Hemodilution Impacts Assessment of Thyroid Status before and after Hemodialysis in Patients with End-Stage Renal Disease

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Abstract

Background: To elucidate the role of hemodilution in the alteration of thyroid hormone levels in end-stage renal disease (ESRD), we compared thyroid function before and after hemodialysis (HD). Methods: Twenty-three male ESRD patients (age <65 years) with either chronic glomerulonephritis (CGN) or diabetic nephropathy (DN), who were enrolled between June 2019 and August 2019, were included in the study. The free thyroxine (fT\textsubscript{4}), free tri-iodothyronine (fT\textsubscript{3}), and thyroid-stimulating hormone (TSH), thyroxine-binding globulin (TBG), and thyroglobulin (Tg), measured before and after HD in 12 patients with CGN (48.7 ± 11.8 years [mean ± standard deviation]) and 11 patients with DN (57.6 ± 6.5 years), were compared with 45 healthy controls (52.5 ± 11.9 years).

Results: The fT\textsubscript{4}, fT\textsubscript{3}, and TBG were significantly low before HD and increased in parallel with an increase in hematocrit and albumin after HD in both ESRD subgroups. The TSH was high before HD and decreased significantly after HD, while Tg remained almost unchanged. In DN, the fT\textsubscript{4} levels were nearly identical, while fT\textsubscript{3} was lower with slightly higher TSH, compared with CGN. The TSH/fT\textsubscript{4} ratios before HD were significantly higher in both subgroups, and the fT\textsubscript{3}/fT\textsubscript{4} ratios after HD were significantly lower in DN than the control. Conclusions: Our findings suggest that the low fT\textsubscript{4} and fT\textsubscript{3} levels found in ESRD are due to hemodilution before HD, resulting in a slightly higher TSH level but almost unchanged Tg level, and that DN is associated with decreased T\textsubscript{4}-to-T\textsubscript{3} conversion.

Introduction

Thyroid function in ESRD has been extensively evaluated with variable results [1–5]. A high prevalence of hypothyroidism has been reported [6] in these patients with ESRD; however, the criteria for thyroid dysfunction were unclear, especially in cases with a mild or subclinical abnormality. The primary reason for ambiguous finding in previous studies is the lack of consistent and well-standardized reference values of thyroid hormone levels, such as free thyroxine (fT\textsubscript{4}) and free tri-iodothyronine (fT\textsubscript{3}), in ESRD. Nevertheless, there is a consensus that serum fT\textsubscript{4} and fT\textsubscript{3} levels are lowered while thyroid-stimulating hormone (TSH) levels are slightly elevated in ESRD [1, 2, 5].
Previously, we evaluated thyroid dysfunction in ESRD and found a very high prevalence of primary hypothyroidism, including subclinical hypothyroidism in 10.3% and overt hypothyroidism in 1.4% of ESRD patients [5]. Moreover, most of the patients with overt hypothyroidism became euthyroid after iodide restriction [7]. This reversible hypothyroidism in these patients is likely due to excess iodide ingestion in Japan [7]. However, the underlying mechanisms for the change in the reference values of thyroid hormone in ESRD compared with healthy controls have been unclear.

In most of the studies in the ESRD patients, serum thyroid hormone levels were measured using the samples taken before hemodialysis (HD). In this study, the influence of hemodilution before HD was evaluated comparing the thyroid function, renal data, calcium (Ca), phosphate (P), albumin (Alb), and hematocrit (Ht) levels before and after HD.

**Patients and Methods**

**Subjects**

Among 116 ESRD patients on maintenance HD at Fukumitsu Clinic (mean age: 67.8 ± 13.3 standard deviation years; age range: 28–90 years; 78 males and 38 females) and 69 patients at Motomura Clinic (mean age: 68.1 ± 10.4; age range: 41–87 years; 40 males and 29 females), thyroid function was evaluated as part of a study protocol in 23 male patients before and after HD. They were enrolled between June 2019 and August 2019. Considering the high prevalence of Hashimoto’s disease in women >40 years, only men were included. Patients with known thyroid disease or severe illness and those aged ≥65 were excluded. Additionally, patients with ESRD secondary to hypertensive nephrosclerosis were not included in this study due to their advanced age (≥65 years).

The 23 male HD patients (<65 years) included in this study had a mean age of 52.9 ± 10.5 (range: 30–64) years. The etiology of ESRD was chronic glomerulonephritis (CGN) in 12 cases (age: 48.7 ± 11.8 [31–64] years) and diabetic nephropathy (DN) in 11 cases (age: 57.6 ± 6.5 [46–64] years). The ESRD patients were compared with 13 male normal healthy controls comprising the staff at Fukumitsu Clinic (mean age: 40.9 ± 11.3 [22–59] years, <65 years).

The present study was performed using a nonrandomized analysis at the 2 centers with a prospective and controlled design. The study procedures were carried out in accordance with the ethical standards of the Human Investigation Committee at Fukumitsu Clinic and Motomura Clinic. All patients gave their oral informed consent.

**Dialysis Schedule**

The patients underwent 4- to 5-h sessions of HD therapy twice (1 case) to thrice (22 cases) a week. We used a standard bicarbonate hollow-fiber dialyzer with the following buffer composition: 140 mEq/L sodium, 2.0 mEq/L potassium, 2.75 mEq/L Ca, 1.0 mEq/L magnesium, 110 mEq/L chloride, 8 mEq/L CH3COO−, 27.5 mEq/L HCO3−, and 125 mg/dL glucose in dialysate. The blood flow rate was 200 mL/min, and the dialysate flow rate was kept constant at 500 mL/min.

**Total Points of Hypothyroid Score Evaluating Hypothyroid Symptoms**

The signs and symptoms suggesting hypothyroidism were evaluated using the hypothyroid score (HS) determined by the summation of points assigned for each of the following symptoms: (1) dry skin, (2) cold intolerance, (3) hyperkeratosis, (4) constipation, (5) decreased exercise tolerance, (6) forgetfulness, (7) rough skin, (8) depressed ventilatory drive, (9) increased time required to fulfill a task, and (10) a low-pitched or hoarse voice. The patients who score all 10 points are in a severe clinical hypometabolic state. Ultrasoundographic thyroid volume study. The estimation of TV was calculated as TV = TV right lobe (mm) + TV left lobe (mm) + TV isthmus (mm). Total points and ultrasoundographic TV study were measured only at Fukumitsu Clinic. CGN, chronic glomerulonephritis; DN, diabetic nephropathy; TPHS, total points of hypothyroid score; TV, thyroid volume; SD, standard deviation. * p < 0.05 compared with control. The difference was not significant between CGN and DN groups.

**Ultrasonographic Thyroid Volume Study**

The thyroid gland of 18 ESRD Japanese patients on HD and 13 healthy controls at Fukumitsu Clinic were examined using ultrasonography (Aplo 300; TOSHIBA Co., Ltd., Tochigi, Japan) with a 7.5 MHz frequency probe (PLT-704 SBT, Electronic Linear Probe, TOSHIBA Co., Ltd., Tochigi, Japan). The ultrasonography estimation of thyroid hormone (TV) was performed as follows: TV (mm) = TV right lobe (mm) + TV left lobe (mm) + TV isthmus (mm) [9].

**Blood Sampling Methods**

The serum levels of Cr, BUN, Alb, Ca, P, fT4, fT3, TSH, thyroxine-binding globulin (TBG), thyroglobulin (Tg), and Ht were assayed from the blood sample drawn immediately before HD (non-heparinized) and after HD (during heparinization).

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**Table 1. TPHS and ultrasonographic TV of the patients with ESRD**

|          | CGN | DN | Total (ESRD) | Control |
|----------|-----|----|--------------|---------|
| N        | 7   | 11 | 18           | 13      |
| TPHS     | 3.0±0.6* | 3.9±2.4* | 3.5±1.9* | 0.9±1.3 |
| Ultrasonographic TV | 37.2±16.8 | 34.9±3.8 | 35.3±10.5 | 30.7±3.6 |

**Abbreviations**

CGN: chronic glomerulonephritis; DN: diabetic nephropathy; TPHS: total points of hypothyroid score; TV: thyroid volume; SD: standard deviation. * p < 0.05 compared with control. The difference was not significant between CGN and DN groups.
Blood Sampling Analysis

The serum levels of TSH, fT₄, fT₃, and Tg were assayed using electrochemiluminescence immunoassays. The TBG levels were determined using the radioimmunoassay for the polyethylene glycol method.

The assays were performed at SRL Co. Ltd., (Fukuoka, Japan). The levels of serum TSH, fT₄, and fT₃ measured in 32 normal male controls (age: 58.8 ± 4.0 [range: 51–64] years, <65 years) in the same laboratory were combined with the values measured in the 13 patients in the control cohort to compute the average control values.

The serum TSH (mU/L)/fT₄ (ng/dL) [10] and fT₃ (pg/mL)/fT₄ (ng/dL) ratios were calculated to evaluate the change in the integrity of thyroid-pituitary axis and the peripheral conversion of T₄ to T₃, respectively. The reference ranges in our laboratory in the control and ESRD patients were 0.8–1.7 and 0.6–1.3 ng/dL for fT₄, 2.2–3.8 and 1.4–3.2 pg/mL for fT₃, 0.42–3.81 and 0.65–4.83 mU/L for TSH, and 1.4–3.6 and 1.4–3.6 for the fT₃/fT₄ ratio, respectively [5]. The reference ranges for Tg and TBG in the control were <30 ng/mL and 14.0–29.4 μg/mL, respectively.

The target hemoglobin level was based on the current recommended guidelines for the treatment of anemia in CKD as established by the National Kidney Foundation [11]. These guidelines suggest hemoglobin in the range of 11–12 g/L (Ht 33–36%) before HD in most patients treated with recombinant human erythropoietin [12].

The following medicines were administered to titrate the serum levels of Ca and P: P binders, vitamin D receptor activator, Ca-sensing receptor, and 2.75 mEq/L Ca++. in the dialysate.

Statistical Analysis

The data are expressed as mean ± SD. Statistical differences were calculated using the unpaired t test with Bonferroni’s method and the paired t test. Correlations between numerical variables were assessed using Spearman’s rank correlation coefficients. A p value of < 0.05 was considered to be statistically significant.

Results

The total points of HS were significantly higher in the ESRD group than the control group (3.5 ± 1.9 vs. 0.9 ± 1.3, p < 0.05) (Table 1). The HS was slightly higher in DN (3.9 ± 2.4) than the CGN subgroup (3.0 ± 0.6), but the difference was not significant (Table 1). As to the correlation between the HS and thyroid function, there was no correlation with the TSH level (r = 0.1765, p = 0.3423), but there was a significant correlation with fT₄ (r = −0.6515, p < 0.0001) or fT₃ (r = −0.5687, p = 0.0008). However, among the patients with ESRD excluding healthy controls, there was no correlation between the HS and TSH (r = 0.1121, p = 0.6578), fT₄ (r = 0.1305, p = 0.6056), or fT₃ (r = −0.1271, p = 0.6153). There was no significant difference in the ultrasonographic TV between the ESRD (35.3 ± 10.5 mm) and the control groups...
(30.7 ± 3.6 mm) or between the CGN (37.2 ± 16.8 mm) and the DN (34.9 ± 3.8 mm) subgroups (Table 1).

The clinical data before and after HD in the ESRD group and their comparison with the control values are shown in Table 2. The body weight and the systolic blood pressure ($p < 0.05$) were higher in the ESRD group than control. Approximately a 3% decrease in body weight was observed after HD, while there was no significant change in blood pressure. The Ht and serum Alb were lower, and Cr, BUN, and P levels were higher in ESRD. Approximately a 10% increase in Ht and serum Alb levels and the expected decrease in serum Cr, BUN, and P levels were observed after HD in ESRD. The serum Alb and P levels after HD were not significantly different from control. There was also a 10% increase in serum Ca levels after HD. The serum fT 4 and fT 3 levels before HD in the ESRD group were significantly lower ($p < 0.05$) than the control group (Table 2). Approximately a 20% increase in the serum fT 4 levels and a 10% increase in the serum fT 3 levels were observed after HD, although the levels remained slightly lower than the control values. The serum TSH levels before HD were higher than those in control; however, the levels were decreased by approximately 20% after HD and were almost the same as the control.

Serum TBG and Tg levels were slightly higher in ESRD than controls, and there was a 10% increase in serum TBG levels during HD, although the serum Tg levels remained unchanged. High TSH and significantly low fT 4 levels before HD resulted in significantly high TSH/fT 4 ratios; however, the ratio almost normalized after HD. The fT 3/fT 4 ratios were almost unchanged during the clinical course of combined ESRD.

The changes in the thyroid function tests during HD were compared between the CGN and DN subgroups as shown in Table 3. Compared with the CGN subgroup, the serum TSH levels were higher and fT 3 levels were lower both before and after HD in the DN subgroup, while the serum fT 4 levels were almost the same in both subgroups. Therefore, TSH/fT 4 ratios were higher and the fT 3/fT 4 ratios were significantly lower after HD in the DN subgroup, compared with the control values. On the other hand, serum TSH/fT 4 and fT 3/fT 4 ratios after HD were not different from control in the CGN subgroup. Serum TBG levels were significantly higher after HD in the CGN subgroup.

**Discussion**

Recently, the peripheral metabolism of thyroid hormone has been a focus of increased attention, including the role of activating (type 1 and 2) or inactivating (type 3) deiodinases and α or β thyroid hormone receptors [13]. The peripheral metabolism of T 4 may be altered in the nonthyroidal illness (NTI), a syndrome of change in thyroid hormone levels in critically ill patients without primary thyroid disease. Previously, ESRD has been shown to exhibit NTI characterized by slightly lower serum fT 4 and fT 3 levels with the slightly elevated TSH levels [5] and the presence of myxedematous symptoms including cold intolerance and constipation. In this study, ESRD patients before HD showed lower serum fT 4 and fT 3 levels than control (Table 2), as previously reported [5, 7], which might partially explain the higher HS in these pa-
tients. However, there was no correlation between HS and fT4, fT3, or TSH level among the patients in ESRD excluding healthy control. Our unpublished data suggested that among the patients with primary hypothyroidism without renal dysfunction, the correlation of HS was high with fT4 (r = −0.4419, p = 0.0079) or TSH (r = 0.5105, p = 0.0017) (n = 35). Therefore, other extrathyroidal mechanisms must be responsible for this high total point of HS observed in ESRD. Serum analysis after HD revealed interesting findings, as shown in Table 2.

The decrease in body weight (3%) after HD suggests a decrease in extracellular body fluid, while the increase in Ht and Alb levels (10%) reflects a correction of hemodilution after HD, although the possibility of a shift of body fluid from interstitial space into the vascular compartment cannot be discounted. Thyroid function analysis revealed similar increase after HD in the serum TBG levels, a thyroid hormone-binding globulin with the molecular weight of 54,000 daltons, which is in the same range as the weight of 66,000 molecular weight of Alb.

Interestingly, serum fT4 and fT3 levels also improved after HD, rising to levels within the control or normal reference range values, especially in the CGN subgroup (Table 3). Notably, the total T4 and T3 values were not measured in this study. The effect of heparin used during HD could not be excluded because heparin might influence the binding of thyroid hormones to its binding protein [14]. Removal of iodine during HD could partly explain the increase in the serum fT4 level by the recovery from the Wolff-Chaikoff effect frequently found in renal dysfunction. However, 4–5 h of HD might be too short, and an increase in the serum fT4 level after HD could be better explained by an improvement of hemodilution. In addition, the achievement of an equilibrium state for thyroid hormones may be delayed dependent upon its uptake through the blood vessel walls and plasma membrane.

Concurrently, a significant decrease (10–30%) in the serum TSH level during the 4–5 h of the HD procedure was observed. TSH is a polypeptide hormone with a molecular weight of 28–30 × 10^3. The serum TSH levels are unstable, and diurnal variation is well documented [15]. Furthermore, the serum TSH levels are promptly reduced in the T3 suppression test. Therefore, the prompt and significant decrease in the serum TSH levels indicates a decrease in the TSH release from the pituitary gland due to feedback inhibition by the elevated serum fT4 and fT3 levels after the improvement of hemodilution.

There was subtle but significant difference between the CGN and DN subgroups in their response to HD. Although the serum fT4 levels were the same before and after HD, the serum fT3 levels and therefore fT3/fT4 ratios were significantly lower in the DN subgroup both before and after HD (Table 3). Moreover, the serum TSH and TSH/fT4 ratio [10] were higher in the DN subgroup both before and after HD. In addition, the recovery of serum TSH levels and TSH/fT4 ratios after HD was apparently slow in the DN subgroup, suggesting decreased T4-to-T3 conversion and decreased availability of thyroid hormone in the central nervous system in these patients.

Another possible mechanism for thyroid dysfunction is the senile change in the thyroid gland with or without immunological perturbation. The ESRD patients were usually old and frequently associated with atherosclerosis. Elevation of the serum TSH levels has been suggested in the elderly patients [16, 17]. The patients with lifestyle-related systemic diseases, such as DN, might be more susceptible to senile visceral damage than the CGN patients, damaging not only the kidney, heart, and brain but also thyroid and other organs. Considering the high prevalence of hypothyroidism in the elderly [16, 17], the effect of longstanding DN not only on the kidney but also on the richly vascularized thyroid gland may require further investigation [18]. The effect of diabetes mellitus itself on the thyroid function should also be considered [19].

Interestingly, there was almost no change in the serum Tg levels before and after HD. With a molecular weight of 669,000, Tg is a protein secreted upon the stimulation of the thyroid gland by TSH [20]. Elevation of Tg levels due to the improvement of hemodilution may be offset by the lowering of serum TSH levels, resulting in decreased stimulation of the thyroid gland.

The HD patients have a substantially high risk of hypothyroidism, as defined by an elevated serum TSH level. The serum TSH levels in the high normal to high range are independently associated with high mortality risk in the HD patients [21]. Therefore, the higher serum TSH level both before and after HD in the DN subgroup than the CGN subgroup may suggest a higher risk of hypothyroidism and eventually higher mortality risk.

There are several important limitations in this ESRD study. First, peripheral metabolism of thyroid hormones, such as the conversion of fT4 to fT3, may be altered in inflammation or malnutrition complicated by ESRD and by a number of medications used in ESRD patients. Second, conventional fT4 (indirect fT4) tests routinely used in the clinical setting may not be accurate in ESRD patients due to their indirect estimate of the minute fraction of fT4 and dependence on thyroid hormone-protein binding which is altered in NTI and by use of heparin and other medications.
In conclusion, hemodialysis has a major influence on thyroid hormonal status before HD in the ESRD patients, resulting in lower serum fT4 and fT3 levels and slightly higher serum TSH levels. The serum TBG levels were also influenced by hemodialysis; however, the serum Tg levels remained almost unchanged, likely due to the balance between hemodialysis and the increased stimulation by the slightly elevated TSH levels. Finally, the thyroid-pituitary axis including the peripheral conversion of T4 to T3 and therefore the regulation of TSH levels is impacted to a greater extent in the DN patients than in those with the CGN, probably reflecting the advanced senile change in the DN subgroup. These findings indicate that the serum thyroid hormone levels might better be measured after HD, and not before HD, when hemodilution has been corrected, to detect the presence of primary thyroid functional disorders complicated with ESRD.

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