Non-alcoholic fatty liver disease and thyroid function in adult patients

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Received: 06 May 2018
Accepted: 25 May 2018

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ABSTRACT

Results from published studies on the association between non-alcoholic fatty liver disease and hypothyroidism are still controversial. Thyroid dysfunction is closely related with components of metabolic syndrome. We conducted this meta-analysis using a comprehensive search of EMBASE, MEDLINE, PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials till 31 January 2018 for prospective observational studies that evaluated the relationship of non-alcoholic fatty liver disease and thyroid function in adult patients. Thirteen studies were included in the present meta-analysis. Meta-analysis of the 13 studies found a high correlation between hypothyroidism and NAFLD (OR=1.48, 95% CI 1.22–1.91, p<0.001). In the meta-regression analyses, we found that study design was a possible source of heterogeneity (p=0.17), but other covariates were not. The present meta-analysis provides strong epidemiological evidence for the relationship between hypothyroidism and NAFLD. Both individuals with subclinical and overt hypothyroidism are at higher risk for NAFLD than euthyroid subjects.

Keywords: Meta-analysis, Non-alcoholic fatty liver disease, Hypothyroidism, Subclinical hypothyroidism

INTRODUCTION

The frequency of non-alcoholic fatty liver disease (NAFLD) has increased significantly throughout the past periods, and it has become the prominent reason of liver disease worldwide with a global prevalence of 25%, which can be moderately recognized to the rising prevalence of obesity.1,2 The term NAFLD at the histological level includes a spectrum of liver damage containing in its common form, or simple steatosis, in addition to nonalcoholic steatohepatitis (NASH), a theoretically progressive form of NAFLD defined by the occurrence steatosis along with hepatocyte ballooning, inflammation and variable degrees of fibrosis. Notably, the occurrence of obesity at least doubles the prevalence of NASH and its progression to cirrhosis, liver failure and hepatocellular carcinoma.3 NAFLD can be categorized into two main histological categories, to be exact nonalcoholic fatty liver and nonalcoholic steatohepatitis, which is the progressive subtype of NAFLD and can further induce liver cirrhosis and hepatocellular carcinoma.4
An expanding number of illnesses have been accounted for to be connected to NAFLD, for example, cancer, cardiovascular ailment, type 2 diabetes, and chronic kidney ailment.\(^5,6\) The treatment and prevention of NAFLD have turned into the focal point of medicinal research as of late, and distinguishing the hazard factors for NAFLD is basic to create viable preventive intercessions against NAFLD. Metabolic disorders, for example, hyperlipidemia, hypertension diabetes, central obesity, and gallstones are known risk factors for NAFLD.\(^6\) Thyroid hormones control all metabolic paths, acting on carbohydrates, protein and lipid metabolism. Low thyroid hormone levels are related with hypometabolism categorized by decreased weight gain, resting energy expenditure, reduced lipolysis, increased cholesterol levels, and reduced gluconeogenesis.\(^9\) Thyroid hormones similarly have a role in hepatic lipid metabolism and hepatic insulin resistance.\(^10\)

The relationship amongst hypothyroidism and NAFLD risk stays in debate up to now. Therefore, the present meta-analysis is to validate the association amongst hypothyroidism and NAFLD.

**METHODS**

**Data sources and searches**

We conducted this meta-analysis using a comprehensive search of EMBASE, MEDLINE, PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials till 31 January 2018 for prospective observational studies that evaluated the relationship of Nonalcoholic fatty liver disease and thyroid function in adult patients. Both semiparametric and parametric methods were used. No language restrictions were imposed. We followed the standard guidelines for conducting and reporting meta-analyses of observational studies.\(^11\)

**Selection criteria**

Studies were included in this meta-analysis if they satisfied the following criteria: cohort, cross-sectional, or case–control studies which investigated the association between hypothyroidism and NAFLD in adult participants, and the investigators reported relative risks (RRs) with 95% CI, the diagnosis of hypothyroidism must be based on biochemical tests including TSH levels and T4/FT4 levels. Included NAFLD patients must be diagnosed with an ultrasound examination or Liver biopsy to make a clear definite diagnosis.

**Data extraction**

The final data were abstracted from each study using standardized form: the first author’s name, year of publication, study design, study location, number of participants, participant baseline characteristics (age and gender), method used to identify and verify NAFLD as well as thyroid function, definition of hypothyroidism including overt hypothyroidism or subclinical hypothyroidism. Flow diagram showing the selection criteria of assessed studies.\(^12\)

**Statistical analysis**

The present meta-analysis utilized Stata version 12.0 software for statistical analysis. Mean difference (MD) were calculated for continuous variables. Pooled odds ratios (OR) were calculated for discrete variables. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified using the I\(^2\) inconsistency test with a significance set at the P-value <0.10 or I\(^2\) score >50%.\(^13\) DerSimonian-Laird random-effect meta-analysis was adopted when obvious heterogeneity existed.\(^14\)

**RESULTS**

We recognized 988 citations using the search strategy. Of these, we excluded 365 after examining the title and abstract including removal of duplicates. We retrieved and evaluated 31 articles in more detail, of which 18 articles were excluded, leaving 13 studies that were eligible for inclusion (Figure 1).\(^15-27\) Main characteristics of included studies have been summarized in Table 1 and 2.

![Flow diagram showing the selection criteria of assessed studies.](image-url)
Table 1: Characteristics of included studies.

| Study          | Year  | Country         | Mean age, years ±SD | Study design         |
|----------------|-------|-----------------|---------------------|----------------------|
| Moustafa       | 2009  | Egypt           | 55±4.6              | Case–control         |
| Gokmen         | 2016  | Turkey          | 49.9±12.5           | Cross-sectional      |
| Bano           | 2016  | Netherlands     | 64.7±9.2            | Cohort               |
| Ludwig         | 2015  | Germany         | 41.3±12.6           | Cross-sectional      |
| Liu            | 2015  | China           | 45.4±10.3           | Cross-sectional      |
| Pagadala       | 2012  | US              | 50.4±10.4           | Case–control         |
| Ittermann      | 2013  | Germany         | 50.5±16.6           | Cross-sectional      |
| Xu             | 2011  | China           | 71.7±4.1            | Cross-sectional      |
| Chung          | 2012  | Korea           | 48.6±11.8           | Cross-sectional      |
| Esrghian       | 2013  | Iran            | 48.2±12.8           | Cross-sectional      |
| Liu            | 2014  | China           | 56.99 ± 7.98        | Cross-sectional      |
| Posadas-Romero | 2014  | Mexico          | 51.9±8.1            | Cross-sectional      |
| Parikh         | 2015  | India           | 44.3±3.2            | Case–control         |

Table 2: Definition of hypothyroidism and diagnosis of NAFLD.

| Study          | Definition of hypothyroidism | Diagnosis of NAFLD | Adjusted factors                                           |
|----------------|------------------------------|--------------------|-----------------------------------------------------------|
| Moustafa       | N/A                          | Ultrasound         | Age, gender                                               |
| Gokmen         | TSH >4.1 mIU/L               | Ultrasound         | Age, gender                                               |
| Bano           | TSH >3.0 mIU/L and FT4 levels <0.85 ng/dl | Ultrasound | Age, sex, cohort, follow-up time, use of hypolipidemic drugs and cardiovascular |
| Ludwig         | TSH >34 IU/mL Total T4 12.8–20.4 pmol/L Total T3 3.9–6.7 pmol/L | Ultrasound | Age, gender, BMI                                           |
| Liu            | TSH >4.78 mIU/L FT3 3.5–6.5 pmol/L FT4 11.5–22.7 pmol/L | Ultrasound | Age, gender, smoking, HTN, BMI, FBG, TG, TC, LDL, HDL, blood urea nitrogen, Cr, uric acid |
| Pagadala       | Overt hypothyroidism         | Histological       | Gender, ethnicity, diabetes, HTN, hyperlipidemia, and hypothyroidism and mean (SD) |
| Ittermann      | TSH >3 mIU/L FT4 7.7–23.2 pmol/L | Ultrasound | Age, physical activity, WC, alcohol use, food intake pattern |
| Xu             | TSH >4.5 mIU/L FT4           | Ultrasound         | Waist circumference, systolic blood pressure, diastolic blood pressure, triglyceride, HDL cholesterol, and fasting plasma glucose |
| Chung          | TSH >4.1 mIU/L and FT4 0.7–1.8 ng/dL | Ultrasound | Age, gender, BMI, triglyceride, hyperlipidemia, hypertension, DM |
| Esrghian       | TSH >5.2 mIU/L FT4 <11.5 pmol/L | Ultrasound | HTN, DM, HLD, ischemic heart disease                      |
| Wang           | TSH >4.2 μU/mL, FT4: 12–22   | Ultrasound         | Age, gender                                               |
| Posadas-Romero | TSH >4.5 mIU/L               | Enzymatic procedures | Age, gender                                               |
| Parikh         | TSH >10 IU/mL                | Ultrasound         | Age, gender, alcohol use, and serum triglycerides         |

As we performed sensitivity analysis, statistically similar results were obtained after sequentially excluding each study at a time in all meta-analyses for FT3, FT4, and TSH, suggesting the results were robust. For assessing the studies for the MD of FT3 and FT4, publication biases are present as there are more studies that favor negative results (decreased FT3 and FT4 in NAFLD compared with controls) but the Egger regression tests showed nonsignificant publication bias (p=0.65 and p=0.78, respectively). For assessing the MD of TSH, the plot excludes bias with the nonsignificant Egger test (p=0.94).
Table 3: The relationship between hypothyroidism and NAFLD.

| Study            | OR   | 95% CI       |
|------------------|------|--------------|
| Moustafa         | 0.35 | (0.24–0.94)  |
| Gokmen           | 1.01 | (0.51–2.32)  |
| Bano             | 1.24 | (1.01–1.53)  |
| Ludwig           | 1.12 | (0.65–2.17)  |
| Liu              | 0.28 | (0.25–0.33)  |
| Pagadala         | 2.10 | (1.10–3.90)  |
| Ittermann        | 2.09 | (1.22–3.60)  |
| Xu               | 2.21 | (1.42–3.44)  |
| Chung            | 1.38 | (1.17–1.62)  |
| Eshraghian       | 1.01 | (0.55–1.86)  |
| Wang             | 1.23 | (0.87–1.73)  |
| Posadas-Romero   | 0.83 | (0.55–1.25)  |
| Parikh           | 14.94| (3.55–62.60) |

Table 4: Summary of the association between hypothyroidism and NAFLD.

| Outcomes                    | Pooled estimates | Heterogeneity |
|-----------------------------|-------------------|---------------|
|                             | OR (95% CI)       | P value       | I² (%)       | P value   |
| Overt hypothyroidism        |                   |               |              |           |
| Total studies               | 1.65 (1.19–2.42)  | <0.002        | 35.7         | 0.17      |
| Studies with adjustment     | 1.78 (1.28–2.41)  | <0.001        | 37.8         | 0.19      |
| Subclinical hypothyroidism  |                   |               |              |           |
| Total studies               | 1.38 (1.08–1.68)  | <0.006        | 0.69         | <0.001    |
| Studies with adjustment     | 1.59 (1.21–2.19)  | <0.002        | 79.5         | <0.001    |
| Hypothyroidism              |                   |               |              |           |
| Total studies               | 1.48 (1.18–1.79)  | <0.001        | 74.8         | <0.001    |
| Studies with adjustment     | 1.65 (1.41–2.18)  | <0.001        | 78.8         | <0.001    |

DISCUSSION

Though earlier investigations suggest that hypothyroidism may assume a critical part in the pathogenesis of NAFLD, some observational examinations neglect to locate an obvious relationship between hypothyroidism and NAFLD. Nevertheless, based on the outcomes of the current study, hypothyroidism assumes a critical part in the pathogenesis of NAFLD. The meta-analysis recommends epidemiological indication for the noticeable association between hypothyroidism and NAFLD, and the influence of hypothyroidism is independent from other recognized risk features for NAFLD. In addition, both subclinical hypothyroidism and overt hypothyroidism are autonomously linked to NAFLD. Our outcomes exhibit that either overt hypothyroidism or subclinical hypothyroidism freely builds the risk of NAFLD. A few examinations have established the framework for the discoveries of the investigation by giving some conceivable clarifications to the molecular mechanism underlying the connection amongst hypothyroidism and NAFLD. There are a few conceivable systems which can clarify the connection amongst hypothyroidism and NAFLD. Evident relations amongst hypothyroidism and metabolic changes have been accounted for, which incorporate IR, dyslipidemia and weight and they have imperative parts in the advancement of NAFLD.28

Even though hypothyroidism is allied with mechanisms of metabolic syndrome and NAFLD is reflected as the hepatic manifestation of metabolic syndrome, while there are numerous reasonable mechanisms that could clarify this conceivable relation, the present study, which included all published observational studies, found a strong epidemiological evidence association between NAFLD and hypothyroidism. Leptin is considered as one of the explanations of this association because it is found to be increased in patients with hypothyroidism and it is also found to be higher in NAFLD as it can promote hepatic insulin resistance and be involved in hepatic fibrogenesis.29 Both IR and obesity are dynamic factors in the development of NAFLD, which are similarly mutual in hypothyroidism patients compared to those general populations. IR can increase liver injury in NAFLD. Besides, Demir et al. found that hypothyroidism can cause NAFLD in rat models, and pointed out that obesity is one of the key factors in the association between hypothyroidism and NAFLD.30

As per the outcomes of the current study, we found a conspicuous occurrence that the relationship between...
overt hypothyroidism and NAFLD was more noteworthy than that between subclinical hypothyroidism and NAFLD. As stated above, overt hypothyroidism is characterized as having a considerably higher TSH level and lower T4 and T3 levels contrasted with subclinical hypothyroidism. The more huge relationship between overt hypothyroidism and NAFLD might be clarified by the synergistic impacts of higher TSH level and lower thyroid hormones in the pathogenesis of NAFLD, on the grounds that TSH itself may incite hepatocyte steatosis by means of TSH receptor flag.11

**CONCLUSION**

The present meta-analysis our meta-analysis provides strong epidemiological evidence for the significant relationship between hypothyroidism and NAFLD. Both individuals with subclinical hypothyroidism and overt hypothyroidism are at a higher risk for the development of NAFLD than those with normal thyroid function. To confirm these results, further studies should be made to make a better understanding to further strengthen the relationship between NAFLD and hypothyroidism. Large-scale and long-term randomized controlled trials in various populations must be carried out in future studies to deliver more significant evidence.

**Funding:** No funding sources

**Conflict of interest:** None declared

**Ethical approval:** Not required

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Cite this article as: Alhussainy F, Alharbi R, Alali A, Almutairi M, Aljawi M, Almodhaibri Y. Non-alcoholic fatty liver disease and thyroid function in adult patients. Int J Community Med Public Health 2018;5:2616-21.