Background and objectives: Subclinical primary hypothyroidism is highly prevalent in the general population, especially in the elderly. However, the prevalence of subclinical primary hypothyroidism in persons with chronic kidney disease (CKD) not requiring chronic dialysis is not well defined.

Design, setting, participants, and measurements: Cross-sectional data from 3089 adult outpatients, who were consecutively referred by general practitioners for routine blood testing over the last two years, were analyzed. Glomerular filtration rate (GFR) was estimated by the abbreviated Modification of Diet in Renal Disease equation. Multivariable logistic regression was used to evaluate the independent association between prevalent subclinical primary hypothyroidism and estimated GFR.

Results: Among 3089 adult participants, 293 (9.5%) had subclinical primary hypothyroidism and 277 (9%) had an estimated GFR < 60 ml/min per 1.73 m². The prevalence of subclinical primary hypothyroidism increased from 7% at an estimated GFR ≥ 90 ml/min per 1.73 m² to 17.9% at an estimated GFR < 60 ml/min per 1.73 m² (P < 0.0001 for trend). Compared with participants with an estimated GFR ≥ 60 ml/min per 1.73 m², those with estimated GFR < 60 ml/min per 1.73 m² had an increased odds of subclinical primary hypothyroidism after adjusting for age, gender, fasting plasma glucose, total cholesterol, and triglyceride concentrations.

Conclusions: These findings suggest that subclinical primary hypothyroidism is a relatively common condition (~18%) among persons with CKD not requiring chronic dialysis, and it is independently associated with progressively lower estimated GFR in a large cohort of unselected outpatient adults.

lesterol, and triglyceride concentrations were assayed by enzymatic procedures on Roche/Hitachi Modular System (Roche Diagnostics GmbH, Milan, Italy), according to manufacturer’s specifications and employing proprietary reagents. Serum TSH and FT4 concentrations were quantified by twosite, chemiluminescent, immunometric assays on the IMMULITE-2000 analyzer (Diagnostics Products, Los Angeles, CA). Functional sensitivity for TSH and FT4 was quoted by the manufacturer as 0.004 mIU/L and 0.3 ng/dl, respectively. Reference values in our laboratory were 0.35 to 4.5 mIU/L for TSH and 0.8 to 1.8 ng/dl for FT4 respectively. No serum thyroid peroxidase antibody measurements were available.

Kidney function was calculated by using the formula developed and validated in the Modification of Diet in Renal Disease study. The Modification of Diet in Renal Disease formula was as follows: estimated GFR = 175.0 × (serum creatinine\(^{-1.154}\)) × (age\(^{-0.203}\)) × 1.212 (if black) × 0.742 (if female) (11).

**Statistical Analysis**

Data are expressed as mean ± SD or proportions. Statistical analyses included the unpaired t test (for continuous measures) and the \(\chi^2\) test with Yates’ correction for continuity (for categorical variables). Skewed variables (triglycerides) were logarithmically transformed to improve normality before analysis. The independent relationship between subclinical primary hypothyroidism (as defined as TSH >4.5 mIU/L with FT4 levels within the reference range) and chronic kidney disease (CKD) (categorized as estimated GFR <60 ml/min per 1.73 m\(^2\)) was tested by multivariable logistic regression analysis. All known potential confounders (age, gender, plasma glucose, total cholesterol, and triglycerides) were entered in the multivariable model to ensure giving an unbiased estimate for the relation between subclinical hypothyroidism and CKD. \(P\) values <0.05 were considered to be statistically significant.

**Results**

Details of the study design are summarized in Figure 1. After excluding participants with abnormal serum FT4 concentrations (i.e., those with FT4 <0.8 or >1.8 ng/dl), cumulative results for main demographic variables, and serum TSH, FT4, lipids, creatinine, and glucose concentrations were retrieved for 3089 adults (78.4% female) with a broad spectrum of age (mean age, 54.9 ± 16.2 yr; range, 18 to 94 yr).

In the whole sample, the mean values of estimated GFR, serum TSH, and FT4 concentrations were 83.3 ± 19.5 ml/min per 1.73 m\(^2\) (range, 8 to 195 ml/min per 1.73 m\(^2\)), 2.30 ± 2.79 mIU/L (range, 0.001 to 47.6 mIU/L), and 1.3 ± 0.2 ng/dl (range, 0.8 to 1.8 ng/dl) respectively. Most participants (\(n = 2613, 84.6\%\)) had serum thyroid function test results within the reference range (i.e., TSH values ranging from 0.35 to 4.5 mIU/L with normal FT4 levels), whereas 9.5% (\(n = 293\)) had subclinical biochemical hypothyroidism (i.e., TSH >4.5 mIU/L with normal FT4 levels), and 5.9% (\(n = 183\)) had subclinical biochemical hyperthyroidism (i.e., TSH <0.35 mIU/L with normal FT4 levels). Overall, 277 (9%) subjects had estimated GFR >60 ml/min per 1.73 m\(^2\), 265 of whom had estimated GFR between 30 and 59 ml/min per 1.73 m\(^2\) and 12 subjects had estimated GFR <30 ml/min per 1.73 m\(^2\); none of them required chronic dialytic therapy. Most participants (\(n = 1741, 56.4\%\)) had an estimated GFR of 60 to 89 ml/min per 1.73 m\(^2\), and 34.6% (\(n = 1071\)) had an estimated GFR >90 ml/min per 1.73 m\(^2\).

As shown in Table 1, participants with subclinical primary hypothyroidism were likely to be older and had higher values of fasting plasma glucose, total cholesterol, and triglycerides, and lower estimated GFR levels than their counterparts with no subclinical hypothyroidism. As expected, serum TSH levels were higher and FT4 levels were lower in the hypothyroid group. No significant difference was found in gender distribution between the groups. The prevalence of participants with estimated GFR <60 ml/min per 1.73 m\(^2\) was remarkably greater among those with subclinical hypothyroidism than among those with no hypothyroidism. Almost identical results were observed when participants with low TSH and normal FT4 levels (\(n = 183\)) were excluded from the nonhypothyroid group (data not shown).

Conversely, as shown in Figure 2, the prevalence of subclinical primary hypothyroidism was increased in persons with progressively lower kidney function, ranging from 7% for persons with estimated GFR ≥90 ml/min per 1.73 m\(^2\) to 17.9% in persons with estimated GFR below 60 ml/min per 1.73 m\(^2\).
Notably, when estimated GFR was subdivided into deciles instead of widely accepted diagnostic categories for CKD stages (Figure 3), the prevalence of subclinical primary hypothyroidism was markedly increased among those in the first decile of estimated GFR (mean estimated GFR, 50.4 ± 10 ml/min per 1.73 m²) compared with those in the highest estimated GFR decile (mean estimated GFR, 121 ± 13 ml/min per 1.73 m²), i.e., 17.1% and 4.0% in the lowest versus highest estimated GFR decile, respectively (P < 0.0001 for trend by the χ² test). Similarly, there was a graded significant decrease in mean serum TSH levels across estimated GFR deciles (range, 2.92 to 1.84 mIU/L; P < 0.0001) in the whole population (Figure 3).

In logistic regression analysis (Table 2), the presence of CKD (included as a categorical measure and defined as estimated GFR <60 ml/min per 1.73 m²) was independently associated with prevalent subclinical primary hypothyroidism after adjustment for age, gender, total cholesterol, triglyceride, and glucose concentrations (adjusted odds ratio = 1.73; 95% confidence interval, 1.20 to 2.48; P = 0.003). Of note, older age was also independently associated with prevalent subclinical hypothyroidism, whereas sex, fasting plasma glucose, and lipid levels were not.

The results remained essentially unchanged even when estimated GFR was included as a continuous variable in the above regression model (adjusted odds ratio = 1.19, 95% confidence interval, 1.10 to 1.28 per unit decrease in estimated GFR; P < 0.001) or when the association between estimated GFR and prevalent subclinical hypothyroidism was examined in subgroups stratified by gender and age (<70 versus ≥70 yr; data not shown).

**Discussion**

In this large cohort of unselected adult outpatients, we found an increased prevalence of subclinical primary hypothyroidism in persons with reduced estimated GFR independent of age, gender, fasting plasma glucose, total cholesterol, and triglyceride concentrations. Moreover, with progressively lower estimated GFR, there was a graded increased likelihood of subclin-

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Table 1. Characteristics of participants with and without prevalent subclinical hypothyroidism (n = 3089)

<table>
<thead>
<tr>
<th></th>
<th>Subclinical Hypothyroidism (n = 293)</th>
<th>No Hypothyroidism (n = 2796)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57.9 ± 17.3</td>
<td>53.2 ± 17.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women [N (%)]</td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>228 (77.8%)</td>
<td>2179 (77.9%)</td>
<td></td>
</tr>
<tr>
<td>Free T₄ (ng/dl)</td>
<td>8.19 ± 5.72</td>
<td>1.69 ± 1.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>1.2 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>105 ± 20</td>
<td>92 ± 16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>209 ± 50</td>
<td>189 ± 43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Estimated GFR (ml/min per 1.73 m²)</td>
<td>124 ± 89</td>
<td>108 ± 53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥90</td>
<td>79.7 ± 40.7</td>
<td>86.6 ± 32.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60-89</td>
<td>169 (57.8%)</td>
<td>1572 (56.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30-59</td>
<td>47 (16.0%)</td>
<td>218 (7.8%)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1 (0.3%)</td>
<td>11 (0.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD or number or proportions. Differences between groups are assessed by the unpaired t test (for continuous variables) and the χ² test (for categorical variables). TSH, thyrotropin; T₄, thyroxine; GFR, glomerular filtration rate.

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Figure 2. Prevalence of subclinical primary hypothyroidism by level of estimated GFR (P < 0.0001 for trend by the χ² test).

Figure 3. Prevalence of subclinical primary hypothyroidism (columns) and serum thyrotropin levels (line) by deciles of estimated GFR (P < 0.0001 for both trends). Persons in the lowest decile are those with lower values of estimated GFR.
Table 2. Determinants of subclinical hypothyroidism in the whole population as evaluated by multiple logistic regression analysis (n = 3089)

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Odds Ratio (± 95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yr)</td>
<td>1.16 (1.06-1.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender (male versus female)</td>
<td>0.96 (0.71-1.30)</td>
<td>0.871</td>
</tr>
<tr>
<td>Fasting glucose (per unit increase)</td>
<td>1.08 (0.96-1.18)</td>
<td>0.602</td>
</tr>
<tr>
<td>Triglycerides (per unit increase)</td>
<td>1.14 (0.97-1.24)</td>
<td>0.297</td>
</tr>
<tr>
<td>Total cholesterol (per unit increase)</td>
<td>1.05 (0.98-1.10)</td>
<td>0.549</td>
</tr>
<tr>
<td>Estimated GFR (&lt;60 versus ≥ 60 ml/min per 1.73 m²)</td>
<td>1.73 (1.20-2.48)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CI, confidence interval; GFR, glomerular filtration rate.
with normal FT₄ levels). Third, the availability of extensive and complete data on a wide range of important risk factors, including fasting plasma glucose and lipid levels, allowed us to ensure giving an unbiased estimate for the relation between subclinical primary hypothyroidism and kidney disease. Finally, we included a large sample size and found a strong, graded association between estimated GFR and thyroid function test results, even within the reference intervals.

**Conclusion**

Subclinical primary hypothyroidism is more common in persons with CKD not requiring chronic dialysis compared with those with normal kidney function in a large sample of unselected outpatient adults. Future clinical and experimental studies should explore potential causal mechanisms linking subclinical primary hypothyroidism and CKD. The possible adverse effects of subclinical hypothyroidism on cardiovascular risk associated with CKD are presently unknown. Whether adult patients with CKD should be routinely screened for subclinical primary hypothyroidism requires further investigation.

**Disclosures**

None.

**References**

3. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklin JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ: Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291: 228–238, 2004