Review Article

The Association Between Thyroid Dysfunction and the Risk of Bone Fractures: A Systematic Review

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ABSTRACT

Thyroid hormones are crucial regulators of bone metabolism. While overt thyroid dysfunction is a recognized risk factor for osteoporosis, the association between subclinical thyroid dysfunction, variations within the euthyroid range, and fracture risk remains complex and less clearly defined. This systematic review aimed to comprehensively evaluate the association between various states of thyroid dysfunction and the risk of incident fractures. A systematic literature search was conducted in accordance with PRISMA guidelines across PubMed, Web of Science, SCOPUS, and ScienceDirect. Studies investigating the association between thyroid dysfunction (overt and subclinical hypo-/hyperthyroidism, euthyroid variations, autoimmune thyroiditis, and thyroid cancer) and fracture risk were included. Two independent reviewers performed study selection, data extraction, and risk of bias assessment using the Newcastle-Ottawa Scale. Thirteen studies met the inclusion criteria. The evidence consistently demonstrated that subclinical hyper-thyroidism and lower thyroid-stimulating hormone (TSH) levels, even within the euthyroid range, were associated with an increased risk of fractures and impaired bone microarchitecture. Several large cohort studies found a lower fracture risk in patients with thyroid cancer, particularly those with postoperative hypoparathyroidism, suggesting a protective effect from intensive calcium and vitamin D supplementation and a low bone turnover state. The relationship between thyroid function and fracture risk is multifaceted. Subclinical hyperthyroidism and low TSH were significant, independent risk factors. The association extends into the euthyroid range, influenced by thyroid hormone sensitivity and autoimmunity. The reduced fracture risk in thyroid cancer patients highlights the critical role of iatrogenic factors and proactive management.

Keyword: thyroid dysfunction, fracture risk, subclinical hyperthyroidism, thyroid-stimulating hormone, systematic review, bone mineral density.

Introduction

A complex interaction of hormonal, mechanical, and nutritional elements carefully control the ongoing remodeling of the human skeleton, which is a dynamic organ system. The thyroid hormones, triiodothyronine (T3) and thyroxine (T4), are among these hormone regulators that are essential for skeletal development, linear growth, and the preservation of adult bone mineral density (BMD) [1]. They exert direct effects

Access this article online	
Quick Response Code:	Website: www.smh-j.com
	DOI: 10.54293/smhj.v6i1.189

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Received: 13 Oct 2025 **Accepted:** 2 Nov 2025

Please cite this article as: Alanazi MMR, Ali AMSMS, Alamri TM, Khan A, Wali RGY, Louhmadi HMA, Al Luhaybi RA, Alotaibi AMS, Alsaeedi SNA, Muhammad JAF. The Association Between Thyroid Dysfunction and the Risk of Fractures: A Systematic Review. SMHJ [Internet]. 2025;6(1):180-190.

SMHJ
Saudi Medical Horizons Journal

on bone cells, stimulating both osteoblastic bone formation and, more potently, osteoclastic bone resorption. Consequently, the maintenance of a euthyroid state is crucial for bone homeostasis, as any significant deviation can disrupt this delicate balance, leading to accelerated bone loss and compromised skeletal integrity [2]. The consequences of overt thyroid dysfunction on bone are well-documented. Clinical hyperthyroidism is a classic secondary cause of osteoporosis, characterized by a high-turnover state where bone resorption vastly outpaces formation. This imbalance results in a rapid reduction of BMD and a significantly increased risk of fragility fractures, particularly at sites rich in cortical bone, such as the hip and forearm [3, 4]. Historically, the focus of clinical concern and research was centered on these overt states. However, with the advent of widespread biochemical screening, a much more common condition has come to the forefront: subclinical thyroid dysfunction. This condition, defined by an abnormal thyroid-stimulating hormone (TSH) level with free thyroid hormone concentrations within the laboratory reference range, affects a substantial portion of the general population, with prevalence increasing with age [5]. A growing body of evidence suggests that subclinical hyperthyroidism is not a benign biochemical finding but is associated with detrimental effects on bone. Numerous epidemiological studies and meta-analyses have linked this condition to reduced BMD and an increased risk of fractures, particularly in postmenopausal women who have lost the protective skeletal effects of estrogen [6, 7]. The association for subclinical hypothyroidism, however, remains less clear, with some studies suggesting a neutral or even potentially protective effect on BMD due to a lower bone turnover rate [8]. Beyond the standard definitions of dysfunction, recent research has begun to explore the impact of variations in thyroid function within the laboratory-defined euthyroid range. The study has indicated that even in individuals with normal TSH and free T4, lower-normal TSH levels may be associated with lower BMD and a higher risk of fractures, suggesting a continuum of risk [9]. The skeletal implications of the mild thyroid hormone excess or deficiency have been the subject of intense investigation and debate over the past two decades. So, this current study aims to conduct a systematic review of the current literature to comprehensively evaluate the association between various states of thyroid dysfunction—including overt and subclinical disease, variations within the euthyroid range, iatrogenic states from thyroid cancer treatment, and autoimmune thyroiditis—and the risk of incident fractures.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were strictly followed in the conduct of this systematic review [10]. The literature was thoroughly and methodically searched using a number of important electronic bibliographic databases, such as PubMed, Web of Science, SCOPUS, and ScienceDirect. The goal of the search technique was to find any pertinent English-language research looking into the relationship between thyroid dysfunction and fracture risk. To guarantee a sensitive and comprehensive search, a mix of regulated vocabulary phrases, including MeSH, and pertinent keywords related to thyroid disorders, thyroid function tests, and fractures was used. Two independent reviewers conducted data extraction, applied the eligibility criteria for study inclusion, screened search results, and evaluated the methodological quality of all included studies using the proper critical appraisal tools in order to reduce bias and improve the reliability of the study selection process. Eligibility Criteria: Predefined inclusion and exclusion criteria were used to choose the studies:

- The inclusion criteria: included research that focused on the association between incident fracture risk and thyroid dysfunction, including overt and subclinical hypothyroidism and hyperthyroidism, thyroid function variations within the euthyroid range, autoimmune thyroid disease, and thyroid cancer. There were no restrictions on the age of participants or the specific anatomical site of the fracture. We included studies published in the English language that provided quantitative data on fracture risk, such as hazard ratios, odds ratios, or incidence rates. Eligible study designs consisted of randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and cross-sectional analyses.
- The exclusion criteria: were applied to studies that did not have thyroid dysfunction and fracture risk as a primary focus, those published in languages other than English, and non-original research publications such as case reports, editorials, narrative reviews, commentaries, and conference abstracts. Studies that did not present extractable data on the association of interest were also excluded. Data Extraction: A systematic approach was employed for data extraction to ensure accuracy and consistency. Initially, the titles and abstracts of all records retrieved from the database searches were screened for relevance against the eligibility criteria. The web-based systematic review

tool Rayyan (QCRI) [11] was utilized to manage the references and facilitate a blinded screening process between reviewers, thereby reducing the potential for selection bias. All studies deemed potentially relevant by either reviewer were advanced to a full-text review. Both reviewers independently assessed the full-text articles for final inclusion. Any discrepancies or disagreements regarding the eligibility of a study were resolved through discussion until a consensus was reached. For each included study, data were extracted using a standardized, piloted data extraction form. The extracted information included the study title, first author, year of publication, country of origin, study design, sample size, population characteristics, specific definition of thyroid dysfunction exposure, method of fracture outcome ascertainment, duration of follow-up for longitudinal studies, and the key quantitative findings with adjusted effect estimates and confidence intervals. Data Synthesis Strategy: The findings from the included studies were synthesized qualitatively. Summary tables were constructed to present the key characteristics and the main results of each study, providing a clear and organized overview of the evidence. These tables detailed the study design, population, exposure, outcome, and principal conclusions. Following the completion of data collection and extraction, the nature and heterogeneity of the included studies were evaluated to determine the most appropriate method for synthesizing the results. A narrative synthesis was chosen to summarize and explain the characteristics and findings of the included studies, grouping them by the type of thyroid dysfunction examined and highlighting the consistency or discordance of the results across different populations and settings. Risk of Bias Assessment: Two independent reviewers used the Newcastle-Ottawa Scale (NOS) for non-randomized studies to objectively evaluate the included studies' methodological quality and risk of bias. The selection of study groups, group comparability, and determining the exposure or outcome of interest are the three areas in which this tool evaluates studies. Assessment criteria for cohort studies included: representativeness of the exposed cohort, selection of the non-exposed cohort, exposure determination, proof that the outcome of interest was absent at the beginning, cohort comparability, outcome evaluation, whether the follow-up period was sufficient for outcomes to occur, and follow-up adequacy. Items pertaining to comparability, exposure ascertainment, and the definition and selection of cases and controls were assessed for case-control studies. Each study's quality was indicated by a star system, where a larger number of stars indicates a reduced chance of bias. Consensus was used to settle any disputes in the quality assessment.

Results

The PRISMA flow diagram shows how studies are identified and chosen for evaluation in a methodical manner. After removing duplicates, the initial database search produced 552 results, down to 243. After screening for titles and abstracts, 184 records were eliminated, leaving 59 reports that needed to be retrieved. Of these, 27 full-text publications were evaluated for eligibility after 32 were deemed unavailable. 13 research ultimately met all inclusion criteria for the final systematic review after 14 studies were eliminated because they were abstracts only (n=5), had the improper population (n=4), or had the wrong outcome (n=4). (Table 1), exhibit considerable diversity in their geographical locations, design methodologies, and population characteristics, which collectively provide a broad and nuanced investigation into the association between thyroid dysfunction and fracture risk. The research spans multiple continents, with significant contributions from large-scale national cohorts in South Korea [15, 20, 23] and the United States [12, 14, 18, 19], alongside important findings from European populations in Switzerland [16], Scotland [21], and Spain [22]. The study designs were predominantly observational, including six retrospective cohorts [15, 20, 23, 24, and parts of 21], three prospective cohorts [12, 16, 22], and four cross-sectional analyses [13, 14, 17, 18]. This methodological variety was complemented by a sophisticated Mendelian randomization approach in one study [21], which offers evidence for a causal relationship. The sample sizes range dramatically from a focused longitudinal cohort of 145 postmenopausal women [22] to vast nationwide studies encompassing over 100,000 participants [20, 23]. The studied populations were equally varied, covering community-dwelling adults [12], patients with overt thyroid conditions such as differentiated thyroid cancer (DTC) [13, 15, 20, 22, 23], post-operative hypoparathyroidism [20, 24], and euthyroid individuals where the focus was on variations within the normal range of thyroid function [16, 18] or the presence of autoantibodies [19]. This heterogeneity underscores the complexity of the field and the importance of considering specific patient subgroups and thyroid conditions when assessing fracture risk. (Table 2), reveal a complex and sometimes counterintuitive relationship between thyroid status

and skeletal health. A consistent theme across multiple studies is the clear association between subclinical hyperthyroidism or low thyroid-stimulating hormone (TSH) levels and an increased risk of fractures. The large prospective cohort by Daya et al. [12] found a 34% increased hazard for fractures in individuals with subclinical hyperthyroidism, while Vendrami et al. [16] demonstrated that even within the euthyroid range, lower TSH levels were associated with worse bone microarchitecture (as measured by Trabecular Bone Score) and a higher 5-year incident fracture risk. This is powerfully supported by the Mendelian randomization study by Soto-Pedre et al. [21], which provided genetic evidence for a causal link, showing that genetically raised TSH concentrations were protective against osteoporotic fractures in men. Furthermore, studies exploring novel aspects of thyroid physiology, such as impaired sensitivity to thyroid hormones [18] and the presence of thyroid peroxidase antibodies (TPOAb) [14, 19], found significant correlations with reduced bone mineral density and an increased prevalence of fractures, particularly in women, highlighting the role of autoimmunity and peripheral hormone action in bone metabolism. However, the narrative becomes more intricate when examining patients with overt thyroid cancer and its treatments. Several studies investigated populations with DTC undergoing TSH suppressive therapy. While, Hawkins Carranza et al. [22] reported a significant deterioration in bone quality (TBS) over time despite stable BMD, two large Korean cohort studies yielded surprising results. Ahn et al. [20] and Ku et al. [23] both reported a significantly lower risk of fractures, especially vertebral fractures, in thyroid cancer patients compared to control groups. Ahn et al. [20] specifically attributed this lower risk to postoperative hypoparathyroidism and its subsequent management, suggesting that the low bone turnover state induced by hypoparathyroidism might be protective against the catabolic effects of TSH suppression or that proactive calcium and vitamin D supplementation plays a key role. This is consistent with the findings of Lui et al. [24], who observed no increased fracture risk in patients with persistent postoperative hypoparathyroidism. (Table 3) presents the comprehensive risk of bias assessment for the 13 included studies, conducted using the Newcastle-Ottawa Scale (NOS). The results indicate a generally low risk of bias across the body of evidence, with the majority of studies (10 out of 13) receiving a rating of 8 or 9 stars, signifying high methodological quality. Key strengths identified were the representativeness of cohorts and adequate control for key confounders in the comparability domain.

Discussion

Our findings confirm the well-established role of subclinical hyperthyroidism as a significant risk factor for fractures, while also shedding light on more intricate relationships within euthyroid populations, in the context of autoimmune thyroid disease, and particularly in the paradoxical setting of thyroid cancer and its treatments. The collective evidence underscores that the association is not monolithic but is profoundly influenced by the specific thyroid condition, patient demographics, and iatrogenic interventions. The most consistent finding across the included studies is the detrimental impact of low TSH levels on skeletal integrity. Our review strongly supports existing literature that identifies subclinical hyperthyroidism as a key modulator of fracture risk. The large, community-based prospective cohort by Daya et al. [12] found a 34% increased hazard for incident fractures (aHR 1.34) among individuals with endogenous subclinical hyperthyroidism over a remarkable median follow-up of 21 years. This aligns perfectly with a meta-analysis by Blum et al. [25], which concluded that subclinical hyperthyroidism was associated with a significantly increased risk of hip and other fractures, with a pooled relative risk of 1.36 for any fracture. The biological plausibility for this association is robust; thyroid hormones directly stimulate bone resorption by activating osteoclasts. Even mild, persistent excess can uncouple the bone remodeling cycle, leading to a net loss of bone mineral density over time [26]. Our review extends this understanding beyond overt dysfunction. The work of Vendrami et al. [16] demonstrated that even within the strict confines of euthyroidism, a lower-normal TSH level was an independent predictor of worse bone microarchitecture, as measured by Trabecular Bone Score (TBS), and a higher 5-year incident fracture risk. This finding is crucial as it suggests a continuous gradient of risk, where the optimal TSH for bone health may lie in the upper part of the reference range, a concept increasingly recognized in endocrine practice. Further deepening the narrative, several studies in our review moved beyond conventional TSH and free thyroxine (FT4) measurements to explore novel physiological aspects of thyroid function. Liu et al. [18] and Wang et al. [14] investigated parameters of thyroid hormone sensitivity, such as the Thyroid Feedback Quantile-based Index (TFQI) and the FT3/FT4 ratio. Their findings revealed that impaired central sensitivity to

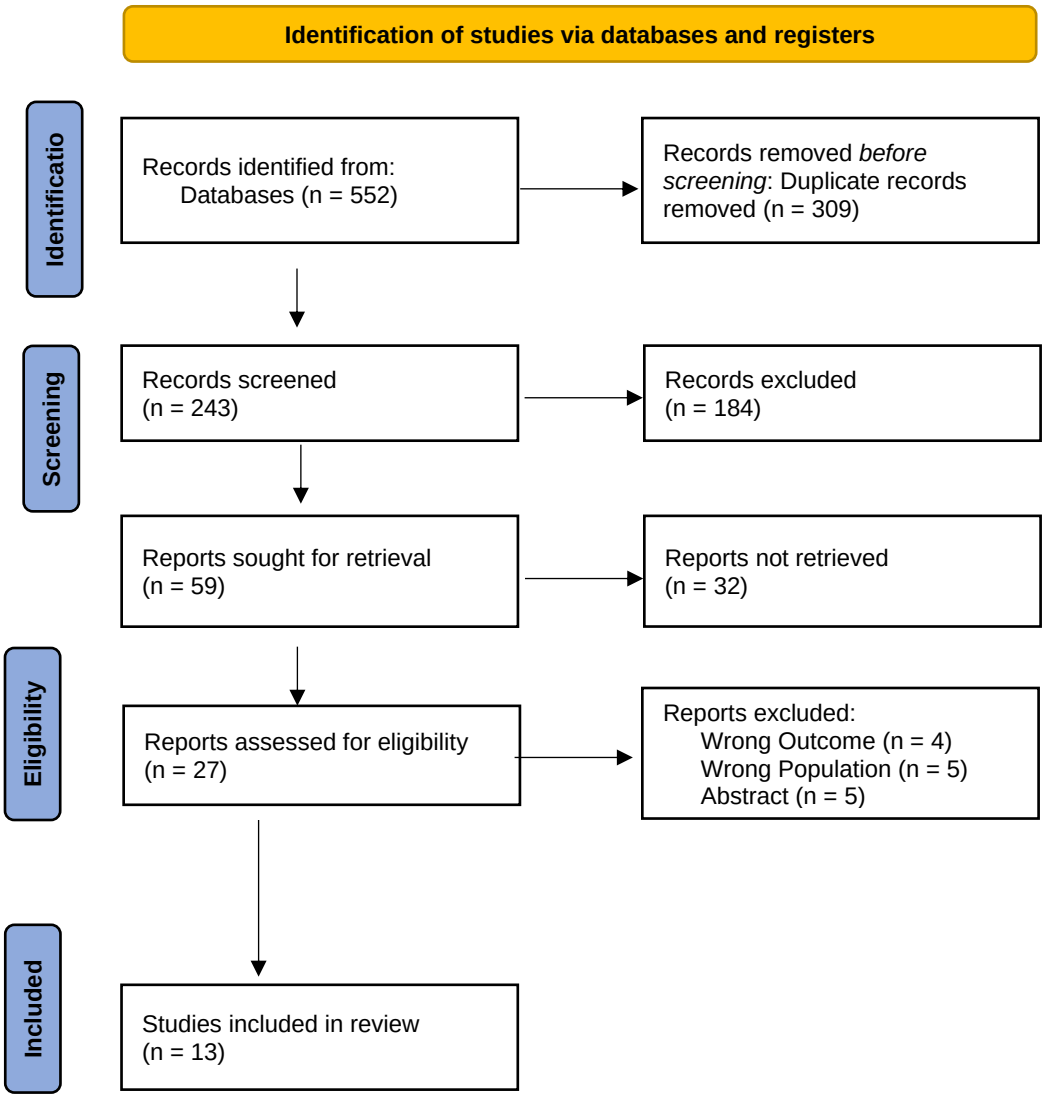

Figure 1: PRISMA Flow Diagram for Study Selection.

Table 1: Study Characteristics and Demographic Details.

Study (Author, Year) [Ref]	Country	Study Design	Sample Size	Population Characteristics	Mean/Median Age (Years)	Female (%)	Follow-up Duration (Years)
Daya NR, 2022 [12]	USA	Prospective Cohort	10,946	Community-dwelling adults; no thyroid meds or fracture history	57.0 (Mean)	54.3%	Median 21.0
Otani H, 2023 [13]	Japan	Matched Case-Control	86 (43 PTC, 43 controls)	Post-operative PTC patients scheduled for RAI vs. healthy controls	NM (Matched for age)	NM	Cross-sectional
Wang Q, 2024 [14]	USA	Cross-sectional	1,844	Participants from NHANES database	NM	NM	N/A (Cross-sectional)
Kim J, 2023 [15]	South Korea	Retrospective Cohort	74,774	Thyroid cancer patients >40 years who underwent thyroidectomy	NM	NM	Median 4.5
Vendrami C, 2022 [16]	Switzerland	Prospective Cohort	533	Euthyroid post-menopausal women from OsteoLaus cohort	68.4 (Mean)	100%	5.0
Jin YJ, 2021 [17]	South Korea	Cross-sectional	164,978 (1,349 TC, 163,629 controls)	Participants from KoGES HEXA data	NM	Subgroup analysis for women	N/A (Cross-sectional)
Liu C, 2023 [18]	USA	Cross-sectional	3,403	Euthyroid men and postmenopausal women ≥50 years from NHANES	NM	NM	N/A (Cross-sectional)
Wu J, 2024 [19]	USA	Cross-sectional	3,865	Participants from NHANES 2007-2010	NM	Analyzed separately	N/A (Cross-sectional)
Ahn SH, 2023 [20]	South Korea	Retrospective Cohort	115,821	Thyroid cancer patients who underwent total thyroidectomy	NM	NM	Mean 4.8
Soto-Pedre E, 2021 [21]	Scotland, UK	Cross-sectional / MR	9,452 (GWAS), 5,599 (MR)	Patients of European Caucasian ethnicity from genetics biobank	NM	Analyzed separately	N/A (Cross-sectional for MR)
Hawkins Carranza F, 2024 [22]	Spain	Longitudinal Cohort	145	Postmenopausal women with DTC on long-term TSH suppression	NM	100%	Long-term (Specific duration NM)
Ku EJ, 2025 [23]	South Korea	Retrospective Cohort	77,934 (2,514 TC, 75,420 controls)	Patients with thyroid cancer and matched controls from NHIS-NSC	NM	Majority (Specific % NM)	NM (2006-2019)
Lui DTW, 2021 [24]	Hong Kong	Retrospective Cohort	4,123	Patients who underwent elective total thyroidectomy	NM	NM	Median 10.3

DTC: Differentiated Thyroid Carcinoma; GWAS: Genome-Wide Association Study; KoGES HEXA: Korean Genome and Epidemiology Study_Health Examinees; MR: Mendelian Randomization; N/A: Not Applicable; NHANES: National Health and

Nutrition Examination Survey; NHIS-NSC: National Health Insurance Service-National Sample Cohort; NM: Not Mentioned; PTC: Papillary Thyroid Carcinoma; RAI: Radioactive Iodine; Ref: Reference; TC: Thyroid Cancer.

Table 2: Study Outcomes and Key Findings Related to Thyroid Dysfunction and Fracture Risk.

Study (Author, Year) [Ref]	Thyroid Condition / Exposure	Fracture Assessment Method	Key Findings (Adjusted Analysis)	Conclusion Summary
Daya NR, 2022 [12]	Subclinical Hyperthyroidism; Subclinical Hypothyroidism	Hospitalization codes; Medicare claims	aHR 1.34 (1.09-1.65) for Subclinical Hyper-thyroidism; aHR 0.90 (0.77-1.05) for Subclinical Hypothyroidism	Subclinical hyperthyroidism is an independent risk factor for fracture.
Otani H, 2023 [13]	Papillary Thyroid Carcinoma (pre-TSH suppression)	Vertebral Fracture assessment (X-ray)	Adjusted OR 5.63 (1.82-17.5) for Vertebral Fracture	PTC is associated with a higher risk of vertebral fracture independent of BMD.
Wang Q, 2024 [14]	Thyroid function indices (FT3/FT4, TPOAb)	DXA (BMC, BMD); Vertebral Fracture assessment	Higher FT3/FT4 associated with lower spinal BMC; Higher TPOAb increased risk of OVF	Higher FT3/FT4 and TPOAb are associated with bone loss and vertebral fracture risk.
Kim J, 2023 [15]	Physical activity in thyroid cancer post-thyroidectomy	National insurance data (diagnosis codes)	aHR 0.848 (0.771-0.932) for any fracture with consistent exercise	Maintaining regular exercise after surgery reduces fracture risk.
Vendrami C, 2022 [16]	TSH within euthyroid range	DXA (BMD); Trabecular Bone Score (TBS); Incident fractures	Positive association between TSH and TBS (β=0.086, $p<0.05$); Lower TSH in fracture group	Higher normal TSH is associated with better bone microarchitecture and lower fracture risk.
Jin YJ, 2021 [17]	Thyroid Cancer	Self-reported osteoporosis/fracture history	Adjusted OR 1.41 (1.18-1.70) for osteoporosis; No significant association with fractures	Thyroid cancer is associated with osteo-porosis, but not with a history of fractures in this cross-sectional analysis.
Liu C, 2023 [18]	Impaired sensitivity to thyroid hormones (indices) in euthyroid	DXA (BMD); Self-reported fracture history	TSHI, TFQI, PTFQI associated with higher odds of osteoporosis (e.g., TFQI OR 1.74); FT3/FT4 protective (OR=0.75)	Impaired thyroid hormone sensitivity correlates with osteoporosis and fractures.
Wu J, 2024 [19]	Thyroid autoantibodies (TgAb, TPOAb)	DXA (BMD); Self-reported fracture history	Higher TPOAb associated with fractures in females (OR provided in text, $p<0.05$)	Higher TPOAb prevalence is related to a higher prevalence of fractures in females.
Ahn SH, 2023 [20]	Postoperative Hypoparathyroidism (PO-hypoPT)	National insurance data (diagnosis codes)	aHR 0.83 (0.70-0.98) for any fracture; aHR 0.67 (0.47-0.96) for vertebral fracture	PO-hypoPT is associated with a lower risk of fractures, particularly vertebral fractures.
Soto-Pedre E, 2021 [21]	Genetically raised TSH (Mendelian Randomization)	Electronic medical records for fracture	OR for fracture in men with high TSH-GRS: 0.59 ($p=0.0024$)	Genetically raised TSH is causally associated with decreased fracture risk in men.
Hawkins Carranza	Long-term TSH suppression in DTC	DXA (BMD); Trabecular Bone	TBS decreased significantly (1.35 to 1.27,	Long-term suppression worsens bone quality

F, 2024 [22]		Score (TBS); Vertebral Fracture (X-ray)	p=0.002); BMD remained unchanged. TBS and RAI therapy distinguished fracture group.	(TBS) without affecting BMD, increasing fracture risk.
Ku EJ, 2025 [23]	Thyroid Cancer (vs. matched controls)	National insurance data (diagnosis codes)	HR 0.81 (0.69-0.94) for any fracture; HR 0.72 (0.60-0.85) in patients >50 years	Thyroid cancer patients, especially older women, have a lower fracture risk, likely due to proactive management.
Lui DTW, 2021 [24]	Persistent Postoperative Hypoparathyroidism	Electronic health records (fracture diagnosis)	No difference in fracture events between groups (p=0.761)	Persistent hypo-para-thyroidism after thyroid-ectomy is common but not associated with increased fracture risk.

aHR: Adjusted Hazard Ratio; BMC: Bone Mineral Content; BMD: Bone Mineral Density; DXA: Dual-energy X-ray Absorptiometry; FT3/FT4: Free Triiodothyronine/Free Thyroxine Ratio; OVF: Osteoporotic Vertebral Fracture; OR: Odds Ratio; PO-hypoPT: Postoperative Hypoparathyroidism; Ref: Reference; TBS: Trabecular Bone Score; TFQI: Thyroid Feedback Quantile-based Index; TPOAb: Thyroid Peroxidase Antibody; TSH: Thyroid-Stimulating Hormone; TSHI: TSH Index.

Table 3: Risk of Bias Assessment for Included Studies**.**

Study (Author, Year) [Ref]	Study Design	NOS Domain: Selection (Max 4)	NOS Domain: Comparability (Max 2)	NOS Domain: Outcome/Exposure (Max 3)	Total Stars (Max 9)	Risk of Bias
Daya NR, 2022 [12]	Prospective Cohort	★★★★	★★	★★★	9	Low
Otani H, 2023 [13]	Case-Control	★★★	★★	★★★	8	Low
Wang Q, 2024 [14]	Cross-sectional	★★★	★★	★★	7	Moderate
Kim J, 2023 [15]	Retrospective Cohort	★★★★	★★	★★	8	Low
Vendrami C, 2022 [16]	Prospective Cohort	★★★★	★★	★★★	9	Low
Jin YJ, 2021 [17]	Cross-sectional	★★★★	★	★★	7	Moderate
Liu C, 2023 [18]	Cross-sectional	★★★★	★★	★★	8	Low
Wu J, 2024 [19]	Cross-sectional	★★★★	★★	★★	8	Low
Ahn SH, 2023 [20]	Retrospective Cohort	★★★★	★★	★★	8	Low
Soto-Pedre E, 2021 [21]	Cross-sectional / MR	★★★★	★★	★★★	9	Low
Hawkins Carranza F, 2024 [22]	Longitudinal Cohort	★★★	★★	★★	7	Moderate
Ku EJ, 2025 [23]	Retrospective Cohort	★★★★	★★	★★	8	Low
Lui DTW, 2021 [24]	Retrospective Cohort	★★★★	★★	★★	8	Low

thyroid hormones (reflected by a higher TFQI) was independently associated with osteoporosis and fractures, while a lower FT3/FT4 ratio (potentially indicating reduced peripheral deiodination) was associated with decreased bone mineral content. This suggests that the body's sensitivity to thyroid hormones is as critical as their circulating levels, a dimension not captured by standard thyroid function tests. Similarly, the role of thyroid autoimmunity was highlighted by Wu et al. [19], who found that the presence of thyroid peroxidase antibodies (TPOAbs) was significantly associated with a higher prevalence of fractures in females, independent of BMD. This aligns with a growing body of evidence indicating that chronic inflammation in autoimmune thyroid disease can directly and adversely affect bone metabolism. A study has shown that cytokines and other inflammatory mediators involved in Hashimoto's thyroiditis can promote osteoclastogenesis and inhibit osteoblast activity, creating a pro-osteoporotic milieu [27]. Perhaps the most intriguing and seemingly paradoxical findings from this review pertain to patients with differentiated thyroid cancer (DTC). While, long-term TSH suppressive therapy is a recognized risk factor for bone loss, our included studies presented a more complex picture. Hawkins Carranza et al. [22] followed postmenopausal women with DTC and found that despite stable BMD over time, their Trabecular Bone Score (TBS) significantly deteriorated, indicating a silent worsening of bone quality that would not be detected by DXA alone. This underscores the limitation of relying solely on BMD for fracture risk assessment in this population. However, counterintuitively, two large nationwide cohort studies from Korea found that DTC patients had a significantly lower risk of fractures compared to matched controls. Ahn et al. [20] reported a 17% lower risk of any fracture (aHR 0.83) and a 33% lower risk of vertebral fractures (aHR 0.67) in patients with postoperative hypoparathyroidism, while Ku et al. [23] found an overall 19% risk reduction (HR 0.81) in thyroid cancer patients, which was more pronounced in those diagnosed after age 50. This protective effect is likely not due to the cancer or TSH suppression itself, but rather to the "osteosclerotic" effect of chronic hypoparathyroidism and, critically, the intensive management these patients receive. Post-surgical hypoparathyroidism leads to low bone turnover, which can increase BMD but, as the TBS data suggests, may not fully reflect bone quality. More importantly, these patients are routinely prescribed high-dose calcium and active vitamin D supplements to maintain normocalcemia. This proactive supplementation may inadvertently provide superior skeletal protection compared to the general population. This hypothesis is supported by a study by Cipriani et al. [28], which showed that postmenopausal women with chronic hypoparathyroidism had higher BMD and a lower risk of vertebral fractures than matched controls. Furthermore, the study by Kim et al. [15] adds another layer, demonstrating that modifiable lifestyle factors like maintaining regular physical activity after thyroidectomy significantly reduced fracture risk (aHR 0.85 for any fracture), highlighting the importance of holistic patient management. The causal inference from the Mendelian randomization study by Soto-Pedre et al. [21] provides a higher level of evidence that is less susceptible to confounding. Their finding that genetically raised TSH levels were causally associated with a 41% reduction in fracture risk in men (OR=0.59) powerfully reinforces the observational data. This genetic evidence solidifies the notion that TSH itself, or the thyroid axis it regulates, plays a direct protective role in bone metabolism. The sex-specific nature of this finding is particularly interesting and warrants further investigation, as it may relate to interactions between thyroid hormones and sex steroids in bone remodeling. This aligns with previous research suggesting that the skeletal effects of thyroid disease may be more pronounced in postmenopausal women due to the loss of the protective effects of estrogen [29]. Limitations of the Study: Despite the robustness of the collective findings, this systematic review was subjected to several limitations. A significant proportion of the included studies were observational in design (cohort and cross-sectional), which inherently prevents the establishment of causality, as residual confounding from unmeasured or imperfectly measured factors (such as detailed dietary calcium intake, level of physical activity, falls risk, and precise duration of thyroid dysfunction) may influence the results. The reliance on administrative data for fracture ascertainment in several large cohort studies [15, 20, 23] introduce the potential for misclassification, as diagnostic codes may not always accurately reflect fragility fractures. Furthermore, there was heterogeneity in the methods used to define thyroid dysfunction and assess fractures, which complicates direct comparison between studies. For instance, the definition of "subclinical" disease varied, and fractures were identified through a mix of self-report, clinical adjudication, and ICD codes. The generalizability of

findings from specific populations, such as Korean thyroid cancer patients, to other ethnic and healthcare settings may be limited. Finally, the cross-sectional studies included [13, 14, 17, 18, 19] were unable to determine the temporal sequence of exposure and outcome, making it difficult to conclude whether thyroid dysfunction preceded the bone pathology or vice versa.

Conclusion

This systematic review confirms that subclinical hyperthyroidism and low-normal TSH levels are significant, independent risk factors for fracture, mediated by detrimental effects on bone density and quality. The relationship extends into the euthyroid range, influenced by individual hormone sensitivity and autoimmunity, while the paradoxical reduced risk in some thyroid cancer patients highlights the protective role of aggressive calcium and vitamin D supplementation. Consequently, fracture risk assessment should be integrated into the routine management of thyroid disorders, particularly for patients with subclinical hyperthyroidism or on TSH-suppressive therapy, with future research needed to develop targeted interventions for these at-risk groups.

Conflict of Interest

None

Funding

None

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