The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone

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Abstract

Background. We hypothesized that the prevalence of low T3 would be increased according to the increase in CKD stage. This study was performed to explore the prevalence in each stage of CKD and relationship with eGFR.

Methods. A total of 2284 cases with normal thyroid-stimulating hormone (TSH) level were enrolled and retrospectively analysed during the recent period, from July 2005 to December 2007.

Results. There was an increasing trend for the population of low T3 according to the increase of a CKD stage (eGFR ≥ 90, 8.2%; ≥ 60 eGFR < 90, 10.9%; ≥ 30 eGFR < 60, 20.8%; ≥ 15 eGFR < 30, 60.6%; eGFR < 15, 78.6%). Also, there was positive relationship between eGFR and serum T3 in male, female and total subjects. After adjusting for age and sex, compared with eGFR ≥ 60 ml/min/1.73 m², eGFR < 60 ml/min/1.73 m² was associated with an increased odds of low T3 [odds ratio 2.40 (CI: 1.5315 to 3.1731)]. In multiple regression analysis, eGFR was positively related with T3 (standardized coefficient 0.143, $R^2 = 0.055$, $P < 0.001$), independent of age and serum albumin.

Conclusion. This study showed that low T3 syndrome was highly prevalent in CKD and was a remarkable finding in early CKD. Furthermore, serum T3 levels were associated with severity of CKD even in the normal TSH level.

Keywords: chronic kidney disease; low T3 syndrome; triiodothyronine

Introduction

The evaluation of thyroid function in systemic illness remains complex because the changes occur at all levels of the hypothalamic-pituitary-thyroid axis. During illness, a decrease in triiodothyronine (T3) and pulsatile thyroid-stimulating hormone (TSH) release and increases in reverse T3 occur [1]. This constellation of findings is termed the low T3 syndrome, the euthyroid sick syndrome or non-thyroid illness [2]. Low T3 syndrome is the most common manifestation in non-thyroid illness and this phenomenon has been believed to be due to inhibition of 5′-deiodinase, which is a catalyzing enzyme for production of T3 from circulating T4 [3]. To date, 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 [4–6]. In 1977, Lim et al. suggested that prevalences of low T3 were 80% in non-haemodialysis patients and 43% in haemodialysis patients, respectively [4]. Recently, another report described that the prevalence of hypothyroidism in patients with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m² was 23.1% and those prevalences were increased according to the decrease of eGFR [6]. Also, the prevalence of low T3 syndrome in congestive heart failure is 18–23% according to recent prospective clinical trials [7,8].

Several lines of evidence suggested that low T3 was an independent predictor of survival in various illness states [9–11]. Furthermore, the recent data proposed that biomarkers of inflammation were associated with low T3 levels in haemodialysis and peritoneal dialysis patients and thyroid dysfunction might be implicated in the pathogenetic pathway which link microinflammation to survival in dialysis patients.

However, there are no data about the prevalence of low T3 in persons with chronic kidney disease (CKD) who do not require maintenance dialysis. We hypothesized that the prevalence of low T3 would be increased according to the increase of a CKD stage. This study was performed to explore the prevalence in each stage of CKD and relationship with eGFR.

Methods

Subjects

This study was performed retrospectively based upon laboratory results during the recent time period, from July
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2005 to December 2007. All data were collected from the database of a laboratory centre and all subjects who checked the serum T3 were included. A total of 2284 cases were enrolled after excluding subjects who were diagnosed with hypothyroidism, hyperthyroidism or thyroiditis, subjects who had active infection, active liver disease or liver cirrhosis and subjects who were younger than 18 years old or pregnant person. We also excluded subjects in whom TSH and FT4 were not checked on the same day. All enrolled subjects had a normal serum TSH level and did not take thyroid hormones.

Laboratory measurement and assessment of kidney function

Thyroid function tests were performed using electrochemiluminescence assay (Elecsys®, Roche Diagnostics, Basel, Switzerland). The normal reference range for T3, FT4 and TSH in our institute was 80–200 ng/dl, 0.93–1.7 ng/dl and 0.27–4.2 µIU/ml, respectively. We estimated GFR (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) equation [eGFR (ml/min/1.73 m²) = 1.86 × (Scr)−1.154 × (Age)−0.203 × (0.742 if female), Scr (serum creatinine, mg/dl)] [12]. Initially, all subjects were classified into two groups according to eGFR (60 ml/min/1.73 m²). Second, the prevalence of the low T3 population was explored according to CKD categories of National Kidney Foundation CKD staging (stage 1, eGFR ≥90; stage 2, 60 eGFR < 90; stage 3, 30 eGFR < 60; stage 4, 15 eGFR < 30; stage 5, eGFR < 15 ml/min/1.73 m²). Low T3 syndrome was defined as a normal serum TSH level and low serum T3 level excluding subjects who were diagnosed as hypothyroidism, hyperthyroidism or thyroiditis. This study was approved by the Ethical Committee of Pusan National University Hospital.

Statistics

All continuous variables are expressed as mean ± SD and proportions are expressed as a number (%). The comparison between two groups was performed using an unpaired t-test and chi-square test as appropriate. The relationship between the serum T3 level and eGFR was explored using linear regression analysis. Also, we performed logistic regression analysis using T3 as the dependent variable to analyse the effect of CKD (eGFR<60 ml/min/1.73 m²) on serum T3. Multiple regression analysis was also performed to elucidate the effect of eGFR on T3 independent of age. Computer software for statistical analysis was MedCalc® (version 8.1.1.0, Mariakerke, Belgium). A value of P < 0.05 was taken to be statistically significant.

Results

Characteristics of subjects according to eGFR (60 ml/min/1.73 m²)

A total of 2284 subjects were enrolled. There was no difference between two groups in sexual proportion, serum FT4 and serum TSH. The subjects with a lower eGFR were older than those in the higher eGFR group (67.8 ± 10.6 years old versus 54.3 ± 13.9 years old, P < 0.001). Serum albumin levels were lower in the lower eGFR group than those in the higher eGFR group (3.99 ± 0.61 g/dl versus 4.34 ± 0.43 g/dl). Serum T3 levels were lower in the lower eGFR group than those in the higher eGFR group (89.5 ± 21.0 ng/dl versus 102.7 ± 18.8 ng/dl, P < 0.001).

<table>
<thead>
<tr>
<th>Variables</th>
<th>eGFR ≥ 60 ml/min/1.73 m²</th>
<th>eGFR &lt; 60 ml/min/1.73 m²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>92.5 ± 20.4</td>
<td>45.3 ± 14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>54.3 ± 13.9</td>
<td>67.8 ± 10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male number (%)</td>
<td>1011 (48.9%)</td>
<td>100 (46.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.34 ± 0.43</td>
<td>3.99 ± 0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td>1.24 ± 0.19</td>
<td>1.27 ± 0.24</td>
<td>0.078</td>
</tr>
<tr>
<td>T3 (ng/dl)</td>
<td>102.7 ± 21.0</td>
<td>89.5 ± 21.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (µIU/ml)</td>
<td>1.75 ± 0.87</td>
<td>1.88 ± 0.94</td>
<td>0.054</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of cohorts according to eGFR (60 ml/min/1.73 m²)

Relationship between eGFR and serum T3

This study was performed using linear regression analysis to explore the relationship between eGFR and serum T3. Results were described after the patients were classified as male, female and total subjects. In males, there was a positive relationship between eGFR and serum T3 (T3 = 0.163 ± eGFR + 88.9197, R² = 0.042, P < 0.001, Figure 1). In females, there was a positive relationship between eGFR and serum T3 (T3 = 0.112 ± eGFR + 89.7160, R² = 0.020, P < 0.001, Figure 2). When we analysed total subjects, a similar positive relationship was found between eGFR and serum T3 (T3 = 0.141 ± eGFR + 88.9759, R² = 0.031, P < 0.001, Figure 3). When we performed the analysis using multiple regression analysis, serum T3 was found to be positively related to eGFR (standardized coefficient 0.143, R² = 0.055, P < 0.001), independent of age and serum albumin (Table 2).

The prevalence in each stage of CKD

Among the 2284 enrolled subjects (11.3%), had low serum T3 levels. The numbers of subjects in each CKD group were as follows: CKD1, N = 1042; CKD2, N = 1025; CKD3, N = 183; CKD4, N = 20; CKD5, N = 14]. After adjusting for age and sex, compared with eGFR ≥ 60 ml/min/1.73 m², eGFR <60 ml/min/1.73 m² was associated with an increased odds of low T3 [Odds ratio 2.40 (CI: 1.5315–3.7311)]. Also, there was an increasing trend for the population of low T3 according to the increase of a CKD stage. Figure 4 demonstrates this finding in a bar chart; eGFR ≥ 90, 8.2% (85/1042); ≥ 60 eGFR < 90, 10.9% (112/1025); ≥ 30 eGFR < 60, 20.8% (38/183); ≥ 15 eGFR < 30, 60.6% (12/20);
Fig. 1. Scatter diagram with regression line of serum T3 against eGFR in males. Equation: $T3 = 0.1634 \times eGFR + 88.9197$, $R^2 = 0.042$, $P < 0.001$.

Fig. 2. Scatter diagram with regression line of serum T3 against eGFR in females. Equation: $T3 = 0.1127 \times eGFR + 89.7160$, $R^2 = 0.020$, $P < 0.001$. 
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Table 2. Multiple regression analysis showing independent contributions to triiodothyronine

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Unstandardized coefficient</th>
<th>Beta</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>0.114</td>
<td>0.143</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>5.815</td>
<td>0.140</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>−0.054</td>
<td>−0.039</td>
<td>0.101</td>
</tr>
</tbody>
</table>

Coefﬁcient of determination $R^2$: 0.055

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 can 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 [14]. Based upon Kaptein et al.’s report in 1988, of 287 euthyroid patients with ESRD, 76% had total T3 levels <100 ng/dl, and 66% had free T3 index values <100 [15]. This observation suggests that the great proportion of ESRD patients have low serum T3 levels irrespective of serum TSH levels. In several reports, thyroid abnormalities can occur within hours of acute illness, and the magnitude of these alterations correlates with severity of disease and survivals. Especially, low free T3 has been considered as an independent predictor of mortality in haemodialysis patients, and ESRD patients with relatively higher serum free T3 had a lower mortality risk than patients with lower serum-free T3 [16]. Another recent survey suggested that low T3 was associated with inflammation and cardiovascular damage in ESRD patients [17]. These observations suggest that low T3 can be a marker of prognosis in persons with renal problems. Thus, we investigated how many subjects had a low T3 in CKD and this study offers the first evidence for demonstrating the low T3

$eGFR < 15$, 78.6% (11/14). Of those with stage 3 CKD, the low T3 population of subjects having $30 \leq eGFR < 45$ was 42.9% (18/42) and the low T3 population of subjects having $45 \leq eGFR < 60$ was 14.2% (20/141).
population at an early stage of CKD subjects in a euthyroid state. According to our results, the great proportion of stage 4 and 5 CKD patients (60.0%, 78.6%) had low T3 levels, consistent with previous reports. Also, in stage 3 CKD (N = 152), a total of 38 subjects (20.8%) have low T3 levels. Of those, the low T3 population of subjects with ≤ 30 eGFR < 45 was 42.9% (18/42) and low T3 population of subjects with ≥ 45 eGFR < 60 was 14.2% (20/141). These results suggested that while the prevalence of low T3 in CKD 3 was lower than that in CKD 4 and 5, a quarter of early CKD patients have low T3 levels and decreased T3 could be an early finding in patients with CKD.

In the healthy elderly patients, there is a normal free T4 but a relatively lower T3, while there is still some disagreement [2]. In the present study, subjects with eGFR < 60 ml/min/1.73 m² had a significant high odds ratio (2.40) for low T3 after adjusting for age and sex. Additionally, T3 was positively related with eGFR independent of age and serum albumin.

There were some limitations in this study. First, the categorization of CKD was performed using only eGFR by the abbreviated MDRD equation (four-variable equation) and other findings of kidney damage such as proteinuria or haematuria were not used in this study. Second, the diet state (calorie intake or dietary composition) or cardiac status affecting thyroid hormonal status was not reflected in exclusion criteria. Third, the number of subjects with CKD 4 and 5 was too small. Last, since this study was conducted retrospectively, we could not fully reflect the patient’s comorbidity and the reason for checkup of the thyroid function test. This limitation may induce the selection bias in this study.

Despite the above-mentioned limitations, this study was valuable in the viewpoint of evaluating the prevalence of low T3 syndrome in CKD patients having a normal TSH level. Especially even in early CKD, we could reveal a decrease of T3.

In the future, follow-up studies of T3 are needed in stage 3 CKD patients and the effect of renal replacement therapy on T3 should be elucidated in the viewpoint of prognosis.

In conclusion, this study showed that low T3 syndrome was highly prevalent in CKD and was a remarkable finding in early CKD. Furthermore, serum T3 levels were associated with severity of CKD even in the normal TSH level. The great proportion of stage 3 CKD patients and the effect of renal replacement therapy on T3 should be elucidated in the viewpoint of prognosis.

Conflict of interest statement. None declared.

References


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