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Low-Normal Thyroid Function Is Associated With Advanced Fibrosis Among Adults in the United States

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The pathogenetic pathways leading to increasing prevalence of advanced fibrosis in the setting of nonalcoholic fatty liver disease (NAFLD) and resulting in higher rates of liver-related and cardiovascular morbidity and mortality in the United States are multi-factorial.¹ The negative health impact of “low–normal” thyroid function, which is defined as a higher level of thyroid-stimulating hormone (TSH) within the euthyroid reference range, may be comparable with overt and subclinical hypothyroidism.^{2–4} We reported a strong association between biopsy-proven advanced fibrosis in NAFLD with increasing TSH levels in a dose-dependent manner even within the euthyroid reference range.⁵ To generalize our findings across all ethnicities, we examined the association of both low–normal thyroid function and subclinical hypothyroidism with advanced fibrosis in the US general population.

Methods

In the National Health and Nutrition Examination Survey for 2007 to 2012, of the 8779 adult (age, >20 y) participants with available for thyroid function test, subjects with significant alcohol consumption, viral hepatitis, steatogenic medication, or pregnancy, as well as those in whom data were missing on body mass index, serum aminotransferase level, platelet level, and albumin level were excluded (n = 886). Participants who were prescribed thyroid medications (n = 458), such as thyroid hormone or antithyroid drugs, and had overt hypothyroidism or hyperthyroidism (n = 176), were excluded. The final study sample consisted of 7259 adults (mean age, 46.0 y; 50.8% men). Subclinical hypothyroidism was defined as a TSH level higher than 4.5 μ U/L, with a normal free thyroxine (T₄) level.⁶ Low–normal thyroid function was defined as higher TSH level (2.5–4.5 μ U/mL) and/or lower free T₄ level within the euthyroid reference range (TSH, 0.45–4.5 μ U/mL; T₄, 0.6–

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Conflicts of interest

The authors disclose no conflicts.

1.6 ng/dL).⁶ “Strict–normal” thyroid function was defined as 0.45 to 2.5 μ IU/mL for TSH and normal T₄ level. The primary outcome variable was advanced fibrosis, defined as the presence of at least 1 of the high probabilities for advanced fibrosis calculated by using 3 noninvasive fibrosis markers (Table 1). Given the sampling design of the National Health and Nutrition Examination Survey, appropriate sample weights (primary sampling unit, strata, and weighting) were used to reconstitute population level data for the entire United States. The association between low–normal thyroid function or subclinical hypothyroidism and advanced fibrosis was examined by univariate and multivariable logistic regression analyses, using STATA 15.1 (Stata-Corp, College Station, TX).

Results

The prevalence of advanced fibrosis was significantly higher in subjects with low thyroid function (defined as both low–normal thyroid function and subclinical hypothyroidism) than in subjects with strict–normal thyroid function (5.9% vs 2.8%; $P < .001$). Among subjects with low thyroid function, the proportion of advanced fibrosis was comparable between subclinical hypothyroidism and low–normal thyroid function (5.4% vs 6.0%; $P = .759$). In multivariable analyses, which included demographic and metabolic risk factors, low thyroid function showed higher odds of advanced fibrosis. For example, compared with subjects with strict–normal thyroid function, those with low thyroid function were 2.0-fold more likely to have advanced fibrosis (odds ratio [OR], 1.96; 95% CI, 1.18–3.26). When insulin resistance was added to the model among subjects who fasted ($n = 3560$), low thyroid function remained an independent predictor of advanced fibrosis (OR, 2.32; 95% CI, 1.21–4.44). Multivariable analysis showed that low–normal thyroid function and subclinical hypothyroidism were associated significantly with a 1.9-fold increase (OR, 1.94; 95% CI, 1.10–3.44) and a 2.1-fold increase (OR, 2.05; 95% CI, 1.01–4.16) in the risk for advanced fibrosis, respectively (P for trend = .005). In a sensitivity analysis despite inclusion of insulin resistance, the association between the severity of thyroid function and advanced fibrosis remained unchanged (P for trend = .005).

Discussion

The prevalence of advanced fibrosis was significantly higher in subjects with low–normal thyroid function and subclinical hypothyroidism than those with strict–normal thyroid function. Because we excluded major etiologies of chronic liver disease, advanced fibrosis largely may be attributable to NAFLD. These results are consistent with our previous observations in Asian population,⁵ and show their generalizability to the Western world across all ethnicities.

The underlying link for this association remains unknown, but may include obesity, insulin resistance, oxidative stress, and mitochondrial dysfunction.^{3,4,7} In addition, some investigators have hypothesized that the thyroid hormone receptor may activate hepatic stellate cells and hepatic fibrogenesis.⁸ The causal relationship could not be determined owing to study design. Although noninvasive fibrosis markers were broadly validated, advanced fibrosis may be underestimated.

In summary, the spectrum of hypothyroidism even within the normal range is associated with advanced fibrosis in a dose-dependent manner. Targeted therapy to improve thyroid function may provide a novel opportunity to prevent NAFLD-related advanced fibrosis.

Abbreviations used in this paper:

NAFLD	nonalcoholic fatty liver disease
OR	odds ratio
T₄	thyroxine
TSH	thyroid-stimulating hormone

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Table 1.
Univariate and Multivariable Analyses: Risk of Advanced Fibrosis Based on TSH Status

	Weighted prevalence	Univariate		Multivariate model 1		Multivariate model 2		
		% (95% CI)	OR (95% CI)	P value	OR (95% CI)	P Value	OR (95% CI)	P value
TSH								
Strict-normal (0.4–2.5 μ U/L; n = 5681)	2.8 (2.2–3.6)	1		1		1		
Low thyroid function (≥ 2.5 μ U/L; n = 1578)	5.9 (4.4–7.9)	2.21 (1.45–3.36)	<.001	1.96 (1.18–3.26)	.010	2.32 (1.21–4.44)	.012	
TSH								
Strict-normal (0.4–2.5 μ U/L; n = 5681)	2.8 (2.2–3.6)	1	<.001 ^a	1	.005 ^a	1	.005 ^a	
Low-normal (2.5–4.5 μ U/L; n = 1299)	6.0 (4.2–8.6)	2.25 (1.40–3.62)	.001	1.94 (1.10–3.44)	.023	2.13 (1.06–4.29)	.035	
Subclinical (>4.5 μ U/L; n = 279)	5.4 (3.2–9.0)	2.01 (1.11–3.65)	.022	2.05 (1.01–4.16)	.046	3.39 (1.29–8.91)	.015	

NOTE. The multivariate model 1 was adjusted for age, sex, race/ethnicity, education level, marital status, economic status, smoking status, waist circumference, hypertension, diabetes, and total cholesterol. The multivariate model 2 was adjusted for the homeostatic model assessment of insulin resistance index in addition to model 1 in subject with fasting data.

Advanced fibrosis was defined as the presence of at least 1 of the high probabilities for advanced fibrosis calculated by using the following 3 noninvasive fibrosis markers. First, NAFLD fibrosis score = $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{body mass index (kg/m}^2\text{)} + 1.13 \times \text{impaired fasting glycemia or diabetes (yes = 1, no = 0)} + 0.99 \times \text{aspartate aminotransferase/alanine aminotransferase ratio} - 0.013 \times \text{platelet } (\times 10^9/\text{L}) - 0.66 \times \text{albumin (g/dL)}$. Two cut-off points were selected to categorize subjects with NAFLD into 3 groups, including those with a high probability (NAFLD fibrosis score, >0.676), intermediate probability (NAFLD fibrosis score, 0.676 to -1.455), and low probability for advanced fibrosis (NAFLD fibrosis score, <-1.455). Second, the FIB-4 score was calculated by the following published formula: $\text{FIB-4} = (\text{age [years]} \times \text{aspartate aminotransferase [U/L]}) / (\text{platelet } [10^9/\text{L}] \times (\text{alanine aminotransferase [U/L]})^{1/2})$. Similar to the NAFLD fibrosis score, subjects with NAFLD were divided into 3 groups, including those with low (FIB-4, <1.30), intermediate (FIB-4, 1.30–2.67), and high probability for advanced fibrosis (FIB-4, >2.67). Third, the aspartate aminotransferase to platelet ratio index was calculated by the following formula: $([\text{aspartate aminotransferase/upper limit of normal}] / [\text{platelet count } [10^9/\text{L}]] \times 100)$. We used the cut-off values for low and high probability of advanced fibrosis as published, 0.5 and 1.5, respectively.

^aP value for the test of trend of odds.