hand, hemodialysis patients would have a higher probability of reduced T3 than would PD patients, due to reduced enzyme activity of 5′- ionodeiodinase, which is responsible for converting T4 into T3 in peripheral tissues.[25] The reason for the elevated TSH levels in CAPD patients was not clear. With regard to the type of dialysis, we found that PD patients had higher levels of T3. This finding is in contrast with the fact that greater losses of T4 and T3 in the effluent are expected in PD.[26]

In our study, a significant inverse correlation between HSCRP and T3 circulating levels was observed in the patients on hemodialysis, but not in PD patients. Zokali and colleagues showed that free T3 is associated with markers of inflammation and endothelial activation in stable hemodialysis patients.[2] In another study, Carrero and colleagues[27] showed that T3 levels were associated with increased inflammation (higher HSCRP, IL-6, and vascular cell adhesion molecule 1) and lower concentrations of both albumin and insulin-like growth factor 1. However, they did not assess the effect of dialysis modality. Enia and associates showed that inflammation is linked to the low T3 syndrome in PD patients.[28] Fernandez-Reyes and colleagues showed in 32 stable dialysis patients (24 hemodialysis and 11 PD) that half of dialysis patients presented decreased levels of free T3 in serum without altered TSH or free T4 (low free T3 syndrome). These levels fundamentally correlated with malnutrition and inflammation.[29] It has been suggested that proinflammatory cytokines may inhibit T3 production or increase tissue turnover.[30] In agreement with previous evidence, our hemodialysis patients are characterized by a significant inverse correlation between T3 and HSCRP in the present study population. However, this is not in agreement with previous evidence indicating that a correlation between T3 and HSCRP exists in PD patients. The different exclusion criteria between PD and hemodialysis groups may contribute to the differences in the reported findings. Higher concentrations of T3 in PD patients compared with the hemodialysis patients could be another possible reason.

Previous studies mostly evaluated free T3 levels. They reported significant correlations between free T3 and inflammatory factors. In our research, we did not evaluate serum level of free T3 and free T4 due to some limitations in their measuring; therefore, we calculated FT3I and FT4I, and our results were just similar to the mentioned studies. A significant correlation between HSCRP and FT3I was observed in patients on hemodialysis but not in PD patients. On the other hand, only a few studies have involved PD patients to evaluate a correlation between serum T3 level and HSCRP. It should be mentioned that CRP concentration showed a relatively weak inverse correlation with T3 and FT3I in patients undergoing HD. In accordance with our finding, Abozena and colleagues showed a relatively weak correlation between CRP concentration and free T3.[16]

We acknowledge that there were several limitations in this study. First, this is a case-control study with relatively small number of patients. All data were collected at a single time, and controlling all possible factors that might influence both the thyroid hormone metabolism and inflammation was impossible. Hence, further studies are required to confirm our results. Second, reverse T3, which is known to be associated with sick euthyroid syndrome, was not determined in our

study population; thus, we could not provide any additional information related to this topic. Third, we did not evaluate correlations between thyroid hormones and other markers of inflammation such as interleukins and tumor necrosis factor.

CONCLUSIONS

Our study revealed a significant inverse correlation between HSCRP and plasma T3 circulating levels in patients undergoing hemodialysis, but not in PD patients. This investigation suggests that inflammation might be involved in the low T3 syndrome in hemodialysis patients. However, it is still unclear whether the low T3 state contributes to the development and progression of inflammatory state in PD patients or not.

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CONFLICT OF INTEREST

None declared.

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