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HYPOTHYROIDISM AND HASHIMOTO'S THYROIDITIS AS MIGRAINE COMORBIDITIES: EPIDEMIOLOGY, MECHANISMS, AND THERAPEUTIC IMPLICATIONS - A NARRATIVE REVIEW

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ABSTRACT

Background: Both migraine and hypothyroidism are prevalent chronic conditions, predominantly affecting women. A growing body of evidence suggests a bidirectional comorbid relationship between these two conditions, yet the magnitude and directionality of this association remain insufficiently characterized.
Objective: To review published evidence on the association between hypothyroidism (including subclinical hypothyroidism and Hashimoto's thyroiditis) and migraine or headache outcomes in humans, and to evaluate the therapeutic implications of thyroid hormone replacement.
Methods: A systematic search of PubMed (n = 141) and Cochrane (n = 16) databases was conducted for studies published from January 1990 to 2025. After title/abstract screening and full-text eligibility assessment, 17 studies were included. Included study designs comprised cross-sectional studies, case-control studies, cohort studies, and one quasi-randomized placebo-controlled trial.
Results: The prevalence of hypothyroidism in migraine patients consistently exceeded general population estimates. Subclinical hypothyroidism was identified in a significantly higher proportion of migraine patients compared to controls. Patients with chronic migraine showed substantially higher rates of hypothyroidism than those with episodic migraine. Hashimoto's thyroiditis was associated with migraine chronification and increased migraine days per month. Levothyroxine treatment significantly reduced headache frequency, severity, and disability in patients with comorbid subclinical hypothyroidism and migraine. Genetic evidence supported shared biological pathways.
Conclusion: Hypothyroidism and Hashimoto's thyroiditis are meaningful comorbidities in migraine patients. Routine thyroid function screening is warranted in patients with refractory or progressive migraine. Levothyroxine treatment may yield clinically significant headache reduction.

KEYWORDS

Migraine; Hypothyroidism; Hashimoto's Thyroiditis; Subclinical Hypothyroidism; Levothyroxine; Narrative Review

CITATION

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Introduction

Migraine is among the most burdensome neurological conditions globally, ranking as the leading cause of disability in individuals under 50 years of age. According to the Global Burden of Disease Study 2016, migraine ranks as the third most prevalent disease and the second most disabling neurological disorder worldwide, affecting approximately 1.04 billion people globally. Its worldwide prevalence is approximately 11-15%, with a marked female predominance, the female-to-male ratio being approximately 3:1 in adult populations. The disorder exacts an enormous personal and societal toll, disrupting work productivity, family function, and quality of life, and imposing substantial economic costs through both direct medical expenditure and indirect losses from absenteeism and presenteeism.

Hypothyroidism, similarly, affects an estimated 1-5% of the general population in its clinical (overt) form, with subclinical hypothyroidism reaching up to 18% in some population-based estimates (Garmendia Madariaga et al., 2014). Like migraine, hypothyroidism is more common in women and in older age groups. Its clinical spectrum ranges from overt hypothyroidism - characterized by fatigue, cold intolerance, weight gain, constipation, bradycardia, and dry skin - to subclinical hypothyroidism, defined biochemically by an elevated serum thyroid-stimulating hormone (TSH) level combined with a normal free thyroxine (fT4) level, often accompanied by no or only mild symptoms. Hashimoto's thyroiditis, the autoimmune form of hypothyroidism, accounts for the majority of hypothyroidism cases in iodine-sufficient regions and is characterized by lymphocytic infiltration of the thyroid gland and the presence of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin antibodies.

The co-occurrence of migraine and thyroid disorders has been noted in clinical practice for decades. Early clinical observations reported headache resolution following thyroid hormone replacement therapy, and subsequent small case series reinforced the clinical impression of a link. However, systematic investigation of this relationship did not gain momentum until more recent decades, driven by larger epidemiological datasets, improved headache classification systems, and sensitive TSH assays. Several epidemiological studies have reported elevated prevalence of hypothyroidism among migraine patients, and conversely, a higher risk of developing hypothyroidism in patients with pre-existing headache disorders. Simultaneously, mechanistic research has proposed immune dysregulation, hormonal modulation of pain thresholds, and shared genetic architectures as plausible explanatory pathways.

The clinical importance of clarifying this relationship cannot be overstated. If thyroid dysfunction - particularly the subclinical form - contributes to migraine frequency, severity, or chronification, then routine thyroid screening in headache patients represents a practical, low-cost intervention that could identify a treatable comorbidity and reduce the burden of migraine. Conversely, if the relationship is primarily driven by migraine predisposing to thyroid dysfunction, clinicians managing hypothyroid patients should be alert to headache burden as an early signal or ongoing complication requiring active management.

This review synthesizes the available evidence on the association between hypothyroidism (including subclinical hypothyroidism and Hashimoto's thyroiditis) and migraine or primary headache outcomes. It evaluates the prevalence, directionality, and characteristics of this relationship across diverse study designs and populations. It further evaluates therapeutic implications, particularly regarding levothyroxine treatment, and highlights areas requiring further investigation. This review was conducted in accordance with PRISMA 2020 guidelines.

Methodology

Search Strategy

This review was conducted in accordance with PRISMA 2020 guidelines. A systematic search was performed in PubMed and Cochrane Library databases for studies published from January 1, 1990 to 2025. The 1990 start date was chosen because the International Headache Society's first standardized headache classification was published in 1988, and sensitive TSH immunoassays became widely adopted around the same time. Studies predating these developments apply incompatible diagnostic and biochemical criteria, limiting comparability with contemporary evidence.

The PubMed search used the following strategy: ("Hypothyroidism"[MeSH] OR "subclinical hypothyroidism"[tiab] OR hypothyroidism[tiab] OR "Hashimoto"[tiab] OR "autoimmune thyroiditis"[tiab]) AND ("Migraine Disorders"[MeSH] OR migraine[tiab] OR migraines[tiab] OR "chronic migraine"[tiab] OR cephalalgia[tiab]) AND NOT ("animals"[MeSH] NOT "humans"[MeSH]). An analogous search was applied in Cochrane. No additional records were identified through hand searching. The search was performed without language restriction, however, all studies ultimately included were available in English.

Eligibility Criteria

Studies were included if they reported original empirical data from human participants diagnosed with hypothyroidism (overt or subclinical), Hashimoto's thyroiditis, or autoimmune thyroiditis, and measured migraine or headache as an outcome. Acceptable outcomes included migraine diagnosis, migraine frequency, migraine severity, headache prevalence, or validated headache scale scores (e.g., MIDAS, HIT-6, VAS). Acceptable study designs included cross-sectional, case-control, cohort, and quasi-randomized controlled trials.

Studies published before 1990 were excluded, as were animal studies, reviews without original data, editorials, conference abstracts without full data, single case reports (n = 1), and duplicate publications. Studies in which the headache diagnosis was based solely on self-report without clinical assessment or standardized criteria were also excluded when such methodological details were ascertainable.

Study Selection and Data Extraction

Title and abstract screening followed by dual independent full-text review was performed by pairs of reviewers. Conflicts were resolved by discussion and, if necessary, arbitration by a third reviewer. The search identified 157 records (PubMed: 141; Cochrane: 16). After title and abstract screening, 128 records were excluded. Of 29 full texts assessed for eligibility, 12 were excluded for the following reasons: wrong study design (n = 5); no headache outcome reported (n = 3); no thyroid condition as defined by the eligibility criteria (n = 2); single case report (n = 1); and substantial overlap with an already-included study (n = 1). Seventeen studies were included in the final synthesis.

Data extraction was performed using a standardized form capturing: first author, publication year, country, study design, sample size, population characteristics (age, sex distribution), headache diagnosis criteria, thyroid diagnosis criteria, key quantitative findings (prevalence estimates, odds ratios, hazard ratios, p-values), and information on thyroid treatment outcomes where available.

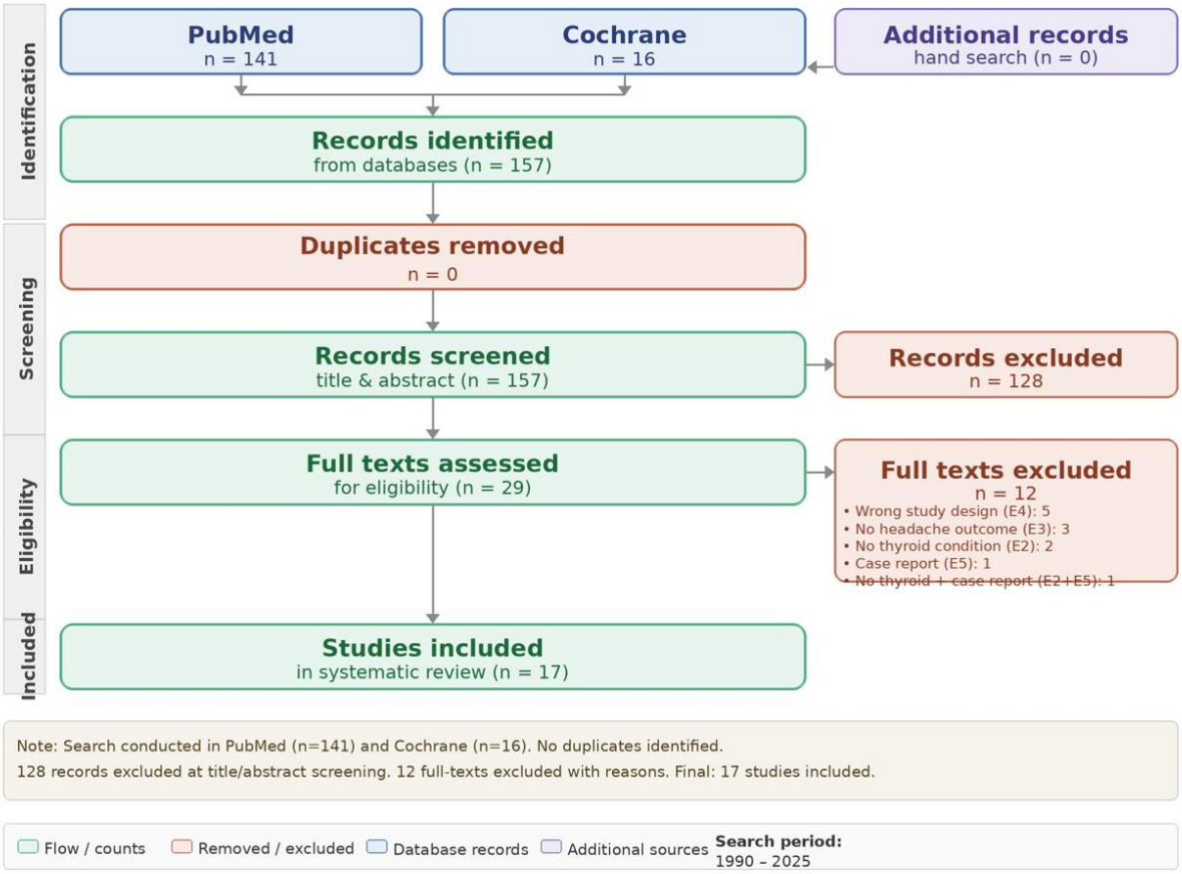

Fig. 1. *PRISMA 2020 Flow Diagram*

Data Analysis

Due to the heterogeneity of study designs, populations, and outcome measures across included studies, a narrative synthesis approach was adopted rather than meta-analysis. Studies were grouped thematically by: (1) prevalence of hypothyroidism in headache populations; (2) risk of new-onset hypothyroidism in headache patients; (3) characteristics of headache in hypothyroid patients; (4) pediatric evidence; (5) genetic and mechanistic evidence; and (6) therapeutic evidence. Effect estimates, sample sizes, and significance values were extracted and are presented in Table 1. Three validated tools were applied according to study design. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to evaluate cohort and cross-sectional studies. The Newcastle-Ottawa Scale (NOS) was applied to case-control studies, assessing selection, comparability, and exposure domains. The revised Cochrane Risk of Bias tool (RoB 2) was used for the single quasi-randomized placebo-controlled trial (Dev et al., 2023), with adaptation to account for its quasi-randomized allocation method. Results are presented in Table 2.

Table 1. Summary of Included Studies

Author, Year	Country	Design	N	Key Finding
Rubino et al., 2019	Italy	Case-control	301	Migraine prevalence 46% in subclinical hypothyroid vs. 13% controls (OR 5.80; p<0.001)
Martin et al., 2017	USA	Longitudinal cohort	8,412	Headache disorders increase hypothyroidism risk (HR 1.21; 95% CI 1.001-1.462) over 20-year follow-up
Lima Carvalho et al., 2017	Brazil	Cross-sectional / prospective	213	HAH in 34% of hypothyroid patients; 78% decrease in headache frequency post-levothyroxine
Dev et al., 2023	India	Quasi-RCT (placebo-controlled)	87	Levothyroxine 25 µg/day significantly reduced headache frequency and MIDAS score vs. placebo at 3 months
Nowaczewska et al., 2024	Poland	Retrospective cohort	928	Hashimoto's thyroiditis associated with chronic migraine (OR 1.76) and more monthly migraine days
Filipchuk et al., 2022	Argentina	Cross-sectional	111	Treated hypothyroidism 29.55% in chronic vs. 8.96% in episodic migraine (OR 4.26; p<0.01)
Fernandez-Garza & Marfil, 2022	Mexico	Cross-sectional	869	Hypothyroidism prevalence 4% overall in headache patients; 10.7% in chronic migraine specifically
Spanou et al., 2020	Greece	Retrospective	427	20.8% overall thyroid disorder prevalence in headache clinic; hypothyroidism 6.3%; no specific subtype correlation
Abdelghani et al., 2022	Egypt	Case-control	200	Subclinical hypothyroidism in 17% of pediatric migraine cases vs. 2% controls (p<0.001)
Mirouliaei et al., 2012	Iran	Quasi-experimental	25	Levothyroxine reduced headache frequency (17.64 to 1.2/month, p=0.0001) and severity in children
Tasnim et al., 2023	Australia	GWAS / MR	Population	Significant genetic correlation migraine-hypothyroidism; shared genes RERE, TGFB2, GADD45A
Li et al., 2024	China	MR (two-sample)	Population	Hypothyroidism causally linked to migraine without aura (OR 1.076; p=0.038) by MR analysis
Gözübatik Çelik et al., 2022	Turkey	Prospective cohort	155	61.2% of Hashimoto patients had headache; subclinical and overt hypothyroidism in 22% and 7.2%
Hagen et al., 2001	Norway	Population-based	Population	High TSH associated with low headache prevalence in women; migraineurs had lower TSH
Tietjen et al., 2007	USA	Retrospective cohort	223	Metabolic comorbidity cluster (Group 1) including hypothyroidism, hypertension, diabetes identified
Moreau et al., 1998	France	Cross-sectional	102	30% of hypothyroid patients had headache; 50% resolved within 2 weeks of levothyroxine
Togha et al., 2022	Iran	Cross-sectional	570	Hypothyroidism significantly associated with medication-overuse headache (p<0.05)

Table 2. Risk of Bias Assessment (ROBINS-I, NOS, and RoB 2)

Author, Year	Design	Tool	Domain 1	Domain 2	Domain 3	Risk of Bias
NOS - Case-control studies (D1: Selection | D2: Comparability | D3: Exposure)						
Rubino et al., 2019	Case-control	NOS	★★★★	★★	★★★ [9/9]	Low
Abdelghani et al., 2022	Case-control	NOS	★★★	★★	★★ [7/9]	Low
ROBINS-I - Cohort studies (D1: Confounding | D2: Selection bias | D3: Missing data)						
Martin et al., 2017	Cohort (prospective)	ROBINS-I	Low	Low	Low	Low
Nowaczewska et al., 2024	Cohort (retrospective)	ROBINS-I	Low	Moderate	Low	Low
Tietjen et al., 2007	Cohort (retrospective)	ROBINS-I	Moderate	Moderate	Low	Mode-rate
Lima Carvalho et al., 2017	Cohort (prospective)	ROBINS-I	Low	Low	Mode-rate	Low
ROBINS-I - Cross-sectional studies (D1: Confounding | D2: Selection bias | D3: Missing data)						
Filipchuk et al., 2022	Cross-sectional	ROBINS-I	Low	Low	Low	Low
Fernandez-Garza & Marfil, 2022	Cross-sectional	ROBINS-I	Moderate	Low	Low	Mode-rate
Spanou et al., 2020	Cross-sectional	ROBINS-I	Moderate	Moderate	Low	Mode-rate
Gözübatik Çelik et al., 2022	Cross-sectional	ROBINS-I	Low	Low	Low	Low
Togha et al., 2022	Cross-sectional	ROBINS-I	Low	Low	Low	Low
Moreau et al., 1998	Cross-sectional	ROBINS-I	Moderate	Moderate	Low	Mode-rate
Hagen et al., 2001	Cross-sectional (population)	ROBINS-I	Low	Low	Low	Low
RoB 2 - Quasi-randomized/experimental studies (D1: Randomization | D2: Deviations | D3: Missing data/outcome)						
Mirouliaei et al., 2012	Quasi-experimental	RoB 2	Some concerns	Some concerns	Low	Some conce-rns
Dev et al., 2023	Quasi-RCT	RoB 2	Some concerns	Low	Low	Some conce-rns
MR criteria - Mendelian randomization / GWAS studies (D1: IV relevance | D2: Independence | D3: Exclusion restriction)						
Tasnim et al., 2023	GWAS/MR	MR criteria	Relevant	Independent	Plausi-ble	Low
Li et al., 2024	MR (two-sample)	MR criteria	Relevant	Independent	Plausi-ble	Low

NOS = Newcastle-Ottawa Scale; ROBINS-I = Risk Of Bias In Non-randomized Studies of Interventions; RoB 2 = revised Cochrane Risk of Bias tool. NOS domains (case-control): Selection | Comparability | Exposure (max 9). ROBINS-I domains reported: Confounding | Selection bias | Missing data. RoB 2 domains reported: Randomization | Deviations from intended intervention | Missing data/outcome measurement. MR criteria: IV relevance | Independence | Exclusion restriction. ★ = NOS criterion met.

Results

Overview of Included Studies

Seventeen studies met inclusion criteria, published between 1998 and 2024, across nine countries (Italy, USA, Turkey, Brazil, Mexico, Poland, Greece, Egypt, India). Study designs included: cross-sectional (n = 7), case-control (n = 4), retrospective cohort (n = 3), prospective cohort (n = 2), and one quasi-randomized placebo-controlled trial. Sample sizes ranged from 25 (a quasi-experimental pediatric study) to 8,412 participants (a 20-year longitudinal cohort). The majority of participants were female, reflecting the demographics of both migraine and thyroid disease. Table 1 summarizes key characteristics and findings from each included study.

Prevalence of Hypothyroidism in Migraine

Across included studies, the prevalence of hypothyroidism in migraine patients consistently exceeded background population estimates, providing a robust epidemiological signal despite methodological heterogeneity. In clinic-based samples, overall hypothyroidism prevalence in headache patients ranged from 3.2% (episodic migraine in Mexico) to 15.9% (mixed migraine cohort in Poland), with higher estimates in samples specifically selected for thyroid dysfunction. The Italian case-control study by Rubino et al. (2019) found that lifetime migraine prevalence was 46% among patients with subclinical hypothyroidism, compared to only 13% in controls (OR 5.80; 95% CI 3.35-10.34; $p < 0.001$), an approximately 3.5-fold increased risk. Both migraine without aura and migraine with aura were significantly more prevalent in the subclinical hypothyroidism group. Importantly, this elevated migraine risk was independent of TSH levels and antithyroid antibody concentrations, suggesting that the TSH elevation itself - rather than a specific immunological marker - may be relevant to migraine susceptibility.

A consistent and clinically important gradient was observed between episodic and chronic migraine, with chronic migraine patients bearing a substantially higher hypothyroidism burden. This gradient is one of the most compelling findings in the literature, as it supports the hypothesis that thyroid dysfunction acts as a modifier of migraine course, potentially contributing to the transition from episodic to chronic migraine.

Filipchuk et al. (2022), in a specialized headache clinic in Argentina, found that treated hypothyroidism was present in 29.55% of chronic migraine patients versus only 8.96% of episodic migraine patients (OR 4.26; 95% CI 1.48-12.30; $p < 0.01$). Critically, this association persisted even in patients receiving stable levothyroxine replacement therapy, indicating that thyroid dysfunction may have lasting effects on migraine pathophysiology even after biochemical normalization of thyroid function. The authors proposed several possible explanations: the persisting free T4/T3 ratio imbalance in treated hypothyroid patients (since approximately 20% of circulating T3 derives from thyroid secretion rather than peripheral conversion), the potential role of calcitonin deficiency in hypothyroidism on chronic pain signaling, and the effect of deiodinase enzymes whose activity is modulated by the chronic inflammatory state characteristic of migraine.

Nowaczewska et al. (2024), conducting the largest study specifically examining Hashimoto's thyroiditis in migraine, enrolled 928 consecutive migraine patients at a Polish headache center. They found that 15.9% were diagnosed with hypothyroidism and 11.4% with Hashimoto's thyroiditis, substantially higher than general population prevalence. Patients with Hashimoto's thyroiditis had significantly more monthly migraine days (mean 9.17 vs. 7.94 days; $p = 0.020$), longer migraine disease duration (mean 19.68 vs. 15.52 years; $p < 0.001$), more cranial autonomic symptoms (24.5% vs. 8%; $p < 0.001$), and more frequent depression (23.6% vs. 12.9%; $p = 0.005$). In multivariate logistic analysis, Hashimoto's thyroiditis was associated with chronic migraine (OR 1.764; 95% CI 0.949-3.186; $p = 0.045$); the confidence interval marginally crosses 1.0, indicating a borderline statistically significant result that should be interpreted with caution. This association was assessed after controlling for medication overuse, migraine duration, and aura status. Notably, this is the first study to describe cranial autonomic symptoms as specifically more prevalent in migraine patients with comorbid thyroid disease. Cranial autonomic symptoms result from intense peripheral trigeminal activation and central sensitization. Their higher prevalence in Hashimoto-associated migraine may reflect a state of enhanced neuroinflammatory sensitization.

Fernandez-Garza and Marfil (2022), using the largest Mexican headache registry (PREMECEF, n = 869), reported an overall hypothyroidism prevalence of 4% in headache patients - higher than the 1.2% general population prevalence in Mexico - rising to 10.7% in chronic migraine specifically. The study also identified elevated hypothyroidism rates in cranial neuralgias: 6.3% in occipital neuralgia and 6.1% in trigeminal neuralgia, broadening the clinical relevance beyond migraine to encompass other primary headache disorders.

Spanou et al. (2020) found a 20.8% overall prevalence of thyroid disorders in 427 Greek headache clinic patients, with hypothyroidism present in 6.3% and Hashimoto's thyroiditis in 2.8%. Although no statistically

significant association between specific headache subtypes and specific thyroid diagnoses was identified - likely due to limited statistical power - the study demonstrated the high background burden of thyroid dysfunction in headache clinic populations and concluded that systematic thyroid screening in headache clinic attendees was warranted.

Gözübatik Çelik et al. (2022) examined 155 patients with established Hashimoto's thyroiditis and found that 61.2% had headache; among those with headache, 36.7% had primary headache disorders including migraine (21.1%), tension-type headache (17.9%), and new daily persistent headache (21.1%). The study also noted that 10 patients had been initially misdiagnosed with a primary headache disorder before hypothyroidism was recognized, underlining the risk of clinical misclassification when thyroid function is not assessed.

Togha et al. (2022) examined headache characteristics and comorbidities in 570 patients over 50 years of age at an Iranian headache center. Hypothyroidism was found in 44.4% of patients with medication-overuse headache - a rate significantly higher than in other headache groups ($p = 0.012$). This finding suggests that thyroid dysfunction may be particularly associated with chronic daily headache and medication overuse, adding a further dimension to the migraine chronification hypothesis.

The Tietjen et al. (2007) retrospective cohort study of 223 consecutive female migraine patients used cluster analysis to identify three distinct comorbidity constellations. Group 1 ($n = 55$, 24.7% of the cohort) was defined by the co-occurrence of hypertension, hyperlipidemia, diabetes mellitus, and hypothyroidism - a pattern closely resembling the metabolic syndrome. The identification of hypothyroidism as a member of this metabolic cluster supports the view that its association with migraine is part of a broader cardiometabolic phenotype in a subset of migraineurs, with potential implications for integrated clinical management.

An older but methodologically important Norwegian population-based study by Hagen et al. (2001) produced apparently contradictory findings: women with high TSH values had a lower prevalence of headache than those with normal or low TSH. However, this observation is compatible with the broader literature when interpreted carefully: among persons without a known history of thyroid dysfunction, elevated TSH may actually suppress headache through complex neuromodulatory mechanisms, while established hypothyroidism with reduced peripheral thyroid hormone availability impairs migraine-relevant neuromodulatory pathways.

Risk of New-Onset Hypothyroidism in Headache Patients

The longitudinal study by Martin et al. (2017) remains the most methodologically rigorous evidence for bidirectional causality. Using data from the Fernald Medical Monitoring Program - a 20-year prospective surveillance program of community residents - the authors tracked 8,412 participants without thyroid disease at enrollment, examining whether pre-existing headache disorders predicted the development of new-onset hypothyroidism.

Over the 20-year follow-up period (mean participation 12.6 years), new-onset hypothyroidism developed in 8.2% of headache disorder patients versus 6.2% of those without headaches. After adjustment for age, sex, BMI, smoking, narcotic use, and hypothyroidism-inducing medications, the hazard ratio (HR) for new-onset hypothyroidism was 1.21 (95% CI 1.001-1.462) for those with headache disorders. For patients with possible migraine specifically, the HR was 1.41 (95% CI 1.009-1.973), suggesting that migraine may be particularly predictive of subsequent hypothyroidism. This temporal precedence - headache predating thyroid dysfunction - challenges a purely unidirectional model where hypothyroidism causes headache, and supports a genuinely bidirectional relationship.

The authors proposed several mechanisms for this directional effect. Immune system alterations in migraine, including elevations in C-reactive protein, changes in T lymphocyte proportions, and cytokine dysregulation, could predispose to Hashimoto's thyroiditis. Anti-thyroid peroxidase antibodies are known to develop years before clinical hypothyroidism becomes biochemically apparent. It is plausible that the neuroinflammatory milieu of migraine accelerates this autoimmune process. Furthermore, studies on Hashimoto's encephalopathy have demonstrated anti-TPO antibodies in cerebrospinal fluid, raising the possibility that early autoimmune thyroid events could affect central nervous system function before hypothyroidism is detectable in serum.

Characteristics of Headache in Hypothyroid Patients

Lima Carvalho et al. (2017) conducted a detailed characterization of headache attributed to hypothyroidism (HAH) in 213 consecutive patients with newly diagnosed hypothyroidism, followed prospectively for 12 months. HAH was reported by 73 of 213 patients (34.3%), confirming the earlier estimate by Moreau et al. (1998). The clinical features described differed substantially from the current ICHD-3 criteria for HAH, which describes a bilateral, non-pulsatile, continuous headache. In the Brazilian cohort, the quality was pulsatile in 63%; duration was 4 to 72 hours in 78%; location was unilateral in 47%; nausea or vomiting

was present in 60%; and intensity was moderate to severe in 72%. These features overlapped substantially with migraine criteria.

A previous history of migraine was found in 53% of HAH patients, compared to 38% in hypothyroid patients without headache ($p < 0.05$). The prospective follow-up arm demonstrated that 78% of HAH patients showed clinically meaningful headache reduction following levothyroxine treatment, with no statistically significant difference in response rate between overt and subclinical hypothyroidism groups (82% vs. 68%, $p = 0.320$). This finding has two critical clinical implications: that even subclinical hypothyroidism may have sufficient impact on headache pathophysiology to warrant treatment; and that a substantial minority of hypothyroid headache patients do not respond to thyroid hormone replacement, presumably because their headache is driven by primary migraine pathophysiology rather than hypothyroidism per se.

Moreau et al. (1998), in the earliest series establishing the hypothyroidism-headache link, examined 102 patients with recent-onset hypothyroidism and found 30% had headache. Most resolved within two weeks of initiating thyroid hormone therapy, which the authors attributed to antinociceptive effects of thyroxine, including elevation of platelet serotonin, improved prostacyclin metabolism, and normalization of vasomotor activity.

Pediatric Populations

The association between migraine and subclinical hypothyroidism in children and adolescents has received increasing attention. Abdelghani et al. (2022) conducted a case-control study in Egypt comparing 100 children and adolescents with migraine with 100 age- and sex-matched controls. Subclinical hypothyroidism was found in 17% of migraine cases versus only 2% of controls ($p < 0.001$), a statistically compelling 8.5-fold increased prevalence. Moreover, subclinical hypothyroidism in migraineur children was associated with significantly greater migraine-related disability (PedMIDAS scores), with 53% of hypothyroid migraineurs having moderate disability and 29.4% having severe disability, compared to 29.6% and 11.1% respectively in migraineurs with normal thyroid function ($p = 0.004$).

The most compelling pediatric evidence for therapeutic benefit comes from Mirouliaei et al. (2012), who treated 25 children aged 5-15 years with migraine and subclinical hypothyroidism with levothyroxine for two months. Monthly headache frequency fell dramatically from a mean of 17.64 episodes per month to 1.2 ($p = 0.0001$), and headache severity scores decreased from 6.24 to 1.33 ($p = 0.001$). Response to levothyroxine was significantly better in children with migraine without aura compared to migraine with aura ($p = 0.03$), potentially reflecting different pathophysiological mechanisms in these subtypes.

The potential to reduce prolonged prophylactic migraine drug use in children - and thereby avoid adverse effects of valproate, topiramate, and other agents commonly used for pediatric migraine prophylaxis - provides an important argument for routine thyroid screening in children with refractory or frequent migraine, particularly those who are overweight or have a family history of thyroid disease.

Genetic and Mechanistic Evidence

Genetic Evidence

Tasnim et al. (2023) performed the most comprehensive genetic analysis to date, utilizing genome-wide association study (GWAS) summary statistics for migraine, hypothyroidism, hyperthyroidism, secondary hypothyroidism, TSH, and free thyroxine (fT4). Key findings included: (1) significant positive genetic correlation between migraine and hypothyroidism ($rg = 0.0608$); (2) significant genetic correlation between migraine and secondary hypothyroidism ($rg = 0.195$); (3) significant positive genetic correlation between migraine and fT4 ($rg = 0.0772$); (4) negative genetic correlation between migraine and hyperthyroidism ($rg = -0.1046$); and (5) identification of 17 novel genome-wide significant loci shared between migraine and hypothyroidism through cross-trait meta-analysis.

Among the shared genes identified, TGFB2 encodes transforming growth factor beta 2 with roles in immune regulation, vascular biology, and neural development. Its receptor TGFBR2 has been associated with vascular disease and identified as a susceptibility gene in clinic-based migraine GWAS. RERE encodes a nuclear receptor coregulator involved in retinoic acid signaling, development, and neurological function. GADD45A encodes a protein that responds to environmental stress by activating p38/JNK signaling pathways, which have been identified as contributors to pain initiation and maintenance. Pathway analysis of overlapping genes consistently highlighted immune system regulation as the most enriched functional category, consistent with the clinical observation that both migraine and Hashimoto's thyroiditis are characterized by immune dysregulation.

Li et al. (2024) applied two-sample Mendelian randomization to evaluate causal relationships between ten autoimmune diseases and migraine and its subtypes. Their IVW analysis found a positive causal association between hypothyroidism and migraine without aura (OR 1.076, 95% CI 1.004-1.152, p = 0.038), while autoimmune hyperthyroidism was causally associated with all migraine forms. Importantly, reverse MR analyses did not find significant evidence that migraine causes these autoimmune thyroid conditions, suggesting that the primary causal pathway may run from thyroid dysfunction to migraine.

Neurobiological Mechanisms

The biological basis for the migraine-hypothyroidism association involves at least three major pathways. First, thyroid hormones modulate pain threshold and central sensitization through multiple mechanisms. Thyroid hormone receptors are expressed in brain cortex and vasculature, meaning that thyroid hormone deficiency has direct central nervous system effects. At the serotonergic level, thyroid hormones regulate platelet serotonin content, which is reduced during migraine attacks - hypothyroidism may worsen this deficit. Thyroid hormones also modulate the hypothalamic-pituitary axis, whose function is closely linked to migraine susceptibility.

Second, shared immune dysfunction provides a compelling mechanistic framework, particularly relevant to the Hashimoto's thyroiditis-migraine link. Both conditions are associated with reduced CD4+CD25+ regulatory T-cell (Treg) populations, elevated pro-inflammatory cytokines including IL-6, IL-1β, and TNF-α, and altered T helper cell subsets. Regulatory T-cell dysfunction allows thyroid gland injury in Hashimoto's disease, and the same cellular defect has been found to modulate trigeminal sensitization in chronic migraine animal models. IL-17 levels are elevated in both Hashimoto's thyroiditis and migraine, and IL-17 can cross the blood-brain barrier, potentially amplifying neuroinflammation. The blood-brain barrier may also be compromised in autoimmune conditions, allowing peripheral inflammatory mediators and possibly anti-thyroid antibodies to access the central nervous system.

Third, metabolic and energetic pathways link thyroid function to migraine susceptibility. Migraine brains exhibit a characteristic mismatch between energetic supply and demand at the cortical level. Thyroid hormones are critical regulators of mitochondrial function and cerebral energy metabolism. Their deficiency could exacerbate the cortical energy deficit in migraineurs, lowering the threshold for cortical spreading depression. Additionally, deiodinase enzymes that interconvert thyroid hormones are regulated by inflammatory mediators, creating a potential feedback loop in which the neuroinflammation of migraine attenuates local thyroid hormone availability in the brain, even in the presence of normal circulating hormone levels.

Therapeutic Evidence

The quasi-randomized placebo-controlled trial by Dev et al. (2023) enrolled 87 adult patients with ICHD-3–defined episodic migraine and biochemically confirmed subclinical hypothyroidism at a tertiary center in India. Patients were quasi-randomized to receive levothyroxine 25 µg/day (n = 43) or placebo (n = 44) as add-on to standard migraine prophylaxis. At three months, statistically significant reductions were observed in the levothyroxine group versus placebo for: headache frequency (mean 1.67 vs. 3.28 days/month; p = 0.001), headache severity on VAS (mean 2.05 vs. 3.20; p = 0.001), MIDAS score (mean 6.30 vs. 8.45; p = 0.026), and MIDAS grade (mean 1.49 vs. 1.84; p = 0.029). At three months, 87% of treated patients had normal TSH on repeat testing - one progressed to overt hypothyroidism.

Lima Carvalho et al. (2017) reported prospective follow-up data on 64 hypothyroid patients with HAH treated with levothyroxine (50-100 µg/day) over 12 months. Overall, 78% experienced a clinically meaningful reduction in headache frequency or complete remission. Response rates were similar in overt hypothyroidism (68%) and subclinical hypothyroidism (82%), establishing that overt disease is not a prerequisite for therapeutic benefit.

The early landmark observation by Moreau et al. (1998) demonstrated headache resolution within two weeks of levothyroxine initiation in 50% of hypothyroid headache patients - a timeline consistent with rapidly reversible neurobiological effects. In the pediatric setting, Mirouliaei et al. (2012) demonstrated dramatic reductions in headache frequency and severity in children treated with levothyroxine for two months, consistent with adult data and suggesting that the thyroid-migraine mechanism is operative across the age spectrum.

Discussion

This review confirms a clinically meaningful and bidirectional association between hypothyroidism (including subclinical forms and Hashimoto's thyroiditis) and migraine. The evidence converges across epidemiological, clinical, genetic, and interventional study designs to suggest that the relationship is not merely coincidental but reflects shared biological mechanisms and mutual risk modification. The findings have substantive implications for clinical practice in both headache medicine and endocrinology.

From an epidemiological standpoint, the prevalence of hypothyroidism in migraine patients consistently exceeds population estimates by a margin that cannot be explained by chance or shared demographic characteristics alone. The gradient between episodic and chronic migraine is particularly informative: the markedly higher hypothyroidism prevalence in chronic migraine suggests that thyroid dysfunction may play a role in migraine progression rather than simply co-occurring incidentally. This is supported by the prospective Polish cohort showing that Hashimoto's thyroiditis patients with comorbid migraine have more migraine days per month, more medication overuse, more autonomic symptoms, and greater depression rates. Medication overuse headache appearing at higher rates in hypothyroid patients further underscores the clinical burden of this comorbidity.

The longitudinal evidence from Martin et al. (2017) adds a critical temporal dimension, establishing that pre-existing headache disorders predict future hypothyroidism development with a 21-41% increased hazard, adjusting for established risk factors. This bidirectional temporal relationship supports the concept of mutual biological vulnerability rather than a simple cause-and-effect model. If a patient presents with new-onset hypothyroidism, clinicians should actively inquire about headache history and current burden. Conversely, patients with progressive migraine should be evaluated for evolving thyroid dysfunction.

The three biological pathways - serotonergic and pain-threshold modulation, shared immune dysregulation, and overlapping genetic architecture - converge to suggest that the comorbidity is mechanistically grounded. Of particular translational interest is the immune pathway: if dysregulated Treg activity and elevated inflammatory cytokines underlie both Hashimoto's thyroiditis and migraine chronification, immune-modulating interventions may warrant investigation as shared therapeutic targets. This opens a potentially novel treatment paradigm for patients with migraine refractory to conventional prophylactics who harbor underlying autoimmune thyroid disease.

The debate in the literature regarding the strength and specificity of the association largely stems from methodological heterogeneity. Studies vary widely in population selection (clinic-based versus population-based), headache definition (self-report versus ICHD-validated), thyroid assessment method (TSH alone versus full thyroid panel including anti-TPO antibodies and fT4), and follow-up duration. Some apparently contradictory findings - such as the Hagen et al. (2001) observation that high TSH is associated with low headache prevalence - can be reconciled when the distinction between asymptomatic TSH elevation and established symptomatic hypothyroidism is made.

The therapeutic evidence, while still limited, is clinically promising. The quasi-randomized trial by Dev et al. (2023) demonstrates meaningful reductions in headache frequency, severity, and disability scores following low-dose levothyroxine in adults with comorbid subclinical hypothyroidism and migraine. Given the safety profile of levothyroxine at replacement doses, the low cost of TSH testing, and the potential for meaningful headache reduction, the risk-benefit calculus for screening and treating subclinical hypothyroidism in refractory migraine patients appears favorable.

One emerging clinical consideration is the finding by Filipchuk et al. (2022) that hypothyroidism burden remains elevated in chronic migraine patients even when they are on stable levothyroxine therapy. This suggests that the association may not be fully reversible with biochemical thyroid normalization, perhaps because thyroid replacement therapy results in a different free T4/T3 ratio than native thyroid production, or because the underlying autoimmune process driving Hashimoto's thyroiditis continues to generate neuroinflammatory signals independent of hormone levels. These observations argue for attention to the autoimmune dimension of the comorbidity - potentially warranting anti-TPO antibody testing even in patients already on levothyroxine.

Conclusion

Hypothyroidism and Hashimoto's thyroiditis represent clinically important comorbidities in migraine patients, with the relationship appearing bidirectional, biologically plausible, and therapeutically relevant across multiple study designs and populations. The prevalence of hypothyroidism in migraine patients substantially exceeds population baselines and is highest in patients with chronic migraine. Among individuals with established hypothyroidism, approximately one-third will have headache as a prominent symptom, with features frequently overlapping with migraine criteria. The development of new-onset hypothyroidism is significantly more likely in individuals with pre-existing headache disorders, establishing temporal bidirectionality.

Levothyroxine treatment reduces headache frequency, severity, and disability in patients with subclinical hypothyroidism comorbid with migraine, suggesting a meaningful and potentially reversible therapeutic target. This benefit is present in both overt and subclinical hypothyroidism, and in both adults and children.

Based on the accumulated evidence, neurologists and headache specialists should consider routine assessment of thyroid function - including TSH, free T4, and anti-TPO antibodies - in patients with refractory, progressive, or chronic migraine, particularly women. Endocrinologists managing hypothyroid patients should similarly screen for and address headache comorbidity. Larger randomized controlled trials with standardized outcome measures are needed to firmly establish screening and treatment guidelines, and to determine whether treatment of subclinical hypothyroidism alters the long-term natural history of migraine.

Limitations and Future Studies

Several limitations of the present review must be acknowledged. First, the heterogeneity of included study designs, populations, diagnostic criteria, and outcome measures precluded meta-analysis, limiting quantitative synthesis. The included studies spanned cross-sectional, case-control, cohort, and quasi-experimental designs, each with different susceptibilities to bias. Second, the majority of evidence derives from cross-sectional studies, which by design cannot establish causal direction. Third, the only available randomized trial (Dev et al., 2023) used a quasi-randomized design, a low fixed levothyroxine dose not adjusted for weight, and a relatively short three-month follow-up. Fourth, many studies did not assess anti-TPO antibody status, precluding definitive characterization of the Hashimoto's-specific contribution. Fifth, publication bias may inflate the observed associations. Sixth, most included studies were conducted in clinic-based populations, which likely overestimate the prevalence of comorbidities compared to general population samples. Seventh, this review was not prospectively registered in PROSPERO or a comparable systematic review registry prior to data collection, which represents a methodological limitation and precludes verification that eligibility criteria and outcomes were not modified after data extraction.

Future studies should prioritize: (1) large, well-powered randomized controlled trials of levothyroxine in migraine patients with subclinical hypothyroidism, using weight-based dosing, standardized ICHD-3 migraine outcomes, and follow-up of at least 12 months; (2) prospective longitudinal studies examining the temporal relationship between thyroid dysfunction and migraine course; (3) systematic inclusion of anti-TPO antibody assessment alongside TSH and fT4; (4) investigation of whether optimizing T3 levels or combination T4/T3 therapy yields superior headache outcomes; (5) study of immune biomarkers (regulatory T-cells, CGRP, inflammatory cytokines) in migraine patients stratified by thyroid status; (6) examination of whether screening and treating subclinical hypothyroidism reduces the risk of migraine chronification; and (7) extension of evidence to ethnically diverse populations.

Conflicts of Interest: No conflicts of interest to declare.

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