

Original paper

Association between hypothyroidism and liver fibrosis risk: a systematic review and meta-analysis

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Abstract

Aim of the study: Non-alcoholic fatty liver disease (NAFLD), which encompasses a wide variety of liver pathology, is now the most common chronic liver disease worldwide. The presence of hypothyroidism has been linked to the development of NAFLD. However, its correlation with liver fibrosis, an important clinical entity in NAFLD, is less clear. We aimed to summarize the association between hypothyroidism and liver fibrosis risk.

Material and methods: We conducted a search of PubMed and ProQuest from inception to June 30, 2021, for studies assessing the association between hypothyroidism and liver fibrosis risk. The quality of included studies was evaluated using the Newcastle-Ottawa Scale (NOS). We analyzed the pooled odds ratios (ORs) with 95% confidence intervals (CIs) using a fixed and random-effects model. Heterogeneity was assessed using I^2 .

Results: Eight studies with a total of 14,588 patients were included. The quality of studies ranged from 6 to 8 stars. Thyroid stimulating hormone (TSH) ≥ 2.5 was significantly associated with increased risk of significant liver fibrosis (OR = 1.61, 95% CI = 1.21-2.15). Subclinical hypothyroidism was also correlated with an increased risk of advanced fibrosis (OR = 2.77, 95% CI = 1.65-4.65). A significant association was found between overt hypothyroidism and non-alcoholic steatohepatitis (NASH) risk (OR = 2.38, 95% CI = 1.61-3.53). However, no significant association was found between subclinical hypothyroidism and significant liver fibrosis.

Conclusions: Hypothyroidism is associated with an increased risk of fibrosis in NAFLD patients.

Key words: systematic review, meta-analysis, hypothyroidism, liver fibrosis, metabolic-associated fatty liver disease.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, and by 2030, it is predicted to be the primary cause of liver transplantation. Its rising prevalence is associated with increased metabolic syndrome, obesity, and insulin resistance [1, 2]. NAFLD presents a vast clinical spectrum from simple steatosis without liver fibrosis to cirrhosis caused by non-alcoholic steatohepatitis (NASH) [3]. NAFLD patients have a higher risk of adverse events compared to the general population. However, mortality risk is not the same across the spectrum, with NASH-related cirrhosis posing the greatest risk of mortality [4-6]. Early identi-

fication of a cohort with liver fibrosis is of paramount importance so that early counseling and treatment, as well as a referral to a transplantation center, can be performed. Because of the critical nature of early identification, an ongoing effort to identify other risk factors that may take part in the development of fibrosis is essential.

Thyroid hormone is essential for lipid and glucose metabolism, as well as mitochondrial function in the liver [7]. Hypothyroidism, both overt and subclinical, has been demonstrated to be an independent risk factor for the development of NAFLD [8]. However, its association with liver fibrosis, the more significant clinical entity, is less clear. We aimed to summarize the association between hypothyroidism and liver fibrosis risk.

Table 1. Search strategy

Search	Query	Results
PubMed		
#1	((“Hypothyroidism”[Mesh]) OR (“Thyrotropin”[Mesh])) OR ((“hypothyroid”[All Fields]) OR (“thyroid stimulating hormone”[All Fields])) OR (“tsh”[All Fields]))	77,497
#2	((“Non-alcoholic Fatty Liver Disease”[Mesh]) OR (“nonalcoholic fatty liver disease”[All Fields]) OR (“naflD”[All Fields])) OR (“liver fibrosis”[All Fields])	40,999
#3	#1 AND #2	111
ProQuest		
S1	(SU.exact(“LIVER DISEASES”) AND SU.exact(“FATTY LIVER”))	3,517
S2	Hypothyroidism OR hypothyroid OR thyrotropin	46,778
S3	1 AND 2	105

Material and methods

Study selection

Our meta-analysis adhered to PRISMA guidelines. Two independent investigators conducted a literature search of PubMed and ProQuest from inception to June 30, 2021, restricting the search to studies involving humans and articles published in English. We used medical subject headings and free-text terms for the keywords, as shown in Table 1.

Eligibility criteria

We included studies if they met the following criteria: 1) the study was a cohort, case-control, or cross-sectional study, 2) the study estimated the association between the presence of hypothyroidism and risk of liver fibrosis or NASH, 3) the study reported odds ratios (ORs) with their respective 95% confidence intervals (CIs) or presented raw data. When the study carried out analyses with adjustment for confounding factors, we chose the adjusted over unadjusted OR. The excluded papers were: 1) studies with causes of liver fibrosis other than NAFLD spectrum, 2) short communication, correspondence, letters to the editor, conference abstracts, review, or case reports, 3) desirable data could not be retrieved, 4) full-text articles were not available, 5) non-English articles.

Assessment of bias risk

The risk of bias of included studies was separately assessed by two investigators using the Newcastle-Ottawa Scale (NOS). Studies with an NOS score < 7 were considered to have a high risk of bias, whereas those with a score ≥ 7 were considered to have a low risk of bias.

Data extraction

The same two investigators independently extracted the following data from each study using a prespecified form: author, year, study design, country, sample size, hypothyroidism definition, NAFLD diagnosis criteria, NASH, significant liver fibrosis, advanced liver fibrosis diagnosis criteria, and adjustment used. We contacted authors for additional data or clarification when needed.

Statistical analysis

We estimated the impact of hypothyroidism on the risk of liver fibrosis and NASH through pooled OR with their corresponding 95% CI. Data were pooled based on fixed-effects or random-effects assumptions. *P*-values < 0.05 were considered to be significant. Higgins' *I*² statistic was used to assess heterogeneity. If the value of *I*² was < 50%, the fixed-effect models could be applied. Otherwise, random effects could be used. We planned to assess publication bias through a funnel plot if included studies reached the minimum number of 10. An asymmetric plot could suggest publication bias. All statistical analyses were performed using Review Manager version 5.4 (The Cochrane Collaboration).

Results

After deleting duplicates and reviewing titles and abstracts for eligibility, 203 of the 216 potential records identified by the search approach were excluded. Eight studies were found to be eligible for qualitative and quantitative synthesis after additional full-text inspections for 13 articles (Fig. 1).

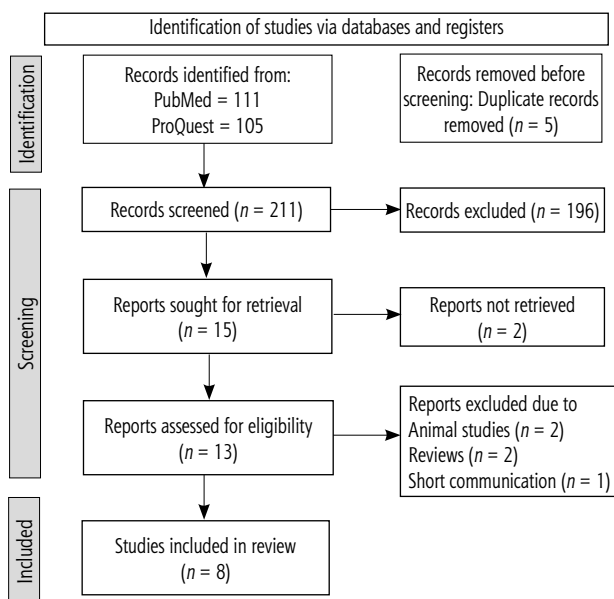


Fig. 1. PRISMA Flow diagram

Study characteristics

The baseline characteristics of the eight studies are summarized in Table 2. The studies involved 14,588 patients, ranging from 103 to 9,419 patients in each study, originating from 7 different countries. Studies were published between 2003 and 2021. Four studies reported the association between overt hypothyroidism and NASH risk. Four studies investigated the impact of subclinical hypothyroidism, defined as an increased level of serum thyroid stimulating hormone (TSH) with normal FT4, and two studies, by Kim *et al.* [9] and Martínez-Escudé *et al.* [10], used a TSH cut-off of ≥ 2.5 , also known as low-normal thyroid function. Low-normal thyroid function was said to be more robust than subclinical hypothyroidism in detecting cardio-metabolic consequences [11, 12]. The diagnosis criteria of NASH, significant liver fibrosis, and advanced liver fibrosis varied across studies, as shown in Table 2.

Quality of included studies

The study quality ranged from 6 to 8, as shown in Table 3. Four studies were found to have a high risk of bias, whereas four were found to have a low risk of bias.

Publication bias

We were not able to conduct publication bias assessment through the funnel plot as the included studies in the subgroup analysis did not reach 10 studies.

Subclinical hypothyroidism and significant liver fibrosis

Studies investigating the association between subclinical hypothyroidism and significant liver fibrosis are limited. Pooled results on the presence of subclinical hypothyroidism and the risk of liver fibrosis are shown in Figure 2. Presence of subclinical hypothyroidism was not significantly associated with significant liver fibrosis (pooled OR = 1.42, 95% CI = 0.81-2.50, $p = 0.22$).

Subclinical hypothyroidism and advanced liver fibrosis

Subclinical hypothyroidism was significantly associated with advanced liver fibrosis, with pooled OR of 2.77, 95% CI = 1.65-4.65, $p < 0.00$. No heterogeneity was present, as shown in Figure 3 ($I^2 = 0\%$, $p = 0.48$).

TSH ≥ 2.5 and significant liver fibrosis

Two studies investigated the association between a TSH cut-off of ≥ 2.5 and significant liver fibrosis in NAFLD patients. A significant association was found between TSH ≥ 2.5 and significant liver fibrosis, shown in Figure 4, with no heterogeneity (OR = 1.61, 95% CI = 1.21-2.15, $I^2 = 0\%$).

Hypothyroidism and NASH

Four studies assessed the relationship between overt hypothyroidism and NASH risk. Overt hypothyroidism was significantly associated with NASH risk with no heterogeneity, as shown in Figure 5 (OR = 2.38, 95% CI = 1.61-3.53, $I^2 = 44\%$).

Discussion

Interpretation

The current research summarized the association between hypothyroidism and liver fibrosis risk from 8 observational studies. From our pooled results, subclinical hypothyroidism was significantly correlated with the development of advanced liver fibrosis in NAFLD patients. There was also a significant association between TSH cut-off of 2.5 and significant liver fibrosis. A significant association between overt hypothyroidism and NASH risk was also reported. However, no significant relationship was found between subclinical hypothyroidism and significant liver fibrosis.

The underlying mechanism has not been fully elucidated. Prior studies have demonstrated various

Table 2. Study characteristics

Author, year, study design, country, sample size	Hypothyroidism definition	NAFLD diagnosis criteria	Outcome	Adjustment used
Liangpunsakul, 2003, case-control, United States, 616	Hypothyroidism was defined as prior prescription of synthetic T4	NS	NASH case was defined as patient attending Hepatology Clinic in Indiana University Hospital with well-documented NASH found in patient database	NA
Mazo, 2011, cross-sectional, Brazil, 103	Hypothyroidism was defined as prior prescription of synthetic T4	NAFLD was diagnosed through liver biopsy	NASH was diagnosed according to NASH activity score	NA
Pagadala, 2012, case-control, United States, 633	Hypothyroidism was defined as presenting a clinical diagnosis of hypothyroidism or prior prescription of synthetic T4	NAFLD was diagnosed through liver biopsy	NASH was diagnosed according to the NASH Clinical Research Network validated histological scoring system	Age, gender, ethnicity, BMI
Parikh, 2015, case-control, India, 800	Hypothyroidism was defined as prior prescription of synthetic T4	NAFLD was diagnosed through liver biopsy	NASH was diagnosed and staged according to Brunt criteria	Age, gender, BMI
Bano, 2016, cohort, Netherlands, 9,419	Subclinical hypothyroidism was defined as serum TSH > 4.0 mIU/l and FT4 levels within the reference range	NAFLD was defined as the presence of fatty liver diagnosed using abdominal US in the absence of secondary causes. When US was not available, FLI measurement was used instead	Significant liver fibrosis was defined as LS \geq 8 kPa, examined using transient elastography Advanced liver fibrosis: NA	Age, sex, cohort, alcohol intake, smoking, follow-up time, use of hypolipidemic drugs, total cholesterol, TG, BMI, HTN, diabetes
Kim, 2017, cross-sectional, South Korea, 425	Subclinical hypothyroidism was defined as serum TSH above 4.5 mIU/l within a normal thyroid hormone level Low-normal thyroid function, defined as TSH \geq 2.5	Ultrasonography-diagnosed fatty liver, shown as increased liver/kidney echogenicity and posterior attenuation Exclusion criteria: significant alcohol consumption, viral hepatitis, and pre-existing chronic liver disease	NASH and liver fibrosis were examined through liver biopsy, assessed according to Brunt and Kleiner criteria Significant liver fibrosis was defined as F2-F4, advanced fibrosis as F3-F4	No adjustment used for significant liver fibrosis Advanced liver fibrosis analysis was adjusted for age, gender, BMI, diabetes, TG, and HOMA-IR
Tahara, 2019, cross-sectional, Japan, 140	Subclinical hypothyroidism was defined as a serum TSH level of > 4 with an FT4 level between 0.90 and 1.80 ng/dl	Fatty liver was observed via ultrasonography when there was increased liver echogenicity ("bright liver") and a contrast between hepatic and renal parenchymal tissues.	Significant liver fibrosis: NA Advanced liver fibrosis was defined as FIB-4 index \geq 2.67	No adjustments used
Martinez-Escude, 2021, cross-sectional, Spain, 2,452	TSH \geq 2.5	NAFLD was diagnosed if the FLI serological marker, which consists of TG, BMI, GGT, and WC, is \geq 60	Significant liver fibrosis was defined as LS \geq 8 kPa, examined using transient elastography Advanced liver fibrosis: NA	Age, sex, alcohol consumption, WC, TG, HDL, BP, glucose

BMI – body mass index, BP – blood pressure, FIB-4 – Fibrosis-4 index, FLI – fatty liver index, FT4 – free T4 hormone, GGT – γ -glutamyl transferase, HDL – high density lipoprotein, HOMA-IR – homeostatic model assessment for insulin, HTN – hypertension, IU – international unit, kPa – kilopascal, LS – liver stiffness, NAFLD – non-alcoholic fatty liver disease, NA – not applicable, TG – triglyceride, TSH – thyroid stimulating hormone, US – ultrasonography, WC – waist circumference

mechanisms underlying the association between hypothyroidism, both subclinical and overt, with NAFLD. Thyroid hormone regulates major metabolic processes, one of which is intrahepatic lipolysis, mediated by lipophagy. Thyroid hormone also promotes lipid droplet entrapment, destruction of the lipid, and accelerated fatty acid oxidation, which will result in reduced steatosis in the liver [13]. In hypothyroid state, a decline

of hepatic lipase activity triggered by reduced triglyceride clearance and hepatic triglyceride deposition can induce NAFLD. *De novo* lipogenesis, as well as a movement of free fatty acids to the liver, can also occur due to insulin resistance associated with hypothyroidism [14-16]. Reports from animal studies have stated that the use of an agonist agent targeting the thyroid receptor in the liver has been shown to re-

Table 3. Quality of included studies

Study	Selection	Comparability	Outcome/Exposure	NOS Score
Liangpunsakul, 2003	3	2	1	6
Mazo, 2011	3		3	6
Pagadala, 2012	1	2	3	6
Parikh, 2015	3	2	3	8
Bano, 2016	3	2	3	8
Kim, 2017	2	1	3	6
Tahara, 2019	3	2	3	8
Martinez-Escude, 2021	3	2	3	8

NOS – Newcastle-Ottawa scale

Study or subgroup	log [odds ratio]	SE	Weight	Odds ratio IV, Random, 95% CI
Bano 2016	0.7608	0.3682	33.2%	2.14 [1.04, 4.40]
Kim 2017	0.1484	0.0966	66.8%	1.16 [0.96, 1.40]
Total (95% CI)			100.0%	1.42 [0.81, 2.50]
Heterogeneity: $\tau^2 = 0.12$, $\chi^2 = 2.59$, $df = 1$ ($p = 0.11$), $I^2 = 61\%$				
Test for overall effect: $Z = 1.22$ ($p = 0.22$)				

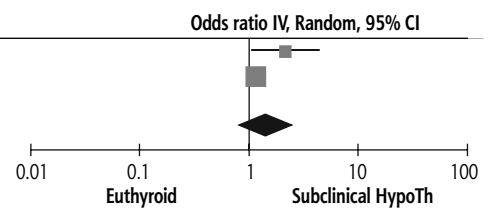


Fig. 2. Forest plot of the association between subclinical hypothyroidism and risk of significant liver fibrosis

Study or subgroup	log [odds ratio]	SE	Weight	Odds ratio IV, Fixed, 95% CI
Kim 2017	0.8755	0.3328	63.3%	2.40 [1.25, 4.61]
Tahara 2019	1.2613	0.4367	36.7%	3.53 [1.50, 8.31]
Total (95% CI)			100.0%	2.77 [1.65, 4.65]
Heterogeneity: $\chi^2 = 0.49$, $df = 1$ ($p = 0.48$), $I^2 = 0\%$				
Test for overall effect: $Z = 3.84$ ($p = 0.0001$)				

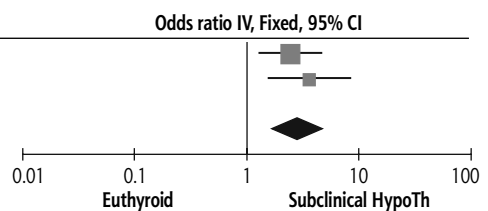


Fig. 3. Forest plot of the association between subclinical hypothyroidism and risk of advanced liver fibrosis

Study or subgroup	log [odds ratio]	SE	Weight	Odds ratio IV, Fixed, 95% CI
Kim 2017	0.4383	0.2185	45.4%	1.55 [1.01, 2.38]
Martinez 2021	0.5128	0.1993	54.6%	1.67 [1.13, 2.47]
Total (95% CI)			100.0%	1.61 [1.21, 2.15]
Heterogeneity: $\chi^2 = 0.06$, $df = 1$ ($p = 0.80$), $I^2 = 0\%$				
Test for overall effect: $Z = 3.25$ ($p = 0.001$)				

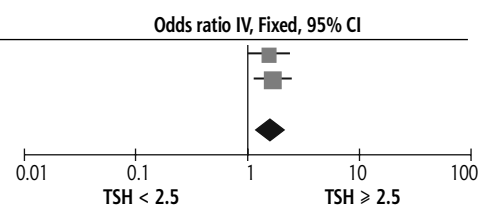


Fig. 4. Forest plot of the association between thyroid stimulating hormone (TSH) ≥ 2.5 and risk of significant liver fibrosis

Study or subgroup	log [odds ratio]	SE	Weight	Odds ratio IV, Fixed, 95% CI
Liagpunsakul 2003	0.8455	0.2827	50.0%	2.33 [1.34, 4.05]
Mazo 2011	0.0431	0.5862	11.6%	1.04 [0.33, 3.29]
Pagadala 2012	0.8183	0.3827	27.3%	2.27 [1.07, 4.80]
Parikh 2015	1.9741	0.6022	11.0%	7.20 [2.21, 23.44]
Total (95% CI)			100.0%	2.38 [1.61, 3.53]
Heterogeneity: $\chi^2 = 5.38$, $df = 3$ ($p = 0.15$), $I^2 = 44\%$				
Test for overall effect: $Z = 4.35$ ($p < 0.0001$)				

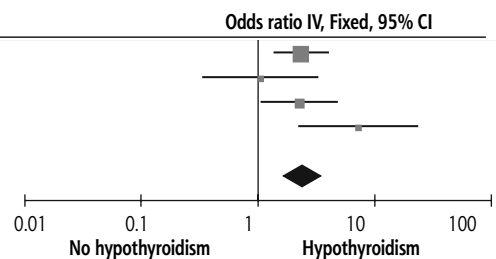


Fig. 5. Forest plot of the association between hypothyroidism and risk of non-alcoholic steatohepatitis (NASH)

duce liver steatosis [17, 18]. Evidence regarding its use in humans, although limited, has been documented. Levothyroxine supplementation was proven to show benefit in a randomized clinical trial of 363 subclinical

hypothyroid patients with dyslipidemia by significantly reducing the steatosis in the liver [19].

However, its association with liver fibrosis, the more important clinical entity, is less clear. Pathophysiologi-

cally speaking, the underlying mechanism may be due to the accumulation of extracellular matrix [20]. Prior research revealed that thyroid hormone might play a regulatory role in the activation of stellate cells in the liver, thus also suggesting its involvement in liver fibrosis signaling [21-24]. Experimental studies on myocardium have also indicated that hypothyroidism can induce upregulation of collagen type 1 gene expression, causing subsequent fibrosis [25-27]. Administration of thyroid hormone promotes metalloproteinase activity, leading to more collagen degradation [28]. This suggests a potential effect of thyroid hormone as NAFLD and fibrosis treatment. Some studies have started to report drugs under development targeting thyroid hormone receptors in the liver as potential nonalcoholic steatohepatitis (NASH) treatment [29, 30]. Another mechanism may also be explained by hepatocellular damage induced by thyroid dysfunction-related oxidative stress. A low thyroid hormone level may disrupt existing adipokines in circulation, such as tumor necrosis alpha, adiponectin, and leptin, causing subsequent hepatic inflammation and liver fibrosis [16, 31, 32]. Additionally, autoimmune-related hypothyroidism is also hypothesized to mediate the association between hypothyroidism and liver fibrosis. Several investigations have revealed that patients with Hashimoto's thyroiditis were more likely to have fibrosis compared to euthyroid [33, 34].

Our meta-analysis presented a significant association between hypothyroidism and liver fibrosis risk despite variation of diagnostic methods. A novel cut-off of TSH ≥ 2.5 , also known as low-normal thyroid function, has been rigorously studied previously, as it better reflects various health problems compared to the traditional cut-off, such as insulin resistance, prediabetes, dyslipidemia, atherosclerotic disease, chronic kidney disease, worse outcome in heart failure patients, and other common cardiometabolic disorders in several population studies [12, 35-37]. However, to date, only three studies have investigated the association between low-normal thyroid function and NAFLD, as well as liver fibrosis risk [9, 10, 38].

Strengths and limitations

This is an updated meta-analysis of the association between hypothyroidism and the risk of liver fibrosis in NAFLD patients. Although having a similar result to a prior meta-analysis [39], our study also presents summarized novel evidence regarding the cut-off of thyroid function which better reflects cardiometabolic disorders. Low-normal thyroid function is reported to be associated with a modest increase of plasma

total cholesterol, LDL cholesterol and triglycerides, thus conveying a pro-atherogenic process which contributes to advanced oxidative stress, which is a huge contributor to liver fibrosis in NAFLD patients. Thus, screening, which then leads to the early treatment of subclinical hypothyroidism, might be of clinical benefit in reducing the risk of liver fibrosis in NAFLD patients [11, 12].

However, our meta-analysis has some limitations. First, the number of powered studies was limited. Second, the methods of NAFLD and fibrosis diagnosis varied and could have contributed to the bias. Significant liver fibrosis in included studies was assessed variously through different methods, through liver stiffness measurement using transient elastography with a cut-off of ≥ 8 kPa and liver biopsy according to Brunt and Kleiner criteria. Advanced liver fibrosis was also estimated by a surrogate marker (FIB-4 index) in 1 study and liver biopsy in another one. Third, because the nature of the studies were all observational, potential cause and effect relationships could not be determined for certain. These data still need to be confirmed with further prospective interventional studies, incorporating thyroid hormone replacement.

Conclusions

Hypothyroidism is associated with an increased risk of significant liver fibrosis and advanced fibrosis in NAFLD patients.

Disclosure

The authors declare no conflict of interest.

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