

Prevalence of Subclinical Hypothyroidism in Patients with Chronic Kidney Disease

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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.

Clin J Am Soc Nephrol 3: 1296–1300, 2008. doi: 10.2215/CJN.00800208

The concept of subclinical primary hypothyroidism has emerged over the past several decades, as our ability to detect subtle changes in thyroid function tests is progressively improved (1,2). Although it is recognized that patients with subclinical primary hypothyroidism may have subtle symptoms of thyroid dysfunction, the definition is purely a biochemical one, defined as elevated serum thyrotropin (TSH) levels but normal free thyroxine (FT₄) levels (3).

Subclinical primary hypothyroidism has been recognized in several studies to be associated with markers of cardiovascular risk and cardiac impairment (4–7). Even minor deviations from serum TSH normal range might accelerate the development of atherosclerosis and have adverse effects on cardiovascular performance in the general population (4–7). Moreover, subclinical primary hypothyroidism has been identified as a strong predictor of all-cause mortality in chronic dialysis patients and as a risk factor for nephropathy and cardiovascular events in type 2 diabetic patients (8,9). There is, however, limited quantitative

evidence regarding the prevalence of subclinical primary hypothyroidism in large samples of individuals, including large non-U.S. cohorts at different levels of estimated glomerular filtration rate (GFR) (10).

To explore this question, we have performed a cross-sectional analysis using a large database from a Clinical Chemistry Laboratory, with the purpose of estimating the prevalence of subclinical primary hypothyroidism at different levels of kidney function.

Materials and Methods

We performed a cross-sectional analysis on the database of the Laboratory Information System of the Clinical Chemistry Laboratory at the Verona University Hospital to retrieve results of serum creatinine, glucose, lipids, and thyroid function tests, which have been performed on 3233 outpatient adults (≥18 yr of age) consecutively referred by general practitioners for routine blood testing over the last 2 yr (from December 2005 to December 2007). For these analyses, we excluded participants who had abnormal serum FT₄ concentrations ($n = 144$); thus, a sample of 3089 adult participants was included in the final analysis (Figure 1). If a subject had more than one blood test ordered over the 2 yr, only the first result was included in analysis. All participants gave their informed consent. The local ethics committee approved the study protocol.

Venous blood from all outpatients was routinely collected in the morning on fasting subjects, and serum creatinine, glucose, total cho-

Received February 15, 2008. Accepted April 27, 2008.

Published online ahead of print. Publication date available at www.cjasn.org.

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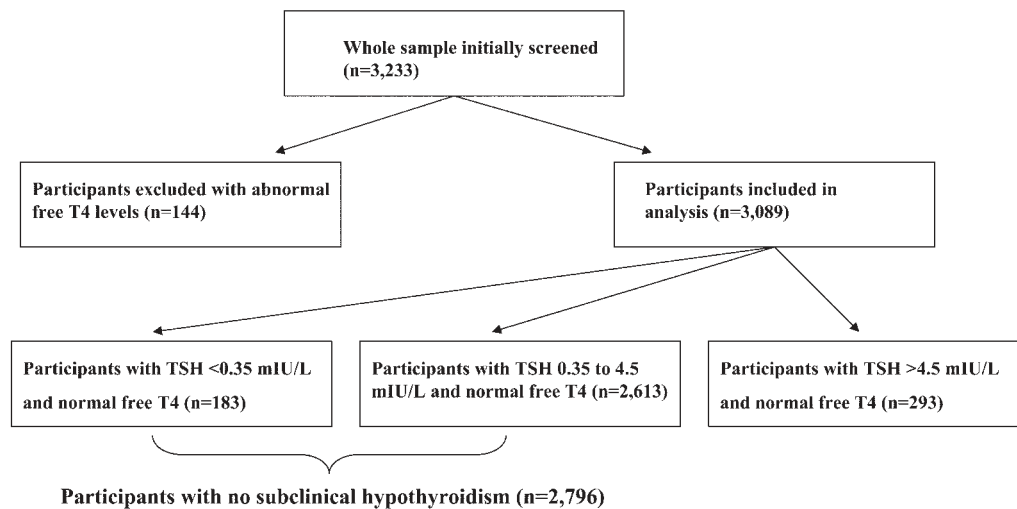


Figure 1. Details of the study design.

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 two-site, 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 χ^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 m²) 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 m² (range, 8 to 195 ml/min per 1.73 m²), 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 m², 265 of whom had estimated GFR between 30 and 59 ml/min per 1.73 m² and 12 subjects had estimated GFR <30 ml/min per 1.73 m²; 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 m², and 34.6% (*n* = 1071) had an estimated GFR >90 ml/min per 1.73 m².

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 m² 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 m² to 17.9% in persons with estimated GFR below 60 ml/min per 1.73 m².

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

	Subclinical Hypothyroidism ($n = 293$)	No Hypothyroidism ($n = 2796$)	<i>P</i>
Age (yr)	57.9 ± 17.3	53.2 ± 17.5	<0.0001
Women [N (%)]	228 (77.8%)	2179 (77.9%)	0.90
TSH (mIU/L)	8.19 ± 5.72	1.69 ± 1.01	<0.0001
Free T ₄ (ng/dl)	1.2 ± 0.2	1.3 ± 0.2	<0.0001
Fasting glucose (mg/dl)	105 ± 20	92 ± 16	<0.0001
Total cholesterol (mg/dl)	209 ± 50	189 ± 43	<0.0001
Triglycerides (mg/dl)	124 ± 89	108 ± 53	<0.0001
Estimated GFR (ml/min per 1.73 m ²)	79.7 ± 40.7	86.6 ± 32.2	<0.001
≥90	76 (25.9%)	995 (35.6%)	<0.0001
60-89	169 (57.8%)	1572 (56.2%)	
30-59	47 (16.0%)	218 (7.8%)	
<30	1 (0.3%)	11 (0.4%)	

Values are mean ± SD or number or proportions. Differences between groups are assessed by the unpaired *t* test (for continuous variables) and the χ^2 test (for categorical variables). TSH, thyrotropin; T₄, thyroxine; GFR, glomerular filtration rate.

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 χ^2 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 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 hypo-

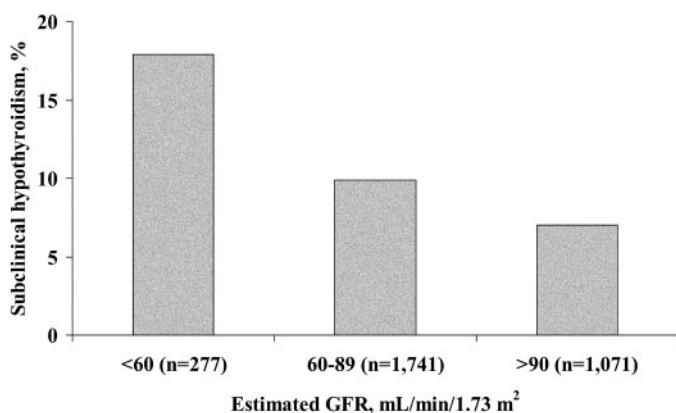


Figure 2. Prevalence of subclinical primary hypothyroidism by level of estimated GFR ($P < 0.0001$ for trend by the χ^2 test).

thyroidism, 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-

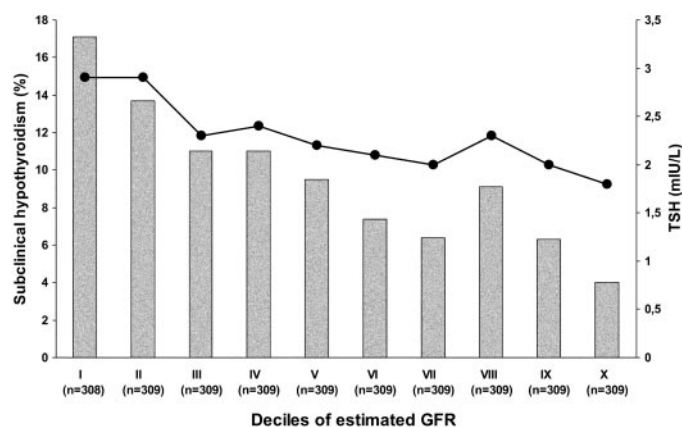


Figure 3. Prevalence of subclinical primary hypothyroidism (columns) and serum thyrotropin levels (line) by deciles of estimated GFR ($P < 0.0001$ for both trends). Persons in the lowest decile are those with lower values of estimated GFR.

Table 2. Determinants of subclinical hypothyroidism in the whole population as evaluated by multiple logistic regression analysis ($n = 3089$)

Independent Variables	Odds Ratio (\pm 95% CI)	P
Age (per 10 yr)	1.16 (1.06-1.23)	0.001
Gender (male <i>versus</i> female)	0.96 (0.71-1.30)	0.871
Fasting glucose (per unit increase)	1.08 (0.96-1.18)	0.602
Triglycerides (per unit increase)	1.14 (0.97-1.24)	0.297
Total cholesterol (per unit increase)	1.05 (0.98-1.10)	0.549
Estimated GFR (<60 <i>versus</i> ≥ 60 ml/min per 1.73 m ²)	1.73 (1.20-2.48)	0.003

CI, confidence interval; GFR, glomerular filtration rate.

ical primary hypothyroidism. Accordingly, there was a significant inverse association between estimated GFR and TSH levels throughout the normal and high TSH ranges.

It has been estimated that the prevalence of subclinical primary hypothyroidism ranges between 4% and 10% in the general population (12–14) and between 7% and 26% in the elderly (15–17). Previous studies have reported a higher prevalence of goiter and/or thyroid hormone abnormalities in persons with end-stage renal disease (18–22). In addition, some of these studies suggest that abnormal thyroid hormone levels (*i.e.*, low plasma free triiodothyronine with normal TSH levels as typically seen in the low T₃ syndrome) in patients requiring chronic dialysis are independent predictors of all-cause and cardiovascular mortality (20–22), likely because of an association with underlying chronic inflammation (19,22). Although numerous contributing factors have been hypothesized, including altered iodine metabolism, decreased peripheral sensitivity to hormones, and autoimmune thyroiditis, the exact underlying mechanisms linking advanced CKD and primary thyroid dysfunction remain unclear. Conversely, in clinically overt primary hypothyroidism (myxedema), the most significant manifestation of changes in renal function is hyponatremia, which results from an impairment in renal diluting capacity leading to water retention (23). Moreover, clinically overt hypothyroidism may also cause renal hemodynamic alterations produced by a decreased cardiac output, which lead to a progressive decline in GFR.

Currently, little is known regarding the epidemiology of thyroid function abnormalities in persons with less severe kidney dysfunction. Lo *et al.* recently noticed that the prevalence of subclinical and clinical primary hypothyroidism increased with progressively lower levels of kidney function in a nationally representative cohort of U.S. adults (10). Among these participants, more than 20% of those with an estimated GFR <60 ml/min per 1.73 m² had clinical or subclinical primary hypothyroidism after controlling for age, gender, and race/ethnicity (10). Their study differed from ours in that their multiethnic U.S. cohort was younger (mean age, 48.7 *versus* 54.9 yr), had a greater prevalence of males, only 56% of hypothyroid cases were considered subclinical, and total T₄ and not FT₄ concentrations were assessed. Thus, our study extends these previous observations by demonstrating a high prevalence of subclinical primary hypothyroidism (~18%) in a large non-U.S. cohort of

persons with CKD not requiring chronic dialysis that is independent of important confounding factors.

Subclinical primary hypothyroidism is most commonly caused by chronic autoimmune thyroiditis, which is typically characterized by a mild asymptomatic goiter with diffuse hypoechogenicity on thyroid ultrasound and by the presence of a high titer of serum thyroid autoantibodies (24). Other less common causes of transient or permanent primary hypothyroidism include drug-induced hypothyroidism, subacute thyroiditis, radiation thyroiditis, and postpartum thyroiditis (25). However, independent of its specific etiology, several studies have shown that subclinical primary hypothyroidism may affect both diastolic and systolic cardiac function, worsen traditional risk factors for cardiovascular disease, including blood pressure, plasma lipid profile, and endothelial function (5–8,26).

This study has several limitations that should be noted. First, because this study is cross-sectional, the present analysis is limited in its ability to establish causal or temporal relationships between subclinical primary hypothyroidism and kidney disease. Second, the definition of kidney function was based on estimated GFR rather than on more precise measurement of kidney function, such as iothalamate clearance. Third, nonthyroidal (*e.g.*, low T₃ syndrome, which is typically seen in some ill patients, including those with end-stage renal disease) and thyroidal (as reported above) causes of subclinical hypothyroidism were not identified. Finally, because our analysis depended on automated databases to establish the presence of subclinical hypothyroidism and kidney disease, it may have led to some misclassification; in particular, we do not have any information on coexisting medical conditions and current use of thyroid medications (thyroid replacement therapy or anti-thyroid drugs). Moreover, thyroid function tests could be requested when there was a (clinical) suspicion of altered thyroid function, thus tending to inflate the magnitude of the estimate of the relation. However, in this study we excluded all patients with low or high FT₄ levels, who are those likely to have clinical symptoms of hypothyroidism or hyperthyroidism, respectively.

Notwithstanding these possible limitations, this analysis has several strengths. First, our clinical laboratory used uniform methods to collect data on serum TSH and FT₄ concentrations. Second, subclinical primary hypothyroidism was diagnosed according to widely accepted diagnostic criteria (*i.e.*, high TSH

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.

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