Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study

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Abstract

Objective: Low thyroid function may be associated with reduced glomerular filtration rate (GFR). We therefore studied the association of thyroid function with estimated GFR (eGFR) in a population-based study.

Design: A cross-sectional, population-based study of 29,480 individuals above 40 years of age, without previously known thyroid disease.

Methods: We calculated geometric mean eGFR and odds ratio (OR) of chronic kidney disease (CKD; eGFR < 60 ml/min per 1.73 m²) according to categories of thyroid function, using people with TSH in the lower third of the reference range (0.50–1.4 mU/l) as the comparison group.

Results: TSH within the reference range (0.50–3.5 mU/l) was negatively associated with eGFR (P for trend < 0.001). Compared with people with TSH in the lower third of the reference range (83.0 ml/min per 1.73 m²), eGFR was lower in people with TSH in the middle (81.6 ml/min per 1.73 m²) and highest third (80.3 ml/min per 1.73 m²) of the reference range, and in people with subclinical (79.3 ml/min per 1.73 m², P < 0.001) or overt hypothyroidism (76.5 ml/min per 1.73 m², P < 0.001). The prevalence of CKD was higher in people with TSH in the middle (OR 1.20, 95% confidence interval (CI) 1.07–1.35) or highest third (OR 1.31, 95% CI 1.13–1.52) of the reference range, compared with people in the reference group. Also, CKD was more common in people with subclinical (OR 1.63, 95% CI 1.38–1.93) or overt (OR 1.98, 95% CI 1.22–3.20) hypothyroidism.

Conclusions: These findings suggest that low thyroid function, also within the clinically normal range, is associated with reduced GFR.

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Introduction

Overt and subclinical hypothyroidism may be associated with low glomerular filtration rate (GFR) (1–14), possibly caused by reduced renal blood flow, which is a vascular characteristic of hypothyroid patients (2, 5, 6, 13). Low thyroid function within the clinically normal range has also been associated with reduced renal blood flow (15), but it is not known if GFR may vary within the normal range of thyroid function.

We therefore assessed the association of thyroid function with estimated GFR (eGFR) in a Norwegian cross-sectional population study of more than 29,000 participants.

Subjects and methods

Study population

All adults living in Nord-Trøndelag county in Norway were invited to participate in the Nord-Trøndelag Health Study (HUNT) between 1995 and 1997 (16). The population is predominantly (ca 97%) Caucasian (16) and considered to have sufficient iodine intake (17). In total, 92,936 individuals were invited, and 66,140 (71.2%) attended the study. The participants were asked to complete a self-administered questionnaire that included a wide range of health-related topics, including history of thyroid diseases (18).

Serum concentrations of creatinine were measured in all participants, and serum concentrations of TSH were measured in subsamples of the population, including all women older than 40 years of age and a 50% random sample of men older than 40 years of age. In total, TSH was measured in 32,819 individuals from these samples. If the TSH concentration was lower than 0.20 mU/l, free thyroxine (FT₄) and total triiodothyronine (T₃) were also measured, and if TSH concentration was lower than 0.20 mU/l, FT₄ and thyroid peroxidase antibodies were measured.
Among 32,819 individuals with TSH measurements, we excluded individuals with previously known thyroid disease (n=2,831) or with missing information on serum creatinine or smoking habits (n=508), leaving 29,480 individuals for analysis in this study.

**Laboratory measurements**

Immediately after blood sampling, serum was separated by centrifugation and placed in a refrigerator. The laboratory analyses were performed within 4 days of serum sampling.

Serum concentrations of TSH, FT₄ and total T₃ were measured at the Hormone Laboratory, Aker University Hospital, Oslo, using DELFIA hTSH Ultra (sensitivity 0.03 mU/l and total analytical variation <5%), DELFIA FT₄ (total analytical variation <7%) and AutoDELFIA T₃ (total analytical variation <5%) kits respectively all from Wallac Oy, Turku, Finland. Thyroid peroxidase antibodies were measured with a luminoimmunoassay from B.R.A.H.M.S. Diagnostica GmbH (Berlin, Germany). The reference range for TSH in this study was defined as 0.50–3.5 mU/l, based on previously published reference ranges for TSH in this population (18). The laboratory reference ranges were 8–20 pmol/l for FT₄, 1.2–2.7 nmol/l for total T₃ and <200 U/ml for thyroid peroxidase antibodies.

Serum concentrations of creatinine were measured at the Central Laboratory, Levanger Hospital, Nord-Trøndelag, using the Jaffe method, on a Hitachi 911 Autoanalyzer (Hitachi) with reagents from Boehringer Mannheim. The day-to-day coefficient of variation was 3.5%. The creatinine values were recalibrated to the Roche enzymatic method (19). From these recalibrated values, we calculated eGFR using the re-expressed 4-variable Modification Diet in Renal Disease (MDRD) formula (20).

**Statistical analyses**

The participants were placed in seven categories according to thyroid function: biochemically overt hyperthyroid function (defined as TSH <0.20 mU/l combined with FT₄ >20.0 pmol/l and/or total T₃ >2.7 nmol/l); probable subclinical hyperthyroid function (TSH 0.20–0.49 mU/l; or TSH <0.20 mU/l and neither FT₄ nor total T₃ above the reference range); three categories of TSH within the reference range (0.50–1.4, 1.5–2.4 and 2.5–3.5 mU/l); probable subclinical hypothyroid function (TSH 3.6–4.0 mU/l; or TSH >4.0 mU/l and FT₄ ≥ 8.0 pmol/l) and biochemically overt hypothyroid function (TSH >4.0 mU/l and FT₄ <8.0 pmol/l).

Using the general linear model, we calculated geometric mean eGFR (with 95% confidence intervals (CI)) within each of the seven categories of thyroid function and compared the eGFR within each category with that of people with TSH in the lower third of the reference range (0.50–1.4 mU/l). Within the reference range of TSH, we also estimated the mean percentage difference in eGFR per unit difference in TSH and tested whether this association displayed a linear trend, expressed as P value for trend.

In a logistic regression analysis, we calculated odds ratios (OR, with 95% CI) of chronic kidney disease (CKD), as indicated by eGFR <60 ml/min per 1.73 m², for each category of thyroid function, using people with TSH 0.50–1.4 mU/l as the reference group.

In people with TSH >4.0 mU/l, thyroid peroxidase antibodies were measured, and in a separate analysis, we assessed the association with eGFR for those with (>200 U/ml; n=749, median TSH 6.1 mU/l) and without (n=708, median TSH 4.9 mU/l) thyroid peroxidase antibodies, using people with TSH 0.50–1.4 mU/l as the reference group.

The results were adjusted for age, sex and smoking (never, former and current smokers). We also assessed whether the associations differed by sex or age (< or ≥ 70 years of age). In a separate analysis, people with diabetes (indicated by self-report or by non-fasting serum glucose ≥11.1 mmol/l) were excluded, but the results remained essentially unchanged after this exclusion. Also, additional adjustment for body mass index (weight divided by height squared) did not substantially change the estimates. All the statistical analyses were conducted using SPSS statistical software, version 14.0, for Windows (SPSS Inc., Chicago, IL, USA).

The HUNT study is a collaborative effort of the Faculty of Medicine, the Norwegian University of Science and Technology, the Norwegian Institute of Public Health and the Nord-Trøndelag County Council. The study was approved by the regional committee for medical research ethics and by the Norwegian Data Inspectorate, and all participants gave their informed consent.

**Table 1** Characteristics of the participants.

<table>
<thead>
<tr>
<th>Women/men, n (%)</th>
<th>19,711 (66.9)/9,769 (33.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>57 (41–98)</td>
</tr>
<tr>
<td>Thyroid function, n (%)</td>
<td>2024 (6.9)</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>71 (0.2)</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>3894 (2.0)</td>
</tr>
<tr>
<td>TSH 0.50–1.4 mU/l</td>
<td>12,130 (41.1)</td>
</tr>
<tr>
<td>1.5–2.4 mU/l</td>
<td>10,822 (36.7)</td>
</tr>
<tr>
<td>2.5–3.5 mU/l</td>
<td>3667 (12.4)</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>2024 (6.9)</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>172 (0.6)</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²), geometric mean</td>
<td>85.1</td>
</tr>
<tr>
<td>Chronic kidney disease*, n (%)</td>
<td>2024 (6.9)</td>
</tr>
<tr>
<td>Never/former/current smokers, %</td>
<td>45.0/27.3/27.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²), geometric mean</td>
<td>26.5</td>
</tr>
<tr>
<td>Hypertension**, n (%)</td>
<td>16,309 (55.3)</td>
</tr>
<tr>
<td>Diabetes**, n (%)</td>
<td>1311 (4.4)</td>
</tr>
</tbody>
</table>

*eGFR <60 ml/min per 1.73 m².
**Systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or current use of antihypertensive medication.

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Results

Characteristics of the study population are shown in Table 1.

TSH within the reference range (0.50–3.5 mU/l) was negatively associated with eGFR \((P\text{ for trend} < 0.001;\text{ Table 2})\). Thus, 1 mU/l higher TSH was associated with 1.9% (95% CI 1.5–2.3%) lower eGFR, and there was no appreciable difference between women (1.8%, 95% CI 1.3–2.3%) and men (2.1%, 95% CI 1.4–2.8%).

Compared with people with TSH in the lower third of the reference range (0.50–1.4 mU/l; 83.0 ml/min per 1.73 m\(^2\)), mean eGFR was lower in people with subclinical (79.3 ml/min per 1.73 m\(^2\), \(P = 0.001\)) or overt hypothyroidism (76.5 ml/min per 1.73 m\(^2\), \(P < 0.001\)). On the other hand, both subclinical hyperthyroid function (84.6 ml/min per 1.73 m\(^2\), \(P = 0.04\)) and overt hyperthyroidism (104.9 ml/min per 1.73 m\(^2\), \(P < 0.001\)) were associated with higher eGFR, compared with the reference group (Table 2).

Table 3 shows that the prevalence of CKD was higher in people with TSH in the middle (OR 1.20) or highest third (OR 1.31) of the reference range, than in people with TSH in the lower third of the reference range. Also, subclinical (OR 1.63) and overt (OR 1.98) hypothyroidism were associated with higher prevalence of CKD. Hyperthyroidism was, however, not clearly related to the prevalence of CKD in these data.

In a separate analysis, we assessed kidney function among people with hypothyroid function (TSH > 4.0 mU/l) in whom thyroid peroxidase antibodies were measured. Among these people, eGFR was reduced both in those with (79.2 ml/min per 1.73 m\(^2\), \(P < 0.001\)) and without (77.7 ml/min per 1.73 m\(^2\), \(P < 0.001\)) thyroid peroxidase antibodies, compared with the reference group (TSH 0.50–1.4 mU/l, 83.0 ml/min per 1.73 m\(^2\)). Also, hypothyroidism both with (OR 1.55, 95% CI 1.19–2.03) and without (OR 1.71, 95% CI 1.34–2.19) thyroid peroxidase antibodies was associated with higher prevalence of CKD, compared to the reference group.

There were no substantial differences by sex (Tables 2 and 3) or age (Tables 4 and 5) in these data.

Discussion

In this cross-sectional population study, high TSH levels, also within the reference range, were associated with reduced eGFR and higher prevalence of CKD, as indicated by eGFR < 60 ml/min per 1.73 m\(^2\).
Results from previous studies suggest that hypothyroidism, also in its subclinical form (1, 3, 11), may be associated with reduced GFR (1–3, 5, 8–12, 14) and high prevalence of CKD (3, 9, 11). Conversely, hyperthyroidism has been associated with high GFR (12, 14, 21). Our results support these observations and, in addition, suggest that low thyroid function within the clinically normal range is associated with reduced GFR.

It has been observed that GFR may increase following T4 treatment of hypothyroidism (1, 4, 5, 7, 8, 10, 13, 22), and that GFR may be reduced after treatment for hyperthyroidism (4) or after withdrawal of T4 treatment (8). These findings suggest that low thyroid function may cause reduced GFR.

Thyroid function, also within the clinically normal range (15), has been positively associated with effective renal plasma flow (2, 5, 6, 13, 21), which is a measure of renal blood flow. Following T4 treatment of hypothyroidism, increased renal blood flow has been observed (5, 13). Thus, renal blood flow could mediate the association of thyroid function with GFR. High vascular resistance and low cardiac output are vascular consequences of hypothyroidism (23), and these effects may be underlying causes of reduced renal blood flow (2, 5, 6).

On the other hand, it is also possible that renal function may influence the thyroid. Thus, renal dysfunction could lead to elevated serum iodine levels, and observations in patients with end-stage renal disease suggest that iodine restriction may improve hypothyroidism in these patients (6).

It has been suggested that autoimmune thyroid disease may lead to the deposition of immunocomplexes in the renal glomeruli (6). In our data, the association with eGFR was roughly similar for hypothyroidism with and without thyroid peroxidase antibodies. This suggests that immunological damage to the kidney caused by autoimmune thyroid disease is not a likely explanation for the association of high TSH with reduced eGFR that we observed in this study.

As in some other studies, we used creatinine-based estimates of GFR. Studies of overt hyperthyroidism suggest that high thyroid function may cause reduced creatinine production and increased tubular secretion of creatinine (12, 21) and therefore reduced serum levels of creatinine. As a consequence, GFR will be overestimated in these circumstances. However, it is not known if creatinine kinetics is influenced by subclinical thyroid dysfunction or thyroid function within the normal range. Studies that have used inulin or 51Cr-EDTA clearance to estimate GFR (2, 5, 7, 13) have found that hypothyroidism may be associated with reduced GFR, and these methods do not depend on creatinine levels to estimate GFR.

Chronic non-thyroidal illness may lead to alterations in the thyroid function, including low levels of T3. Patients with CKD may frequently have low T3 levels (24), and in patients with end-stage renal disease, low T3 levels may be associated with poorer survival (25). We could not assess the association of eGFR with T3 in our study, since T3 levels were measured only in participants with TSH below 0.20 mU/l.

In conclusion, we found a negative association of TSH levels with eGFR. Our results suggest that low thyroid function, also within the clinically normal range, is...
associated with reduced renal function. However, the association of TSH within the reference range with eGFR was modest, and the clinical relevance of this association is uncertain.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

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Thyroid function and eGFR