# Preservation of Renal Function by Thyroid Hormone Replacement Therapy in Chronic Kidney Disease Patients with Subclinical Hypothyroidism

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**Context:** Subclinical hypothyroidism is not a rare condition, but the use of thyroid hormone to treat subclinical hypothyroidism is an issue of debate.

**Objective:** This study was undertaken to investigate the impact of thyroid hormone therapy on the changes in estimated glomerular filtration rate (eGFR) in subclinical hypothyroidism patients with stage 2–4 chronic kidney disease.

**Patients:** A total of 309 patients were included in the final analysis.

**Main Outcome Measure:** The changes in eGFR over time were compared between patients with and without thyroid hormone replacement therapy using a linear mixed model. Kaplan-Meier curves were constructed to determine the effect of thyroid hormone on renal outcome, a reduction of eGFR by 50%, or end-stage renal disease. The independent prognostic value of subclinical hypothyroidism treatment for renal outcome was ascertained by multivariate Cox regression analysis.

**Results:** Among the 309 patients, 180 (58.3%) took thyroid hormone (treatment group), whereas 129 (41.7%) did not (nontreatment group). During the mean follow-up duration of 34.8 $\pm$ 24.3 months, the overall rate of decline in eGFR was significantly greater in the nontreatment group compared to the treatment group ($-5.93 \pm 1.65$ *vs.* $-2.11 \pm 1.12$ ml/min/yr/1.73 m$^2$; $P = 0.04$). Moreover, a linear mixed model revealed that there was a significant difference in the rates of eGFR decline over time between the two groups ($P < 0.01$). Kaplan-Meier analysis also showed that renal event-free survival was significantly lower in the nontreatment group ($P < 0.01$). In multivariate Cox regression analysis, thyroid hormone replacement therapy was found to be an independent predictor of renal outcome (hazard ratio, 0.28; 95% CI, 0.12–0.68; $P = 0.01$).

**Conclusion:** Thyroid hormone therapy not only preserved renal function better, but was also an independent predictor of renal outcome in chronic kidney disease patients with subclinical hypothyroidism. (***J Clin Endocrinol Metab*** **97: 2732–2740, 2012)**

Because thyroid hormone has numerous effects on the kidney, heart, and vascular system, thyroid dysfunction can cause significant changes in renal and cardiovascular functions (1–3). In particular, hypothyroidism is known to be associated with reduced renal plasma flow (RPF) and low glomerular filtration rate (GFR). In addition, decreased renal sodium reabsorption and decreased renal ability to dilute urine, resulting in hyponatremia, are

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Abbreviations: Anti-TPO, Antithyroid peroxidase antibody; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated GFR; ESRD, end-stage renal disease; FMD, flow-mediated dilatation; fT4, free $T_4$; GFR, glomerular filtration rate; HR, hazard ratio; LDL, low-density lipoprotein; RPF, renal plasma flow.

frequently observed in patients with hypothyroidism (2, 3). Moreover, the number of risk factors for coronary heart disease, including hypertension, dyslipidemia, and hyperhomocysteinemia, are increased in hypothyroidism patients, which is in part associated with more coronary heart disease events and higher cardiovascular mortality (4, 5).

Subclinical hypothyroidism, defined as elevated serum TSH but normal free $T_4$ (fT4) level, is not a rare disease. The prevalence of subclinical hypothyroidism has been reported to be about 4 to 10% in the adult population and to increase with age, especially in females after the age of 45 yr (6). In addition, subclinical hypothyroidism is more common in women than men, in whites than blacks, and in areas of high iodine intake (7, 8). Factors such as previous history of hyperthyroidism or head and neck cancer treated with external beam radiation, a family history of thyroid disease, and ingestion of amiodarone, an iodine-containing drug, also raise the likelihood of subclinical hypothyroidism (6). Moreover, previous studies have shown a close interrelationship between chronic kidney disease (CKD) and subclinical hypothyroidism (9–11). The prevalence of CKD was high in patients with overt as well as subclinical hypothyroidism (12). The risk of nephropathy was increased in type 2 diabetic patients with subclinical hypothyroidism (13). Conversely, subclinical hypothyroidism was frequently observed in CKD patients (14). Cardiac abnormalities, such as impaired left ventricular diastolic function at rest and systolic dysfunction with exertion, were also associated with subclinical hypothyroidism (15). Furthermore, even a minor elevation of TSH was surmised to play a role in the development of atherosclerosis and to have adverse effects on cardiovascular performance in the general population (8, 16).

Replacement of thyroid hormone is fundamental in the treatment of hypothyroidism patients. It not only relieves the symptoms of hypothyroidism, but also alleviates the deleterious effects of hypothyroidism on the kidney and heart (10, 17–20). Normalization of RPF and GFR were demonstrated in primary hypothyroidism patients treated with thyroid hormone (21, 22). In addition, restoration of euthyroidism improved GFR in CKD patients with overt hypothyroidism (10, 18, 19). Cardiovascular complications of overt hypothyroidism were also abrogated by thyroid hormone replacement (20). However, between several existing guidelines, there has been a lack of consensus on whether to treat subclinical hypothyroidism patients with thyroid hormone or not. Some previous studies have shown that L-thyroxine improves cardiac function and lowers the low-density lipoprotein (LDL)-cholesterol level in patients with subclinical hypothyroidism (23–26), whereas other studies failed to demonstrate the beneficial effects of L-thyroxine supplement in these patients (27). On the other hand, the impact of thyroid hormone replacement has not been extensively studied in CKD patients with subclinical hypothyroidism. In particular, it has not been evaluated whether the restoration of euthyroidism is beneficial in terms of preserving renal function in these patients. In this study, therefore, we explored the effect of thyroid hormone replacement for subclinical hypothyroidism on the changes in GFR in adult CKD patients.

## Subjects and Methods

### Ethics statement

This study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Yonsei University Health System Clinical Trial Center. All patients participating in the current study were aware of this investigation. However, because this study was a retrospective medical record-based study and the study subjects were de-identified, the IRB waived the need for written consent from the patients.

### Study subjects

For this study, we initially recruited 570 patients who had stage 2–4 CKD and were biochemically diagnosed with subclinical hypothyroidism at Yonsei University Health System, Seoul, Korea, between January 2005 and December 2010. Of these patients, 226 were excluded for the following reasons: age below 18 yr (n = 27) or above 75 yr (n = 20), heavy proteinuria including nephrotic syndrome (n = 31), terminal malignancy (n = 28), pregnancy (n = 5), already on thyroid hormone or other hormone treatment (n = 66), and follow-up duration less than 12 months (n = 49). We also excluded 35 patients whose TSH level was higher than 10 $\mu$IU/ml. Thus, a total of 309 patients were included in the final analysis.

### Data collection

Demographic and clinical data at the time of diagnosis of subclinical hypothyroidism, including age, gender, comorbidities such as cardiovascular disease, and blood pressure, were recorded. Cardiovascular disease was defined as a history of coronary, cerebrovascular, or peripheral vascular disease; coronary disease was defined as a history of angioplasty, coronary artery bypass grafts, myocardial infarction, or angina; cerebrovascular disease was defined as a previous history of transient ischemic attack, stroke, or carotid endarterectomy; whereas peripheral vascular disease was defined as a history of claudication, ischemic limb loss and/or ulceration, or peripheral revascularization procedure. The results of the following concurrent laboratory tests were also collected: serum calcium, phosphate, albumin, total cholesterol, and triglyceride levels. Estimated GFR (eGFR) (ml/min/1.73 $m^2$) was calculated using the four-variable Modification of Diet in Renal Disease study (MDRD) equation (28): eGFR (ml/min/1.73 $m^2$) = $175 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if the subject is female) or $\times$ 1.212 (if the subject is black). In addition, the stages of CKD were defined according to the American National Kidney Foundation

(29): stage 1, eGFR of 90 ml/min/1.73 $m^2$ or greater; stage 2, eGFR 60–89 ml/min/1.73 $m^2$; stage 3, eGFR 30–59 ml/min/1.73 $m^2$; stage 4, 15–29 ml/min/1.73 $m^2$; and stage 5, eGFR less than 15 ml/min/1.73 $m^2$ or dialysis.

### Thyroid function test and definition

In all patients, serum $T_3$, fT4, TSH, and antithyroid peroxidase antibody (anti-TPO) concentrations were measured. Serum $T_3$, fT4, and TSH levels were determined by chemiluminescence microparticle immunoassay on the Architect-i2000SR analyzer (Abbott Laboratories, Abbott Park, IL) and anti-TPO concentration by chemiluminescence assay on a Roche Cobas E601 analyzer (Hitachi, Hitachinaka, Japan). The diagnosis of subclinical hypothyroidism was solely based upon the results of a thyroid function test and was defined as normal serum fT4 but elevated TSH levels, irrespective of clinical symptoms of hypothyroidism. Because there was a possibility of transient elevation of serum TSH concentration, the measurement of serum TSH level was repeated within 3 months to confirm the diagnosis. The reference ranges of $T_3$, fT4, and TSH were 0.58–1.59 ng/ml, 0.70–1.48 ng/dl, and 0.35–4.94 $\mu$IU/ml, respectively.

### Treatment of subclinical hypothyroidism

Because this was a retrospective clinical study, replacement of thyroid hormone was not randomly performed. We surmise that patients with dyslipidemia, high titers of anti-TPO, and nonspecific symptoms of hypothyroidism, such as fatigue, constipation, and depression, were prone to receiving thyroid hormone treatment.

The treated patients were initially administered L-thyroxine with the lowest dose necessary to normalize serum TSH level, usually 25 $\mu$g/d. After the start of thyroid hormone supplement, serum TSH concentration was remeasured at 5 or 6 wk in most patients. If the level of TSH remained above the normal reference range, the dose of L-thyroxine was increased by 25 $\mu$g/d until the patient's serum TSH concentration was reduced to the normal reference range. The dose of L-thyroxine was adjusted every 3 months according to the follow-up level of TSH.

### Statistical analysis

Statistical analysis was performed using SAS software (version 9.1.3; SAS Institute Inc., Cary, NC). Continuous variables were expressed as mean ± SD and categorical variables as a number (percentage). To compare differences between the two groups, Student's *t* test or the $\chi 2$ test was used. The slope of the decline in renal function over time was calculated by linear regression analysis of serial eGFR for each patient; the slope was expressed as the regression coefficient (ml/min/yr/1.73 $m^2$). The changes in eGFR over time were compared between patients with and without thyroid hormone replacement therapy using a linear mixed model. In our implementation of the mixed model, the intercept and the regression coefficient for the follow-up time were treated as random effects such that each subject had a unique intercept and regression coefficient. Cumulative survival curves were generated by the Kaplan-Meier method to determine the effect of thyroid hormone on renal outcome, 50% reduction of eGFR, or end-stage renal disease (ESRD), and between-group survival was compared by a log-rank test. The independent prognostic value of subclinical hypothyroidism treatment on renal outcome was ascertained by multivariate Cox proportional hazards regression analysis, which included all covariates with a *P* value less than 0.1 on univariate analysis. In addition, Pearson's correlation analysis was performed to elucidate the relationships between eGFR and TSH level. A *P* value less than 0.05 was considered statistically significant.

## Results

### Baseline characteristics of patients

The baseline demographic, clinical, and biochemical data of CKD patients with subclinical hypothyroidism are shown in Table 1. The mean age was 62.2 ± 12.5 yr, and 173 patients (56.0%) were male. Among the 309 patients, 180 (58.3%) took thyroid hormone, whereas 129 (41.7%) did not. The proportion of diabetes mellitus (DM) patients (34.4 *vs.* 39.5%; $P = 0.36$) and the serum creatinine concentration tended to be lower (1.3 ± 0.5 *vs.* 1.4 ± 0.6 mg/dl; $P = 0.54$) in treated subclinical hypothyroidism patients with CKD, but the difference between them and the nontreated patients did not reach statistical significance. Serum cholesterol (180.0 ± 39.2 *vs.* 161.3 ± 48.0 mg/dl; $P < 0.01$) and triglyceride levels (162.7 ± 121.0 *vs.* 125.6 ± 63.3 mg/dl; $P < 0.01$) were significantly higher in patients with thyroid hormone treatment compared with nontreated patients. The measurement of anti-TPO concentration was performed in 140 patients— 81 in the treatment group and 59 in the nontreatment group. Among these 140 patients, high titers of anti-TPO (≥60 IU/ml) were demonstrated in 26 patients, all of whom were in the treatment group (32.1%). In contrast, the mean age, the proportion of patients with previous history of cardiovascular disease, systolic and diastolic blood pressure, and serum albumin, calcium, phosphate, $T_3$, fT4, and TSH concentrations were comparable between the two groups (Table 1). Meanwhile, Pearson's correlation analysis revealed that there was a significant inverse correlation between eGFR and TSH levels ($r = -0.31$; $P < 0.01$) and a significant positive association between eGFR and serum $T_3$ concentrations ($r = 0.27$; $P < 0.01$).

### Serum TSH levels and blood pressure during follow-up

Serum TSH levels and blood pressure at various time points during the follow-up period are listed in Table 2. Serum TSH concentrations in the treatment group were significantly decreased to the normal range at 3 months ($P < 0.01$) and were maintained within the normal range during the follow-up period, whereas there was no significant change in serum TSH levels in the nontreatment group, resulting in significant difference in serum TSH values between the two groups ($P < 0.01$). In contrast, the

**TABLE 1.** Baseline demographic, clinical, and biochemical characteristics of the subjects

| Characteristic | Treated patients[a] | Nontreated patients[b] | *P* value |
|---|---|---|---|
| n | 180 | 129 | |
| Age (yr) | 61.6 ± 12.4 | 63.7 ± 13.5 | 0.14 |
| Male, n (%) | 102 (56.7) | 71 (55.0) | 0.78 |
| Body weight (kg) | 63.7 ± 11.1 | 62.6 ± 12.4 | 0.44 |
| DM, n (%) | 62 (34.4) | 51 (39.5) | 0.36 |
| Hypertension, n (%) | 110 (61.1) | 79 (61.2) | 0.98 |
| Cardiovascular disease, n (%) | 27 (15.0) | 25 (19.4) | 0.31 |
| Systolic blood pressure (mm Hg) | 126.3 ± 16.7 | 123.4 ± 19.2 | 0.26 |
| Diastolic blood pressure (mm Hg) | 74.4 ± 11.4 | 71.8 ± 12.5 | 0.12 |
| Follow-up duration (months) | 32.0 ± 25.1 | 36.7 ± 23.5 | 0.91 |
| $T_3$ (ng/ml) | 1.07 ± 0.28 | 1.04 ± 0.29 | 0.39 |
| fT4 (ng/dl) | 1.12 ± 0.56 | 1.09 ± 0.25 | 0.72 |
| TSH ($\mu$IU/ml) | 6.83 ± 1.46 | 6.73 ± 1.48 | 0.68 |
| Anti-TPO ≥ 60 IU/ml, n (%) | 26/81 (32.1) | 0/59 (0) | |
| Serum creatinine (mg/dl) | 1.32 ± 0.50 | 1.36 ± 0.59 | 0.54 |
| eGFR (ml/min/1.73 $m^2$) | 57.8 ± 17.0 | 56.1 ± 19.0 | 0.43 |
| CKD stage, n (%)[c] | | | 0.31 |
| Stage 2 | 85 (47.0) | 53 (41.1) | |
| Stage 3 | 82 (45.8) | 64 (49.6) | |
| Stage 4 | 13 (7.2) | 12 (9.3) | |
| Serum albumin (g/dl) | 4.26 ± 0.57 | 4.16 ± 0.76 | 0.18 |
| Serum calcium (mg/dl) | 9.14 ± 0.65 | 9.08 ± 0.65 | 0.50 |
| Serum phosphate (mg/dl) | 3.64 ± 0.61 | 3.75 ± 0.65 | 0.14 |
| Serum cholesterol (mg/dl) | 180.0 ± 39.2 | 161.3 ± 48.0 | <0.01 |
| Serum triglyceride (mg/dl) | 162.7 ± 121.0 | 125.6 ± 63.3 | <0.01 |
| Medication use, n (%) | | | |
| ACEI or ARB | 73 (40.6) | 62 (48.1) | 0.19 |
| Calcium channel blockers | 52 (36.1) | 44 (39.6) | 0.33 |
| $\beta$-blockers | 46 (25.6) | 29 (22.5) | 0.53 |
| Diuretics | 62 (34.4) | 48 (37.2) | 0.61 |
| Other antihypertensive drugs | 13 (7.2) | 12 (9.3) | 0.51 |
| Statins | 53 (29.4) | 34 (26.4) | 0.55 |

Values are expressed as mean ± SD or number (percentage). eGFR is calculated by MDRD-4 equation. ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

[a] Patients who were treated with thyroid hormone for subclinical hypothyroidism.

[b] Patients who were not treated with thyroid hormone for subclinical hypothyroidism.

[c] Stage 2, eGFR 60–89 ml/min/1.73 $m^2$; stage 3, eGFR 30–59 ml/min/1.73 $m^2$; stage 4, 15–29 ml/min/1.73 $m^2$.

blood pressures in the two groups were comparable during the follow-up period.

### Comparison of renal function over time in patients with and without thyroid hormone replacement therapy

The results of eGFR were available for at least four time points within a 6-month interval in all patients. As shown in Fig. 1 and Table 3, patients in the nontreatment group tended to have lower baseline eGFR compared with treated patients, although the difference was not significant. At 12 months, however, eGFR become significantly lower in patients who did not receive thyroid hormone therapy ($P = 0.04$). In addition, the overall rate of decline in eGFR was significantly greater in the nontreatment group compared with that in the treatment group ($-5.93 \pm 1.65$ *vs.* $-2.11 \pm 1.12$ ml/min/yr/1.73 $m^2$; $P = 0.04$). Moreover, a linear mixed model revealed that there was a significant difference in the rate of eGFR decline over time between patients with and without thyroid hormone replacement therapy [coefficient ($-0.18$, $-0.01$); $P < 0.01$].

### Renal outcome in patients with and without thyroid hormone replacement therapy

During the mean follow-up duration of 34.8 ± 24.3 months, a 50% decrease in eGFR occurred more often in the nontreatment group (27 patients; 20.9%) compared with the treatment group (15 patients; 8.3%), resulting in rates of 7.96 and 2.75 per 100 patient-years, respectively ($P < 0.01$). The incidence of ESRD was also significantly higher in the nontreatment group relative to the treatment group (2.36 *vs.* 0.37 per 100 patients-years; $P = 0.01$). The relative risk reduction for halving the eGFR and achieving ESRD by thyroid hormone replacement therapy was 64% [95% confidence interval (CI), 0.19–0.67; $P = 0.001$] and 85% (95% CI, 0.03–0.71; $P = 0.006$), respectively (Table 4). Kaplan-Meier analysis also indicated that renal event-free survival was significantly lower in the nontreatment group ($P < 0.01$) (Fig. 2).

**TABLE 2.** Comparison of changes in TSH levels and blood pressure over time in patients with and without thyroid hormone replacement therapy

| | TSH levels | | Blood pressure (mm Hg) | | |
|---|---|---|---|---|---|
| | Treated patients[a] | Nontreated patients[b] | | Treated patients[a] | Nontreated patients[b] |
| n | 180 | 129 | | 180 | 129 |
| Baseline | 6.83 ± 1.46 | 6.73 ± 1.48 | SBP | 126.3 ± 16.7 | 123.4 ± 19.2 |
| | | | DBP | 74.4 ± 11.4 | 71.8 ± 12.5 |
| 6 months | 1.94 ± 1.38#* | 6.92 ± 1.03 | SBP | 128.8 ± 17.6 | 126.7 ± 19.9 |
| | | | DBP | 76.9 ± 11.1 | 74.8 ± 12.9 |
| 12 months | 1.80 ± 1.25#* | 7.53 ± 1.13 | SBP | 134.6 ± 17.6 | 132.8 ± 19.2 |
| | | | DBP | 78.2 ± 11.3 | 80.2 ± 1.27 |
| 18 months | 1.89 ± 1.41#* | 7.12 ± 1.36 | SBP | 136.7 ± 16.5 | 132.0 ± 17.8 |
| | | | DBP | 80.6 ± 11.3 | 82.9 ± 12.5 |
| 24 months | 2.16 ± 1.57#* | 7.25 ± 1.29 | SBP | 133.1 ± 12.6 | 129.6 ± 119.9 |
| | | | DBP | 78.79 ± 12.7 | 76.6 ± 12.4 |
| 30 months | 2.00 ± 1.66#* | 7.60 ± 1.62 | SBP | 133.9 ± 12.6 | 130.5 ± 19.9 |
| | | | DBP | 76.4 ± 12.7 | 77.2 ± 12.5 |
| 36 months | 1.99 ± 1.43#* | 7.41 ± 1.51 | SBP | 135.1 ± 17.7 | 136.8 ± 19.7 |
| | | | DBP | 79.7 ± 11.3 | 76.1 ± 12.6 |

Values are expressed as mean ± SD. SBP, Systolic blood pressure; DBP, diastolic blood pressure.

[a] Patients who were treated with thyroid hormone for subclinical hypothyroidism.

[b] Patients who were not treated with thyroid hormone for subclinical hypothyroidism.

* $P < 0.001$ *vs.* nontreated patients.

# $P < 0.001$ *vs.* baseline.

### Independent predictive value of thyroid hormone replacement therapy on renal outcome

Univariate Cox regression analysis revealed an increase in the risk of halving eGFR and ESRD with DM [hazard ratio (HR), 2.94; 95% CI, 1.58–5.45; $P < 0.01$]. In addition, male gender (HR, 0.40; 95% CI, 0.21–0.40; $P < 0.01$) and thyroid hormone therapy (HR, 0.36; 95% CI, 0.19–0.67; $P < 0.01$) were found to be associated with a lower risk of renal event. The impact of thyroid hormone replacement therapy on renal outcome remained significant even after adjustment for age, sex, DM, eGFR, and serum cholesterol and triglyceride concentrations (HR, 0.28; 95% CI, 0.12–0.68; $P = 0.01$) (Table 5).

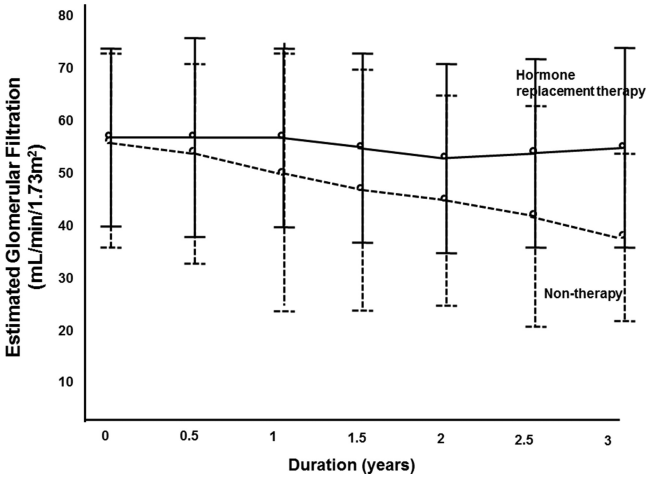


**FIG. 1.** Changes in eGFR over time in subclinical hypothyroidism CKD patients with (*solid line*) and without (*dotted line*) thyroid hormone replacement therapy. Data are presented as means and SD values.

## Discussion

Although some previous studies have demonstrated that restoration of euthyroidism exerts beneficial effects on

**TABLE 3.** Comparison of changes in eGFR over time in patients with and without thyroid hormone replacement therapy

| | Treated patients[a] | Nontreated patients[b] | *P* value |
|---|---|---|---|
| n | 180 | 129 | |
| eGFR (ml/min/1.73 m²) | | | |
| At baseline | 57.8 ± 17.0 | 56.1 ± 19.0 | 0.43 |
| At 6 months | 57.8 ± 19.3 | 52.8 ± 19.6 | 0.21 |
| At 12 months | 57.6 ± 17.0 | 50.3 ± 25.4 | 0.04 |
| At 18 months | 56.5 ± 18.5 | 47.7 ± 23.1 | <0.01 |
| At 24 months | 54.4 ± 18.8 | 45.8 ± 20.1 | <0.01 |
| At 30 months | 55.8 ± 18.9 | 41.9 ± 21.5 | <0.01 |
| At 36 months | 57.8 ± 19.3 | 38.9 ± 16.1 | <0.01 |
| The slope of decline in eGFR (ml/min/yr/1.73 m²) | −2.11 ± 1.12 | −5.93 ± 1.65 | 0.04 |

Values are expressed as mean ± SD. eGFR is calculated by the MDRD-4 equation.

[a] Patients who were treated with thyroid hormone for subclinical hypothyroidism.

[b] Patients who were not treated with thyroid hormone for subclinical hypothyroidism.

**TABLE 4.** Incidence of patients with 50% reduction in eGFR or ESRD according to thyroid hormone replacement therapy

| | Treated patients[a] | | Nontreated patients[b] | | | |
|---|---|---|---|---|---|---|
| | n (%) | Rate (100 patient-yr) | n (%) | Rate (100 patient-yr) | Risk reduction with therapy, % (95% CI)[c] | *P* value |
| Halving of eGFR | 15 (8.3) | 2.75 | 27 (20.9) | 7.96 | 64 (0.19–0.67) | 0.001 |
| ESRD | 2 (1.1) | 0.37 | 8 (6.2) | 2.36 | 85 (0.03–0.71) | 0.006 |

eGFR is calculated by MDRD-4 equation.

[a] Patients who were treated with thyroid hormone for subclinical hypothyroidism.

[b] Patients who were not treated with thyroid hormone for subclinical hypothyroidism.

[c] The reduction in risk associated with thyroid hormone replacement therapy was calculated as (1 − hazard ratio with thyroid hormone treatment) × 100.

cardiac dysfunction in patients with subclinical hypothyroidism (15, 30), whether to treat subclinical hypothyroidism is still an issue of debate (31). In addition, the impact of thyroid hormone therapy on the changes in renal function in CKD patients with subclinical hypothyroidism has never been explored. The results of the present study showed that thyroid hormone replacement for subclinical hypothyroidism preserved renal function in CKD patients. Moreover, thyroid hormone treatment was found to be an independent predictor of renal outcome in these patients.

Accumulating evidence has shown that subclinical hypothyroidism is not a rare disorder in CKD patients. The data of 14,623 adult participants from the third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of the United States population, revealed that the prevalence of hypothyroidism increased with reduced GFR, occurring in 10.9% of patients with stage 2 CKD, 21.0% with stage 3 CKD, and 23.1% with stage 4 or 5 CKD, and that there was an independently higher risk of hypothyroidism in stage 2–5 CKD patients even after adjusting for age, sex, and ethnicity (12). Among these hypothyroidism patients, 56% were considered subclinical (12). Recently, Chonchol *et al.* (14) showed that the prevalence of subclinical hypothyroidism was 17.9% in patients with stage 3–5 CKD, and that it was increased in persons with reduced eGFR independent of age, sex, and fasting plasma glucose, total cholesterol, and triglyceride concentrations. Moreover, there was a graded increase in the likelihood of subclinical hypothyroidism with progressively lower GFR and a significant inverse association between eGFR and TSH levels throughout the normal and high TSH ranges. Conversely, a cross-sectional, population-based study of 29,480 adults without previously known thyroid disease demonstrated that the prevalence of CKD was higher in people with TSH in the middle and highest thirds of the reference range and that CKD was more common in people with subclinical hypothyroidism (32). Furthermore, TSH within the normal range was also negatively associated with eGFR (32). In the present study, we did not determine the prevalence of subclinical hypothyroidism in CKD patients or the prevalence of CKD in patients with subclinical hypothyroidism. However, although the TSH concentrations of our subjects were above the normal range, a significant negative correlation was found between eGFR and TSH levels, which was in accordance with previous studies (32, 33).

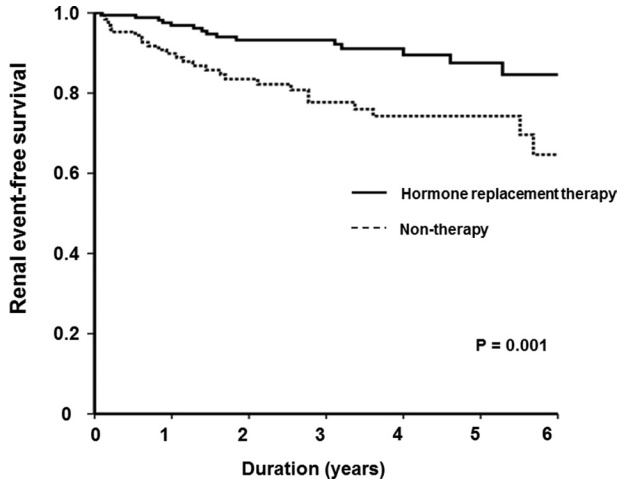


**FIG. 2.** Kaplan-Meier plots for renal event-free survival in subclinical hypothyroidism CKD patients with and without thyroid hormone replacement therapy. Renal events were defined as halving of eGFR or ESRD. The cumulative renal event-free renal survival was significantly higher in patients treated with thyroid hormone.

**TABLE 5.** Multivariate Cox regression analysis for renal outcome

| Covariate | HR (95% CI) | *P* value |
|---|---|---|
| Age | 1.01 (0.98–1.05) | 0.47 |
| Male (*vs.* female) | 0.75 (0.33–1.71) | 0.49 |
| DM | 2.71 (1.16–6.32) | 0.02 |
| Hormone replacement therapy (*vs.* no treatment) | 0.28 (0.12–0.68) | 0.01 |
| eGFR (ml/min/1.73 $m^2$) | 0.98 (0.96–1.00) | 0.10 |
| Serum cholesterol (mg/dl) | 1.00 (0.99–1.01) | 0.67 |
| Serum triglyceride (mg/dl) | 1.00 (1.00–1.01) | 0.35 |

eGFR is calculated by MDRD-4 equation.

Thyroid hormone affects nearly all organ systems in the body. In the kidney, it is involved in renal development and growth, renal hemodynamics, and sodium and water homeostasis (3). GFR is also known to be influenced by thyroid dysfunction (2). Reduction in RPF and GFR, an increase in serum creatinine concentration, and hyponatremia are frequently observed in primary hypothyroidism patients (2, 3), and these renal derangements are nearly normalized by thyroid hormone replacement therapy (17, 21). In addition, one previous case study showed that a progressive deterioration of renal function in a CKD patient with severe hypothyroidism was reversed by L-thyroxine (10). Moreover, thyroid hormone treatment resulted in a rapid improvement of renal function in hypothyroid patients with ischemic nephropathy (18). However, these renal complications are not common in patients with subclinical hypothyroidism. This may be partly explained by the difference in plasma volume between overt hypothyroidism and subclinical hypothyroidism patients. Plasma volume, RPF, and GFR were demonstrated to be significantly decreased in patients with overt primary hypothyroidism, whereas there was no clear abnormality in blood volume in subclinical hypothyroidism patients (21). Based on these findings, it was inferred that the impact of thyroid hormone therapy on the changes in eGFR in our patients was not a result of its effect on plasma volume.

There are several theories as to why thyroid hormone replacement preserved renal function in the subjects of the present study. One possibility is that thyroid hormone might improve cardiac dysfunction associated with subclinical hypothyroidism. Prolonged isovolumic relaxation time, lower early-late ratio of Doppler-derived transmitral peak flow velocities, reduced Doppler-derived mean aortic acceleration, and impaired systolic function with exertion were observed even in subclinical hypothyroid patients (15, 34, 35). In addition, all these abnormalities were normalized by L-thyroxine (30, 34). Therefore, the consequence of thyroid hormone replacement therapy in the present study may be attributed to its beneficial effects on cardiac function; however, this cannot be verified due to the lack of baseline and follow-up echocardiography results in our patients. Another possibility is that endothelial dysfunction associated with subclinical hypothyroidism may be reversed by thyroid hormone replacement. Lekakis *et al.* (36) found that TSH level was inversely correlated with endothelium-dependent dilatation and that flow-mediated dilatation (FMD), a marker of endothelial function, was impaired in patients with subclinical hypothyroidism as well as overt hypothyroidism. A study by Cikim *et al.* (37) also demonstrated that FMD value was significantly lower in the subclinical hypothyroid group relative to the euthyroid group without any differences in biochemical and metabolic parameters, suggesting that subclinical hypothyroidism may have adverse effects on endothelial function independent from other well-known atherosclerotic risk factors. Lastly, thyroid hormone may improve dyslipidemia in subclinical hypothyroidism patients. Several previous studies have shown that serum total and LDL-cholesterol concentrations were significantly higher in patients with subclinical hypothyroidism than in normal patients (8, 38). Moreover, restoration of euthyroidism by L-thyroxine reduced both total and LDL-cholesterol levels, which were more pronounced in patients with higher pretreatment serum cholesterol and TSH concentrations (16, 23). In the present study, we did not examine changes in the levels of serum cholesterol or triglyceride. However, considering the baseline serum cholesterol and triglyceride concentrations and the results of multivariate Cox regression analysis, the effect of thyroid hormone replacement therapy was presumed to be independent of dyslipidemia in the study subjects. To explore the exact mechanism of renal function preservation in subclinical hypothyroidism patients by thyroid hormone therapy, further additional studies with baseline and follow-up echocardiography and/or FMD are needed.

There has been controversy with regard to the management of subclinical hypothyroidism patients. Some studies have found that L-thyroxine improves cardiac dysfunction and dyslipidemia and reduces symptoms of hypothyroidism, including neuropsychiatric symptoms, in patients with subclinical hypothyroidism (24–26, 39), whereas others did not note any beneficial effects (27, 40). We assume that the difference in the definition of subclinical hypothyroidism and the heterogeneous age, sex, and ethnicity of the study subjects may contribute to such conflicting findings. However, in general, accumulating evidence indicates that subclinical hypothyroidism patients with TSH level exceeding 10 $\mu$IU/ml would benefit from L-thyroxine therapy (6). For this reason, we excluded patients with extremely high TSH level in the final analysis of the present study. Patients already on thyroid hormone treatment were also excluded because the most common cause of subclinical thyroid dysfunction was known to be related to L-thyroxine therapy (6). On the other hand, it is clearly recommended to carefully monitor the consequences of thyroid hormone replacement due to a potential risk of overtreatment, resulting in a possibility of inducing or exacerbating angina pectoris or cardiac arrhythmia, especially in elderly patients (31). In our study, therefore, fT4 and TSH concentrations were regularly followed up every 3 months, and the dose of L-thyroxine was appropriately adjusted in all patients.

In the present study, serum cholesterol and triglyceride levels at baseline were significantly higher in the treatment

group compared with the nontreatment group. In addition, not all patients underwent anti-TPO testing, and high titers of anti-TPO were observed only in the treatment group. The evidence is insufficient to recommend either for or against routine measurement of anti-TPO (41). Moreover, previous studies have shown that subclinical hypothyroidism patients with serum TSH level less than 10 mIU/liter are more likely to be treated when they have positive anti-TPO (42). These can partly explain why only 45.3% of subjects in this study underwent anti-TPO testing and why there was no patient with high titers of anti-TPO in the nontreatment group. Furthermore, anti-TPO was positive in only 18.8% (26 of 140) of our CKD patients with subclinical hypothyroidism, in whom the test was performed. The underlying mechanisms of subclinical hypothyroidism besides autoimmunity in patients with CKD are still unclear, but there have been some suggested potential mechanisms linking CKD and subclinical hypothyroidism. Serum iodine level can be elevated due to reduced renal clearance, resulting in prolonged Wolff-Chaikoff effect (12, 43). In addition, decreased peripheral sensitivity to thyroid hormones, chronic metabolic acidosis, and the potential effects of retained solutes, such as organic acids and guanidino compounds, has been inferred to be associated with subclinical hypothyroidism in patients with CKD (44–46). In the current study, however, the causes of subclinical hypothyroidism were not investigated in detail. On the other hand, because the current study was a retrospective medical record-based study, the differences in lipid profiles and autoimmunity are supposed to be attributed to the lack of randomization of patients, but the possibility of selection bias cannot be completely ruled out. Despite this limitation, multivariate Cox regression analysis revealed that thyroid hormone replacement was a significant independent predictor of the renal outcome. Therefore, we believe that this retrospective study provides useful information on the impact of thyroid hormone replacement on the decline of eGFR in CKD patients with subclinical hypothyroidism.

In conclusion, thyroid hormone therapy not only preserved renal function, but also was an independent predictor of renal outcome in CKD patients with subclinical hypothyroidism, suggesting that thyroid hormone replacement should be considered in these patients.

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