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Thyroid Dysfunction in the Pathogenesis and Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease: A Systematic Review

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Universidad del Cauca.**ADMINISTRATIVE INFORMATION****Support** - Universidad del cauca.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100131**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 October 2026 and was last updated on 31 October 2026.**INTRODUCTION**

Review question / Objective In people with or at risk of metabolic dysfunction-associated steatotic liver disease (MASLD), what is the association between thyroid dysfunction — encompassing clinical hypothyroidism, subclinical hypothyroidism, euthyroid thyroid hormone profiles, and tissue-level thyroid hormone action — and the prevalence, incidence, severity, and progression of MASLD? Objective. To systematically review and synthesize the human evidence on whether thyroid dysfunction is independently associated with the development and progression of MASLD, and whether impaired thyroid hormone sensitivity — rather than absolute hormone deficiency — better explains this relationship than isolated hormone concentrations.

Rationale MASLD is the most prevalent chronic liver disease worldwide, and thyroid hormones (T3/T4) exert major control over hepatic lipid handling,

cholesterol synthesis, mitochondrial biogenesis, and autophagy. Despite this strong mechanistic rationale, the clinical literature linking thyroid dysfunction to MASLD has accumulated unevenly, with effect estimates ranging from strong independent associations to null findings after adjustment for adiposity and insulin resistance. Subclinical hypothyroidism — elevated TSH with free T4 within the reference range — has drawn particular attention given its high population prevalence and potential reversibility. The TSH concentration at which hepatic risk begins, the extent of confounding by shared metabolic determinants, the prognostic role of thyroid autoimmunity, and the relevance of composite thyroid hormone sensitivity indices (proposed to capture impaired tissue-level signaling — "acquired hepatic thyroid resistance" — more faithfully than isolated hormone measurements) remain unresolved. No prior systematic review has synthesized this evidence across all four of these dimensions jointly, stratifying explicitly between primary human clinical evidence, human tissue-

level evidence, and non-human mechanistic evidence.

Condition being studied Thyroid dysfunction (clinical and subclinical hypothyroidism and hyperthyroidism, euthyroid thyroid hormone variation, and thyroid autoimmunity) and metabolic dysfunction-associated steatotic liver disease (MASLD), in human participants of any age (pediatric and adult populations analyzed as separate strata).

METHODS

Search strategy This review was conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) statement. Seven electronic databases and search engines were searched for human studies published between January 2000 and August 2026: PubMed, Web of Science, Scopus, ScienceDirect, SpringerLink, the Cochrane Library (Cochrane Database of Systematic Reviews and CENTRAL), and Google Scholar. The central search concept, "Thyroid dysfunction" AND "Pathogenesis and progression of steatotic liver disease associated with metabolic dysfunction," was translated into database-specific logical expressions (full strategies provided as Supplementary Table S2 of the manuscript). Only articles in English were considered. The combined search yielded 663 records before deduplication and screening. In this study, the PEO (Population–Exposure–Outcome) strategy was used.

Participant or population Participant or population Human participants of any age with or at risk of MASLD or non-alcoholic fatty liver disease (NAFLD); pediatric and adult cohorts were synthesized as separate strata rather than pooled, given differing diagnostic criteria.

Intervention Exposure Clinical hypothyroidism and hyperthyroidism, subclinical thyroid dysfunction, serum TSH, free T4, free T3, total T3 and T4, thyroid peroxidase and thyroglobulin antibodies, and derived thyroid hormone sensitivity indices (FT3/FT4 ratio, TSH index, thyroid feedback quantile-based index).

Comparator Euthyroid / normal thyroid function status, or lower values of the exposure variable within the studied population, depending on study design.

Outcomes Imaging-defined or biopsy-defined hepatic steatosis, steatohepatitis, fibrosis stage, cirrhosis, and hepatocellular carcinoma, as well as

validated noninvasive fibrosis scores, with MASLD or NAFLD ascertained by histology, imaging, or validated biochemical indices.

Study designs to be included Randomized controlled trials, prospective and retrospective cohort studies, cross-sectional and case–control studies, systematic reviews, and meta-analyses, reflecting the predominantly observational nature of the evidence base.

Eligibility criteria Studies reporting original data on the relationship between at least one thyroid function parameter and MASLD/NAFLD in human participants of any age, with MASLD or hepatic steatosis objectively defined by accepted imaging, histological, or biochemical criteria. Excluded: studies reporting thyroid parameters only as descriptive baseline characteristics without analysis relative to hepatic outcomes; case reports, editorials, commentaries, letters without original data, and conference abstracts lacking sufficient methodological detail; duplicate publications or overlapping cohorts (most comprehensive report retained); studies with irreconcilable data-extraction problems.

Information sources PubMed, Web of Science, Scopus, ScienceDirect, SpringerLink, the Cochrane Library (CDSR and CENTRAL), and Google Scholar (see Search strategy above).

Main outcome(s) Fifty-nine studies met the eligibility criteria. Hypothyroidism, particularly subclinical hypothyroidism, was consistently associated with higher MASLD prevalence and severity, including advanced fibrosis, even at TSH within the upper reference range. Thyroid hormone sensitivity indices outperformed absolute hormone concentrations in predicting MASLD risk.

Additional outcome(s) Tissue-level evidence indicated acquired hepatic thyroid resistance despite normal circulating hormone concentrations. Evidence on thyroid hormone replacement remained inconclusive, and thyroid autoimmunity showed a complex, occasionally protective, relationship with MASLD.

Data management Two reviewers independently screened titles and abstracts against the eligibility criteria; disagreements were resolved by discussion, with a third reviewer adjudicating when consensus could not be reached. For each eligible study, study characteristics, population demographics, thyroid exposure definitions, hepatic outcome definitions, effect estimates with confidence intervals, and adjustment sets

(adiposity, insulin resistance, dyslipidemia) were extracted. Eligible evidence was organized into three explicitly labeled layers: Layer 1 (primary human clinical evidence, contributing to prevalence/incidence/severity/progression claims), Layer 2 (human tissue-level evidence, supporting mechanistic inference only), and Layer 3 (non-human mechanistic evidence, interpreted only as hypothesis-generating context).

Quality assessment / Risk of bias analysis Risk of bias was assessed using design-specific instruments: the Cochrane Risk of Bias 2 (RoB2) tool for randomized controlled trials; the Newcastle–Ottawa Scale (NOS) for cohort and case–control studies; an adapted Newcastle–Ottawa Scale for cross-sectional designs; and the AMSTAR 2 instrument for systematic reviews and meta-analyses. Studies were not excluded solely on the basis of quality score; ratings were instead used to weight the narrative synthesis and to contextualize inconsistent findings.

Strategy of data synthesis Given the heterogeneity of thyroid exposure definitions and MASLD ascertainment methods across the included studies, findings were synthesized narratively rather than quantitatively (no meta-analytic pooling). Studies were grouped into four thematic dimensions: (1) clinical thyroid dysfunction and MASLD risk; (2) euthyroid thyroid hormone profiles and MASLD severity; (3) tissue-level thyroid hormone action in MASLD; and (4) thyroid-targeted therapeutic and mechanistic evidence. Certainty of evidence for each principal association was assessed using the GRADE approach, adapted for prognostic/associational observational evidence, starting at low certainty and adjusted for risk of bias, inconsistency, indirectness, imprecision, effect size, dose–response gradients, and genetic instrumental-variable support.

Subgroup analysis Pediatric and adult cohorts were analyzed and reported as separate strata given differing MASLD diagnostic criteria and pathophysiology; no lower or upper age limit was applied at the eligibility stage.

Sensitivity analysis Not applicable. No quantitative pooling or meta-analysis was performed, given the heterogeneity of thyroid exposure definitions and hepatic outcome ascertainment across studies; this is stated explicitly as a limitation of the review rather than omitted.

Language restriction English.

Country(ies) involved Colombia.

Other relevant information None.

Keywords MASLD; hypothyroidism; thyroid hormone sensitivity; hepatic thyroid resistance; thyroid hormone receptor β ; subclinical hypothyroidism.

Dissemination plans Publication in a peer-reviewed journal.

Contributions of each author

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