Endocrine

Prevalence of hypothyroidism and thyroid nodule in chronic hemodialysis Iranian patients

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Abstract

Introduction: End stage renal disease (ESRD) reasons several changes in the function of thyroid gland as; lower levels of thyroid hormones, altered hormone metabolism, and increased iodine storage. The aim of this study was to evaluate the prevalence of nodular goiter and hypothyroidism in hemodialysis (HD) patients compared with normal population. Methods: This cross-sectional study was conducted among HD patients and healthy people as the control group for thyroid function evaluation. Thyroid gland was evaluated by physical examination and ultrasonography. Blood level of FT3, FT4, TSH, TPO Ab, and urinary iodine excretion were checked in both groups. Data were analyzed using SPSS-17 and P-value less than 0.05 was considered as the significance level. Findings: Eighty six HD patients (57.2 ± 17.2 mean age, 48 men) and 86 healthy people (56.6 ± 16.8 mean age, 48 men) were enrolled in this study. Goiter was confirmed by physical examination in 29.0% of the HD patients and 12.8% of the control group (P = 0.04). Nodular goiter that was shown by ultrasonography was found in 27.9% and 3.5% of the HD and control groups, respectively (P = 0.01). HD patients had a higher frequency of reduced FT3 (40.9% vs. 4.6%, P < 0.01) and increased TSH (18.6% vs. 8.1%, P < 0.03). TPO Ab was positive in 15.1% of the HD and 11.6% of the control groups (P = 0.14). Discussion: The high incidence of nodular goiter and hypothyroidism in ESRD patients shows that screening for thyroid dysfunction and goiter, using appropriate laboratory tests, should be considered in evaluations of ESRD patients.

Key words: ESRD, nodular goiter, TSH, thyroid gland, urinary iodine excretion

INTRODUCTION

Chronic renal failure (CRF) causes various changes in the thyroid gland and its function, including lower levels of circulating thyroid hormone, altered peripheral hormone metabolism, decreased binding to carrier proteins, and increased iodine storage in the thyroid gland.1

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Despite considerable overlap in the symptoms related to hypothyroidism and advanced CRF (as fatigue, lethargy, cognitive, and sexual dysfunction), relatively little is known about the prevalence or severity of thyroid abnormalities in the end stage renal disease (ESRD) patients. Increased prevalence of goiter and thyroid gland volume has been reported in ESRD patients. It has been suggested that hypothyroidism may be more common in ESRD patients. Thyroid hormone abnormalities have been reported in ESRD including reduction of TT3, FT3, TT4, and FT4. Thyroid disorders in hemodialysis (HD) patients in previous studies was variable. In a study, prevalence of subclinical hypothyroidism in HD patients was 21.8% compared with 7.1% in the control group. In another study, the prevalence of hypothyroidism (TSH > 5 mU/L) in ESRD was 2.6% versus 1.1% in the control groups. This study was designed to evaluate the thyroid morphology, thyroid function tests, and also determine the prevalence of nodular goiter and hypothyroidism in HD patients in Iran compared with normal population.

**PATIENTS AND METHODS**

**Study sitting and study population**

This was a cross-sectional study conducted at two HD centers with 382 HD adult patients in Shiraz University of Medical Sciences, South of Iran, Fars province. Of them, 86 HD patients (48 men and 38 women) with more than 100 cc urine per day were selected. All participants had been dialyzed for at least 3 mo before entering the study. The patients who had a history of thyroid disease or used anti-thyroidal drugs or levothyroxine, lithium, amiodarone or iodine were excluded from the study. In all patients, bicarbonate-based dialysate fluid containing sodium (Na) 136 meq/L, potassium (K) 2 meq/L, Mg 0.5 mmol/L, and calcium (Ca) 1.25 mmol/L was used. Blood and dialysate flow rates were 300–350 and 500 mL/min, respectively. It must be mentioned that those settings were the same for all patients during the HD session. A total of 86 healthy subjects with normal kidney function, and no abnormal findings on routine urinalysis, matched by gender, age, and weight were recruited from general practice clinics and used as the control. None of these subjects had any known thyroid disease and none of them was on thyroid hormone supplementation and/or anti-thyroid drugs. This study complies with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent.

**Data measurement and data collection**

In both HD patients and control groups after obtaining consent, examination of thyroid gland was done by an intern. An oral questionnaire was administered to each person. Thyroid gland was palpated from the front. Goiter was defined as a visible thyroid gland on physical examination and/or when it was at least twice the expected size. Also, the thyroid gland was examined by ultrasonography using a real-time sonography device Logic 7 general electronic, USA with a 7.5 MHz linear high frequency transducer. Enlargement of the thyroid gland is defined as a thyroid volume exceeding 18 mL for females and 25 mL for males.

The patients’ blood samples were collected from the arterial line immediately before a mid-week single dialysis session before heparin administration in a fasting state, which were centrifuged and frozen at −70°C before the measurements. In these subjects, complete biochemical tests for ESRD follow-up including creatinine (Cr), urea (BUN), hematocrit (HTC), K, Ca, phosphorus (P), albumin, and parathyroid hormone (PTH) were performed. Also, Aliquots of 10 cc from pre- and post-HD fluid were collected and frozen at −70°C to measure the iodine level.

In addition, measurement of blood levels of FT4, FT3, thyroid-stimulating hormone (TSH), anti-Tpo Ab was done in both groups. The following laboratory tests were carried out: free T3 by radioimmunoassay using: RIAF3 Kit (Immuneotech Beckman coulter Company, Czech Republic, reference range [RR] 2.5–5.8 pmol/L, sensitivity 0.5 pmol/L), free T4 by radioimmunoassay using: RIAF4 Kit (Immuneotech Beckman coulter Company, Czech Republic, reference range [RR] 11.5–23 pmol/L, sensitivity 0.5 pmol/L), TSH by immune radiometric assay using TSH IRMA Kit (Immuneotech Beckman coulter Company, Czech Republic, RR: 0.17–4.05 mIU/mL, sensitivity 0.025 pmol/L), anti-TPO antibody levels using Anti-TPO RIA Kit (Immuneotech Beckman coulter Company, Czech Republic, RR < 30U/mL, sensitivity 2 IU/mL). Urinary iodide excretion was checked in both groups by chloride acid digestion method.

Hypothyroidism is characterized by a high serum TSH concentration (more than 5 mIU/mL as our laboratory
rang) and a low serum FT4 concentration (lower than 11.5 pmol/L as our laboratory rang). Subclinical hypothyroidism is defined as a normal serum FT4 and an elevated TSH.9,10

Mean UIE with WHO classification was defined as11 mean UIE < 2 μg/dL → severe iodide deficiency, mean UIE: 2–4.9 μg/dL → moderate iodide deficiency, mean UIE: 5–9.9 μg/dL → mild iodide deficiency, mean UIE: 10–19.9 μg/dL → normal, mean UIE: 20–29.9 μg/dL → excess for normal ranges, mean UIE ≥ 30 μg/dL → very excess for normal ranges.

**Statistical analysis**

Data were presented as number, percent, mean, and standard deviation using chi-square and Student t-test. We used statistical Package for Social Sciences (SPSS) version 17.0 (IL. Chicago, USA) and p-value < 0.05 was considered as the significance level.

**RESULTS**

The mean age of the HD patients was 57.2 ± 17.2 y and mean time on HD was 29.0 ± 6.5 mo. The clinical and biochemical data of HD patients are shown in Table 1. The most common cause of renal failure in HD patients was diabetes mellitus (31.3%, 27 cases) and the second cause was hypertension (HTN), (30.2%, 26 cases). The most common symptoms in HD patients with hypothroidism were fatigue 61.6% (53 patients), constipation 55.8% (48 patients) and the most common sign was HTN (30%, 26 cases).

According to WHO classification and as shown in Table 2, goiter was demonstrated by physical examination in 29.0% (25 cases) of the HD patients versus 12.8% (11 person) of the control groups (P = 0.04).

In addition, nodular goiter shown by ultrasonography was found in 27.9% (24 cases) of the HD patients versus 3.5% (3 cases) of the control groups (P = 0.01). There was no correlation between goiter and Kt/V, PTH, HCT, Alb, Ca, and erythropoietin use and duration of HD (P > 0.05).

We diagnosed 16(18.6%) of HD patients with hypothyroid (50.0% of them had subclinical hypothyroidism) compared to 7(8.1%) of control group (41.6% of them had subclinical hypothyroidism), (P = 0.030).

HD patients had a higher frequency of reduced FT3 (40.9% vs. 4.6%, P < 0.01) and increased TSH than the control group (18.6% vs. 8.1%, P < 0.03). There is no correlation between the prevalence of hypothyroidism with sex and age in this study (P > 0.05). TPO Ab positive in 15.1% (13 cases) of HD patients and 11.6% (10

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<table>
<thead>
<tr>
<th>Table 1 Clinical and biochemical characteristics of hemodialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Dialysis duration (mo)</td>
</tr>
<tr>
<td>Kt/V</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
</tr>
<tr>
<td>Serum sodium (meq/L)</td>
</tr>
<tr>
<td>Serum potassium (meq/L)</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
</tr>
<tr>
<td>Serum phosphorous (mg/dL)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
</tr>
<tr>
<td>Urinary Iodide excretion (μg/L, mean ± SD)</td>
</tr>
<tr>
<td>Goiter prevalence (n, %)</td>
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<td>Nodular goiter prevalence (n, %)</td>
</tr>
<tr>
<td>Hypothyroidism prevalence [TSH &gt; 5 miu/mL and FT4 &lt; 11.5 pmol/L-n, %]</td>
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* TIBC = Total iron binding capacity.
cases) of control groups (P = 0.14). Urinary iodine excretion is lower in HD patients versus the control group (4.6 ± 1.35 vs. 17.6 ± 9.8, P = 0.035).

Comparing iodine dialysis solution before and after HD was 3.7 ± 1.8 and 4.7 ± 2.1 μg/dL, respectively (P = 0.045), indicating that iodine was removed from the patients by HD. Of the total ESRD patients with hypothyroidism, 62.5% (10 cases) had a high titer of anti-TPO while only 4.2% (three cases) of those with normal thyroid function had a high titer of anti-TPO (P < 0.001). Mean of urine iodine in hypothyroid patients was 2.3 ± 1.1 compared to 4.3 ± 1.2 μg/dL in patients without hypothyroidism (P < 0.01).

Thyroid sonography in patients with hypothyroidism showed 31.2% (five patients) diffuse goiter and 43.7% (seven patients) nodular goiter and only four patients (25%) had normal thyroid sonography.

DISCUSSION

This study demonstrated a higher prevalence of nodular goiter and hypothyroidism in our HD population compared to normal population. There was no correlation between age and sex with goiter or hypothyroidism; this is in the same line with Kaptein et al.’s study results, but some studies showed that nodular goiter was more prevalent in females and also increased by age.12

In previous studies, the prevalence of goiter in HD patients ranges from 0% in London to 58% in Utah due to different methods of recognition of goiter.3 Kaptein et al. reported the prevalence of goiter in ESRD patients was 43% versus 6.7% in the control groups.3 Kutlay et al. detected nodular goiter in 36.8% of the ESRD patients and 17.1% of the control groups.13 Da Costa et al.’s study demonstrated a clear tendency for HD patients to present with more thyroid nodules compared to control group (24.1% vs. 7.9%); the difference was not statistically significant.7 Patients with uremia have an increased thyroid volume compared with people with normal renal function and a higher incidence of goiter.11 We found nodular goiter by ultrasonography in 27.9% of HD patients vs. 3.5% of the control group, which confirmed the most previous studies.

Thyroid hormone abnormalities in ESRD have been reported with reduced total T3, free T3 (FT3), total T4 and free T4 (FT4).14 We found that HD patients had a significantly higher frequency of reduced FT3 (40.9% vs. 4.6%) and increased TSH (18.6% vs. 8.1%). In Costas’s study, the serum FT4 and T3 levels were significantly lower in patients with ESRD, and subclinical hypothyroidism was more prevalent in patients with ESRD (21.82% vs. 7.14% in the control group).7 Lin et al. observed that hypothyroidism was significantly more frequent in uremic patients than in the control group (5.4% vs. 0.7%).12 In Kutlay’s study, the incidence of primary hypothyroidism, characterized by persistently elevated TSH values above 5.5 mIU/mL and decreased FT4 levels, was 3.4% in ESRD patients and 0.6% in the controls.13

The exact underlying mechanisms concerning uremia and primary thyroid disease remain unclear. Many contributing causes such as autoimmune thyroiditis, iodine metabolism alternation, and decreased peripheral sensitivity to hormones have been hypothesized.15 The hypothalamic-pituitary axis is intact in patients with chronic kidney disease (CKD), because TSH can elevate in patients with CKD and primary hypothyroidism, and TSH is suppressed in CKD patients with hyperthyroidism.16 The reduction in T3 levels is the most frequently observed thyroid abnormality in uremic patients.3,17 Peripheral synthesis of T3 from T4 decreases in the chronic metabolic acidosis associated with the uremic patients and correction of chronic metabolic acidosis normalizes the plasma FT3 concentration.18 Although in uremic patients free and total T4 concentrations are normal or slightly low, it might be high due to the effect of heparin used during HD which inhibits T4 binding to thyroid binding proteins.19

Serum TSH concentrations are usually normal or elevated in uremia, but its response to its releasing hormone (TRH) is usually low.2,20 Among a representative sample of adults in the USA, reduced GFR was associated with a higher hypothyroidism prevalence, with many subclinical cases.21

Although in our study TPO Ab was positive in 15.1% of the HD patients and 11.6% of the control groups, 62.5% of the ESRD patients with hypothyroidism had a significantly high titer of anti-TPO while only 4.2% of ESRD patients with normal thyroid function had a high titer of anti-TPO. Otherwise, the titer of anti-TPO Ab was significantly higher in HD patients compared to the control group. Kutlay et al.’s study showed no difference between the patient and control groups for titers of thyroid autoantibody.13 Lim et al.’s study revealed that autoimmune thyroid disease was not more frequent in CRF patients, because the incidence of positive thyroglobulin and thyroid microsomal antibodies was low.2 In Kaptein’s study, compared to the total group of ESRD patients, the hypothyroid patients had a significantly higher frequency of positive antimicrosomal antibody titer (50% vs. 6.7%).3 Targher showed 10.7% subclinical hypothyroidism in subjects who had eGFR <60 mL/min/1.73 m². And 23.3% of them had increased anti-thyroid
antibodies and conclude that thyroid autoimmunity and subclinical primary hypothyroidism are highly prevalent in CKD individuals.\textsuperscript{22} Our study indicated that UIE significantly was lower in HD patients (4.35 ± 1.35 vs. 17.6 ± 9.8 in control group). Iodine is an essential component of thyroid hormones; either low or high intake may lead to thyroid disease. High iodine intake may trigger and exacerbate autoimmune thyroiditis, increasing the subclinical and overt hypothyroidism.\textsuperscript{23,24} Teng observed an increase in the prevalence of overt and subclinical hypothyroidism, and autoimmune thyroiditis with increasing iodine intake in China.\textsuperscript{25} High iodine intake has been reported to initiate and exacerbate the of thyroid infiltration by lymphocytes in genetically susceptible BB/W rats.\textsuperscript{26}

Comparing iodine dialysis solution before (3.7 ± 1.8 µg/dL) and after (4.7 ± 2.1 µg/dL) HD showed that iodine was removed from the patients by HD. Although inorganic iodide is removed by HD, serum iodide has been reported to be increased in HD patients.\textsuperscript{27} The use of povidone-iodine for disinfecting arteriovenous fistulas for HD may contribute to the rise in serum iodide in some dialyzed patients.\textsuperscript{6} Decreased UIE and thus increased serum iodide may result in thyroid gland enlargement and subsequent goiter formation. Sanai et al. reported the improvement of serum TSH level after iodide restriction in ESRD patients.\textsuperscript{28}

In addition, there was an association between hypothyroidism and mortality in ESRD patients,\textsuperscript{29} that is important association and further studies need for showing that.

CONCLUSION

Considering the current study, the clinical manifestations of hypothyroidism in ESRD patients may be mask due to coexisting uremia, malnutrition, and non-thyroidal illness. Thyroid hormone abnormalities, nodular goiter, and hypothyroidism are more common in HD patients compared with controls. Otherwise, there was an association between hypothyroidism and mortality in ESRD patients, suggesting that this association may be managed by thyroid hormone supplementation. We recommend screening for thyroid dysfunction and goiter using appropriate tests and sonography should be considered in evaluation of every ESRD patients.

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AUTHORS’ CONTRIBUTIONS

Pakfetrat M and Dabbaghmanesh MH contributed to the design of the study, critical revision of the content and final approval of the article. Karimi Z and Nikoo MH contributed to data acquisition, drafting the article and final approval of the article. Malekmakan L contributed to data analysis and interpretation of data, drafting the article and final approval of the article. Rasekhi A contributed to perform ultra sonography as a part of the data collection, drafting the article and final approval of the article.

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