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Hypothyroidism Relationship with Non-Alcoholic Fatty Liver Disease: A Meta-Analysis

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ABSTRACT

Thyroid hormones play an important role in the regulation of body weight, lipid metabolism and insulin resistance. Therefore, it is predictable that thyroid hormones may play an important role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). In this study, we reviewed the all current research articles and literatures on the association between hypothyroidism (thyroid dysfunction) and NAFLD/NASH. In this study, we conducted a meta-analysis using a comprehensive search of PubMed, MEDLINE, EMBASE, Scopus, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trails till April 2019 for evaluating the relationship between hypothyroidism (thyroid dysfunction) and non-alcoholic fatty liver disease. Sixteen studies were included in the present meta-analysis. The present meta-analysis provides strong epidemiological evidence for the relationship between hypothyroidism and NAFLD. Both individuals with sub-clinical hypothyroidism and overt hypothyroidism are at higher risk for NAFLD than euthyroid subjects.

Keywords: Hypothyroidism, Meta-analysis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis.

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INTRODUCTION

Endocrine hormones are generally involved in the regulation of body fat, cell metabolism and regulation of energy in the human body. Thereby, they play an important role in the development of metabolic abnormalities. The thyroid hormone significantly involved in energy homeostasis, lipid and carbohydrate metabolism, regulation of body weight and adipogenesis [1,2].

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in worldwide. NAFLD is the most common cause of abnormal liver function [3]. The growing pattern of NAFLD is generally attributed to a global increase in the prevalence of obesity and other metabolic disorders, such as type II diabetes mellitus, impaired glucose tolerance and central obesity. These are the risk factors for NAFLD [4-7]. NAFLD can be categorized into two main categories, non-alcoholic fatty liver and no-alcoholic steatohepatitis (NASH), which is the progressive subtype of NAFLD and can further induce liver cirrhosis and hepatocellular carcinoma [8].

In a clinical background, subclinical hypothyroidism has been associated with metabolic disorder, cardiovascular mortality and disturbance of lipid metabolism [9,10]. In recent years, growing body of evidence has lead to speculation on the relationship between hypothyroidism and NAFLD/NASH.

ELIGIBLE CRITERIA OF THE STUDIES

All studies were reviewed and carefully appraised for inclusion in this review. All descriptive or analytical cross-sectional studies, case-control studies, and clinical trials with proper methods for assessment of NAFLD and NASH and that evaluated thyroid function were included. Additionally, only studies that used either ultrasonography or liver biopsy for the assessment of NAFLD were included. Studies on patients with liver disease other than NAFLD/NASH or on NAFLD/NASH in the context of other liver diseases *i.e.*, chronic viral hepatitis, liver cirrhosis, acute liver failure, hepatocellular carcinoma or drug-induced hepatitis were excluded.

DATA EXTRACTION

Initial screening procedure involved the extraction of finally selected 16 articles out of 236 randomly found articles through electronic search database (Figure 1). A comprehensive search resulted to found articles from PubMed, MEDLINE, EMBASE, Scopus, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trails.

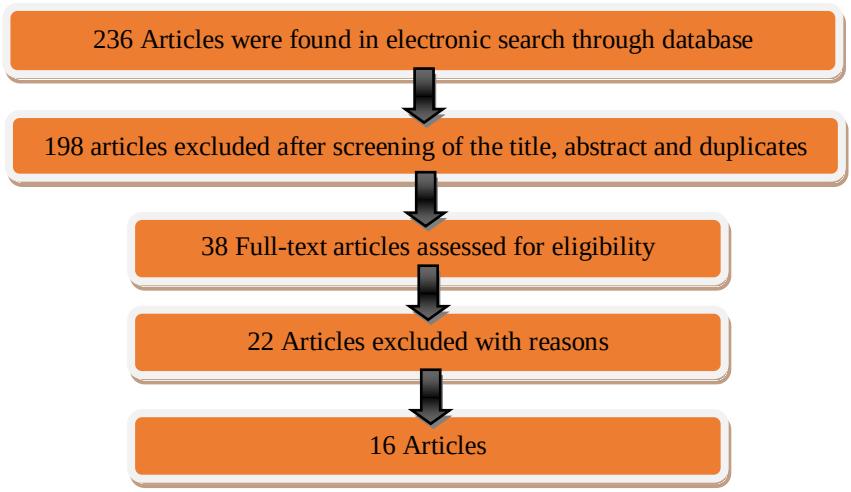

Figure 1: Screening procedure for extraction of articles

The data from relevant articles were analyzed to get the following information i.e. first author's name, site of the study, year of publication, study design, sample of the study (number of the participants), subclinical & overt hypothyroidism status and method used to identify and verify NAFLD. Relevant data from articles reporting thyroid hormone abnormalities and NAFLD/NASH were outlined in a Table-1.

Table-1: Characteristics of studies on the relationship between hypothyroidism and NAFLD.

AUTHERS	COUNTRY	YEAR	STUDY DESIGN	STUDY SAMPLE (MEAN AGE; FEMALE, %)	STATUS OF HYPOTHYROIDISM	SOURCE OF NAFLD DIAGNOSIS
Kaltenbach et al.[11]	Germany	2016	Cross-sectional	332 individuals including 99 NAFLD patients (14.1 ± 1.9; 33.3%) and 233 control subjects (13.9 ± 1.8; 58.8%)	Subclinical hypothyroidism (TSH > 4 µU/mL, normal FT4)	Ultrasound
Bano A et al.[12]	Netherland	2016	Cohort	9,419 individuals (64.7 years; 56.5%)	Subclinical hypothyroidism Serum TSH > 4.0 mIU/L and normal FT4. Overt hypothyroidism was defined as serum TSH > 4.0 mIU/L and FT4 levels < 0.85 ng/dl	Ultrasound
Gokmen FY et al.[13]	Turkey	2015	Cross-sectional	115 individuals including 69 NAFLD patients and 46 controls (49.9±12.5 years; 72.2%)	TSH >4.1mIU/L	Ultrasound
Lee KW et al.[14]	Korea	2015	Cohort	18,544 individuals including 2,348 NAFLD patients and 16,196 controls (39.2±5.9; 53.3%)	Subclinical hypothyroidism (TSH > 4.2 mIU/L, normal FT4); overt hypothyroidism (TSH > 4.2 mIU/L, FT4 < 10.97 ng/dL)	Ultrasound
Liu G et al.[15]	China	2015	Cross-sectional	2,576 euthyroid subjects (45.4±10.3 years)	TSH >4.78 mIU/L FT3 3.5–6.5 pmol/L FT4 11.5–22.7 pmol/L	Ultrasound
Ludwig U et al.[16]	Germany	2015	Cross-sectional	1,276 individual including 349 NAFLD and 927 controls	TSH >34 IU/mL, Total T4 12.8-20.4 pmol/L, Total	Ultrasound

				(40.7±12.7 years; 47.2%)	T3 3.9-6.7 pmol/L	
Parikh P et al.[17]	Western India	2015	Case–control	800 individuals including 500 NAFLD patients (44.3 ± 3.2; 64.6%) and 300 controls (41.6 ± 3.89; 66%)	Subclinical hypothyroidism (TSH > 5.5 IU/mL but <10 IU/mL) and overt hypothyroidism (TSH > 10 IU/mL)	Ultrasound
Posadas-Romero et al.[18]	Mexico	2014	Cross-sectional	753 individuals including 133 NAFLD cases and 620 controls (51.9; 63.9%)	Subclinical hypothyroidism (TSH > 4.5 mIU/L; normal FT4)	Enzymatic procedures
Wang et al.[19]	China	2014	Cross-sectional	806 individuals (56.99 ± 7.98; 81.3%)	Subclinical hypothyroidism (TSH > 4.2 μU/mL, FT4: 12–22 pmol/L)	Ultrasound
Eshraghian et al.[20]	Iran	2013	Cross-sectional	832 individuals including 127 NAFLD patients (48.2 ± 12.8) and 705 controls (36.9 ± 18.7) (61.3%)	Subclinical hypothyroidism (TSH > 5.2 mIU/L, normal FT4); overt hypothyroidism (TSH > 5.2 mIU/L, FT4 < 11.5 ng/dL)	Ultrasound
Pacifico L et al.[21]	Italy	2013	Cross-sectional	402 individuals (6–16 years) 144 children with NAFLD and 258 controls.	Subclinical hypothyroidism (TSH > 4.1 mIU/L with normal FT4); overt hypothyroidism (TSH > 4.1 mIU/ L with FT4 < 0.7 ng/dL)	Ultrasound
Ittermann et al.[22]	Germany	2012	Cross-sectional	3,661 individuals (48.1±16.1 years; 47.56%)	Hypothyroidism was defined by increased TSH concentrations (3mIU/L) and decreased FT3 or FT4 concentrations (FT4 7.7-23.2 pmol/L)	Ultrasound
Chung GE et al.[23]	South Korea	2012	Cross-sectional	4,648 individuals (48.6 ± 11.8 years; 62.4%)	Subclinical hypothyroidism (TSH > 4.1 mIU/L; normal free T4 concentration); Overt hypothyroidism: FT4 level < 0.7-1.8 ng/dL	Ultrasound
Pagadala et al.[24]	US	2012	Case–control	663 individuals (50.4; 56.2%)	Overt hypothyroidism	Histological
Xu et al.[25]	China	2012	Case–control	654 individuals including 327 subclinical hypothyroidism patients and 327 controls	Subclinical hypothyroidism (TSH > 4.5 mIU/L; normal FT4)	Ultrasound
Liangpunsakul et al.[26]	USA	2003	Case–control	616 individuals including 174 NAFLD and 442 control (49 ± 13; 59%)	Overt hypothyroidism	Enzymatic procedures

CONCLUSION:

The present meta-analysis provides strong epidemiological evidence for the significant relationship between hypothyroidism and NAFLD. Individuals with subclinical hypothyroidism and overt hypothyroidism, both 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.

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