Thyroid Dysfunction in Ménière's Disease: A Comprehensive Review

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Keywords

Autoimmune · Hypothyroidism · Ménière's disease · Otology · Sensorineural hearing loss · Thyroid · Update

Abstract

Introduction: The precise etiology of Ménière's disease (MD) remains unknown; however, given the association of MD with serum antibodies and human leukocyte antigen (HLA) complex, several studies have proposed a relationship between MD and thyroid disorders. Similarly, multiple hypotheses exist regarding the metabolic disturbances of fluctuating thyroid hormone as a potential contributing agent in the development of MD. **Methods:** A total of 171 abstracts were identified and screened by 2 independent reviewers. Based on inclusion and exclusion criteria, 8 studies were selected for final analysis. Due to heterogeneity of clinical data, meta-analysis was not feasible. **Results:** The prevalence of autoimmune thyroid disease and hypothyroidism in MD varied significantly from 1 to 38%. Notable bias was introduced given the lack of standardization of diagnostic criteria across studies. Articles that described autoimmune thyroid-specific antibodies and HLA types also presented inconclusive results. Multiple studies noted a potential etiologic role of hypothy-

roidism in MD, which was often confounded by thyroxine supplementation. **Conclusions:** Despite a potential correlation in the medical literature between thyroid disorders and MD, there is currently no definitive causal relationship. Although most of the present medical literature focuses on autoimmunity, dysregulated thyroid hormone levels may also be implicated in the association of MD with thyroid disorders.

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Introduction

Ménière's disease (MD) is an inner ear disorder that manifests as episodic vertigo, fluctuating hearing loss, tinnitus, and aural fullness. Characteristics of MD include a typical age of onset from the fourth to fifth decades, female predominance, and predilection for those of Northern European descent [1, 2]. Histopathologic confirmation of MD can only be performed postmortem but classically demonstrates endolymphatic hydrops [3].

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Currently, the precise etiology of the disrupted regulation of endolymphatic fluid remains unknown and may be due to multiple factors including metabolic disorders, hormone dysfunction, psychological factors, and immunologic disease [4, 5]. Specifically, autoimmunity as a potential causative factor of MD is strongly supported in the medical literature [6–8].

Evidence supporting the role of autoimmunity in MD patients includes a positive steroid response, serum inner ear antigen antibodies, and circulating immune complexes [9, 10]. Furthermore, MD has been associated with several autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, autoimmune hypothyroidism, and psoriasis [11]. Several studies have also proposed a specific relationship between MD and autoimmune thyroid disease (TD) due to a significantly higher prevalence of antithyroid autoantibodies in MD [12, 13]. However, debate exists as to whether the dysregulated metabolic state in hypothyroid patients serves alone as a separate etiology of MD, unrelated to autoimmunity. Given these prior research efforts, the goal of this work was to perform a systematic review of the medical literature and evaluate evidence on the prevalence of thyroid autoimmunity and the role of dysregulated thyroid hormone levels in MD.

Materials and Methods

This study was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol and exempt from Institutional Review Board Review at Penn State Milton S. Hershey Medical Center [14]. Independent searches of PubMed and MEDLINE databases were performed on June 21, 2018, by 2 separate authors to validate studies which described both thyroid disorders and Ménière's disease using the Boolean method and relevant search term combinations, that is, "thyroid" and "Ménière's disease." All languages were included in the search algorithm, but only English studies were selected for final analysis [15]. Full-length original articles were assessed for data extraction eligibility and screened by 2 independent reviewers. Duplicated articles and abstracts were excluded, along with non-English (4), nonfull text (1), not Ménière's disease (4), and not thyroid disorders (2). A qualitative synthesis of the available studies was employed to integrate study results (Fig. 1).

Results

Inclusion Criteria and Study Design

A total of 171 abstracts were identified via the employed search strategy. Based on inclusion and exclusion

Fig. 1. Search strategy protocol.

criteria, 8 retrospective studies were selected for final analysis [5, 16–18]. Four of 8 studies, including the 3 most recently conducted studies, characterized MD using criteria of AAO-HNS Subcommittee on Equilibrium and its Measurement (Table 1) [5, 19–21]. In addition to using clinical symptomatology, neuro-otological evaluation (sensorineural hearing impairment, SISI score, ABLB, stapedial reflex decay, Bekesy audiometry, tone decay test, and ENG) was performed in half of the studies.

In order to determine the effect of thyroid and allergy treatment on MD symptom control, Powers et al. [5] evaluated 98 MD patients with FTA-ABS, neuro-otological, allergic, and metabolic studies including T4 free index test and T4 serum-bound test. Kinney et al. [15] identified 180 out of 384 total MD patients from May 1976 through May 1979 that had thyroid screening as part of their MD workup. The authors used the classification of Arenberg and Stahle for hearing stage determined by pure-tone average.

Karjalainen et al. [17] compared 91 MD patients to 149 osteosclerotic patients in regard to carbohydrate and lipid metabolism. Meyerhoff et al. [16] retrospectively reviewed 211 patients with MD symptoms in regard to clinical symptomatology, diagnostic testing, and laboratory abnormalities. Both Karjalainen et al. [17] and Meyerhoff et al. [16] used formal audiological and vestibular testing for the diagnosis of MD.

Evans et al. [18] screened serum of 164 patients diagnosed with classic MD, although with unspecified diagnostic criteria, for autoantibodies (thyroglobulin and antithyroid microsomal), immune complexes, and human leukocyte antigen (HLA) status. Brenner et al. [19] performed a retrospective case-control study with 50 MD pa-

Table 1. Study design of reviewed articles

	Author	Year	Country	MD cases	TD cases	Control group	MD diagnostic criteria	MD evaluation	Type of TD associated with MD	TD evaluation
1	Powers et al. [5]	1978	USA	98	26	None	AAO-HNS	Neuro-otological evaluation	Hypothyroidism	Serum cholesterol T ₄
2	Kinney et al. [15]	1980	USA	180	2	None	Arenberg and Stahle hearing stage	MD symptoms Ménière's pure-tone average	Hypothyroidism	Lipid profile T ₃ and T ₄ TSH
3	Meyerhoff et al. [16]	1981	USA	211	1	None	Not specified	Neuro-otological evaluation Glycerol test	Hypothyroidism	TSH T ₃ and T ₄
4	Karjalainen et al. [17]	1984	Finland	91	0	149 (otosclerosis)	Not specified	Neuro-otological evaluation	None	Serum cholesterol TSH T ₃ and T ₄
5	Evans et al. [18]	1988	England	164	(17%)	None	Not specified	Not specified	Autoimmune thyroid disease (antithyroid microsomal)	Antithyroid microsomal antibody HLA status serum autoantibody Serum immune complexes Thyroglobulin antibody
6	Brenner et al. [19]	2004	USA	50	16	50 (isolated dizziness)	AAO-HNS Kitahara	Audiogram MD symptoms	Hypothyroidism	History of autoimmune diseases Thyroid hormone supplementation
7	Fattori et al. [20]	2008	Italy	50	19	82 (healthy 50 (acute vestibulopathy))	AAO-HNS	Neuro-otologic evaluation	Autoimmune thyroiditis	Antithyroid microsomal antibody HLA
8	Santosh et al. [21]	2016	India	35	12	None	AAO-HNS Kitahara	Audiogram Unterberger test	Hypothyroidism	T ₃ and T ₄ TSH

MD, Ménière's disease; TD, thyroid disease; HLA, human leukocyte antigen.

tients and 50 matched control patients. Participants were contacted using phone interviews to evaluate for hypothyroidism or a history of systemic autoimmune disease.

Fattori et al. [20] compared 50 MD patients to 2 matched control groups (healthy individuals and acute unilateral peripheral vestibulopathy patients) and collected HLA and antithyroid titers. Cochlear-vestibular function was assessed with audiometry, and VNG analysis performed during acute attacks of vertigo. Last, Santosh et al. [21] evaluated 35 MD patients using audiogram and assessed the subjective rate of symptom improvement after 3 weeks, 3 months, and 6 months of thyroxine supplementation.

Prevalence of Thyroid Disease in MD

Of the 8 included studies, 5 studies concluded MD correlated with TD. Powers et al. [5] and Evans et al. [18] both discovered a 17% prevalence of MD patients associated with nonmyxedematous hypothyroidism and autoimmune TD, respectively (Table 2) [5, 18]. Brenner et al. [19], Santosh et al. [21], and Fattori et al. [20] reported a prevalence of hypothyroidism and autoimmune thyroiditis ranging from 32 to 38% [19–21]. Brenner et al. [19] found that 32% (16 of 50) of MD patients were taking thyroid hormone supplementation compared to controls. Among MD patients taking thyroid hormone supplementation versus MD patients not taking thyroid hormone supplementation, Brenner et al. [19] concluded that there was no significant difference in the prevalence, severity, or pattern of hearing loss and found that 4 of 16 patients with corrected hypothyroidism had other systemic autoimmune diseases.

Several studies, however, did not demonstrate this relationship. Kinney et al. [15] found that of 168 patients who underwent a lipid profile, 104 patients (62%) had elevated cholesterol and/or triglyceride levels, but only 2 MD patients were found to have hypothyroidism. Meyerhoff et al. [16] found that out of 211 MD patients, only 1 patient had abnormal thyroid studies. Finally, Karjalainen et al. [17] demonstrated that of 91 MD patients after a 12-h fast, 15% of patients had hyperlipidemia, but 0 patients demonstrated abnormal thyroid studies.

MD Management: Thyroid Hormone Supplementation

Multiple studies have noted a potential etiologic role of hypothyroidism in MD, which is often confounded by thyroxine supplementation [5, 19, 21]. Powers et al. [5] found that MD symptoms were controlled with elimination of vertigo and hearing improvement in 3% of pa-

tients with thyroid hormone replacement alone which increased to 14% in combination with endocrine or allergy treatment for 17 months (Table 2) [5]. Kinney et al. [15] found that dietary management was the most effective method of management in 65% of MD patients with hyperlipidemia, specifically types II and IV.

Brenner et al. [19] found that 16 of 50 MD patients (32%) were taking thyroid hormone supplements compared to 2 (4%) of the 50 controls and that age was directly correlated with MD patients taking thyroid hormone supplementation. A significant difference was also noted between 5 of 26 MD patients (19%) younger than 60 years of age taking thyroid hormone supplementation compared to the 11 of 24 patients (46%) MD patients 60 years of age and older [19].

Santosh et al. [21] identified 12 of 35 MD patients treated with thyroxine supplementation and evaluated symptom improvement at 3 weeks, 3 months, and 6 months. After 12 weeks of treatment, subjective improvement in all symptoms, including vertigo, tinnitus, sensorineural hearing loss, and aural fullness, was appreciated in all cases of hypothyroidism and MD. Elevated TSH levels were also noted in all 12 hypothyroid MD patients who became euthyroid after medical treatment. In addition, mean vertigo score for rotatory sensation, tinnitus, aural fullness, and hearing loss was reduced, and a normal Unterberger test was found in all patients after 12 weeks of thyroid hormone supplementation. The mean improvement in vertigo scores before and after 12 weeks of treatment was a change of 1.42–0.5 for rotation, 1.5–0.5 for tinnitus, 1.33–0.67 for aural fullness, and 2–1.33 for hearing loss.

Serological Testing

Evans et al. [18] and Fattori et al. [20] were the only 2 studies that performed autoimmune serological testing. Evans et al. [18] found that 73 of 150 MD patients had 1 autoantibody, specifically 23.3% antinuclear, 17% antithyroid microsomal, and 13% smooth muscle (Table 2) [18]. Roughly 50% of patients had more than 1 antibody in both groups. Further testing indicated that 53 MD patients had the HLA Cw7 antigen. Furthermore, the HLA Cw7-positive group had significantly elevated IgM and C1q levels of immune complexes as well as significantly lower levels of IgA than controls. Overall, increased antithyroid microsomal and antinuclear antibodies were mainly found in MD patients 40–60 years of age.

Fattori et al. [20] found that 38% of MD patients had elevated serum antithyroid autoantibodies compared to 7% in healthy controls and 12% in non-MD vestibulopa-

Table 2. Study characteristics of Ménière's disease and thyroid disorders

	Author	Year	MD, N	TD, N	Mean age	Gender (F:M)	Bilateral MD	Thyroid disorder	Point prevalence	Laboratory studies	Treatment	Response
1	Powers et al. [5]	1978	98	26	n/a	n/a	n/a	Hypothyroidism (metabolic dysfunction)	17%	Low protein-bound iodine test Low T3 resin uptake Cholesterol levels	100% thyroid hormone supplementation	3% with thyroid hormone supplementation 14% thyroid hormone supplementation or allergy treatment
2	Kinney et al. [15]	1980	180	2	41–60	1:1	34%	Hypothyroidism	1%	Cholesterol levels (62% high) T4 (1% low)	100% thyroid hormone supplementation	15% was not adequately controlled by metabolic deficiency correction/therapy
3	Meyerhoff et al. [16]	1981	211	1	47	1.3:1	12%	Hypothyroidism	0.5%	T3 and T4 (0.5% low)	n/a	n/a
4	Karjalainen et al. [17]	1984	91	0	49	1.1:1	17%	None	0%	TSH T3 and T4 (0% abnormal)	n/a	n/a
5	Evans et al. [18]	1988	150	(17%)	Cw7(+) 48.8, Cw7(–) 46	n/a	n/a	Autoimmune (antithyroid microsomal)	17%	ANA (23.3%) Clq IgA complexes IgM complexes TPO-Ab HLA Cw7 antigen (65.3%)	n/a	n/a
6	Brenner et al. [19]	2004	50	16	n/a	n/a	n/a	Hypothyroidism	32%	Autoimmune disease (25%)	32% thyroid hormone supplementation	No difference in hearing loss severity or prevalence
7	Fattori et al. [20]	2008	50	19	47.4±12.8	1.3:1	6%	Autoimmune (antithyroid microsomal)	38%	TPO-Ab (68.4%) TPO-Ab + TR-Ab (10.5%) Tg-Ab, TPO-Ab + Tg-Ab (5.2%)	16% thyroid hormone supplementation	n/a
8	Santosh et al. [21]	2016	35	12	n/a	n/a	75%	Hypothyroidism	34%	TSH T3 and T4	34% thyroid hormone supplementation	Euthyroid for TSH and T3 No change in T4

thy (Table 2). Out of the 19 MD patients with high antibody titers, 68.4% had only thyroid peroxidase antibodies, 10.5% had only thyroglobulin antibodies, 15.8% had thyroid receptor antibodies, and 5.2% had both thyroid peroxidase and thyroglobulin antibodies. Of the 50 MD patients, 8 were previously treated with thyroid supplementation, and 6 of these patients had an elevated anti-thyroid antibody. Furthermore, there was no relationship between the severity of hearing loss measured by PTA and autoantibody titers, suggesting a lack of an association between overall disease severity of MD and autoimmune thyroiditis.

Discussion

Out of the 8 included studies, 5 found an association between hypothyroidism and MD [5, 18–21]. Case reports suggesting control of hearing impairment with thyroid hormone supplementation date back to the 1950s [22]. Godlowski et al. [23] first proposed hypometabolism as a potential factor in MD. Spencer et al. [24] concluded that a significantly high incidence of abnormal lipid metabolism occurs in MD. Powers et al. [5] further developed this hypothesis specifying that nonmyxedematous hypothyroidism may be associated with MD along with hyperglycemia, hyperlipidemia, and hypoadrenal dysfunction [15]. Improvement in MD symptoms after thyroid hormone supplementation suggests that thyroid hormone dysfunction and related metabolic disorders may account for a reversible onset of endolymphatic hydrops and a potential subset of MD patients [19, 21, 25, 26].

Conversely, 3 studies did not find a strong association between hypothyroidism and MD, suggesting TD screening and metabolic function tests may not be useful or cost-effective measures in patients without a history specifically concerning for these select disorders [15–17]. Kinney et al. [15] recommended dietary management of hyperlipidemia and abnormal carbohydrate metabolism rather than thyroid hormone replacement due to the higher correlation between MD and hyperlipidemia. Although Kinney et al. [15], Meyerhoff et al. [16], and Karjalainen et al. [17] involved large patient populations ranging from 81 to 180 MD patients, these studies were performed before the discovery of autoimmune thyroid laboratory studies, including autoantibody titers, complement, or immune complexes. Furthermore, some MD patients in these studies were already taking thyroid hormone supplementation and likely achieving a euthyroid state.

Fattori et al. [20] concluded a significant relationship between thyroid autoimmunity and MD, hypothesizing an immune response in the form of autoantibodies against inner ear antigens [10, 27, 28]. Fattori et al. [20] also noted that the pendrin protein associated with Pendred syndrome may be a target for autoantigens as it is expressed in both thyroid and inner ear cells. Hadj et al. [29] further extrapolated and indicated that Pendred syndrome may predispose patients to autoimmune TD. Previous studies have found antibodies in MD against ganglion cells, anti-collagen II, and antiphospholipid. Fattori et al. [20] further discussed that pendrin, associated with Pendred syndrome, may be a target for an autoantigen as it is expressed in both the thyroid gland and inner ear. Additionally, Fattori et al. [20] suggested that autoantibodies in MD may predispose patients to other autoimmune diseases and manifest clinically as polyendocrine syndrome including multiple gland autoimmune syndromes [30]. For example, Hashimoto's thyroiditis has been seen in multiple gland autoimmune syndromes such as systemic lupus erythematosus, pernicious anemia, and rheumatoid arthritis [31, 32]. A higher prevalence of antithyroid autoantibodies in MD patients than healthy controls has been previously documented.

Evans et al. [18] discussed the possibility of humoral immunity based on increased IgM levels in circulating complexes and high levels of complement. Elevation of these serum proteins is comparable to other autoimmune diseases like systemic lupus erythematosus and polyarteritis nodosa, which can be associated with sensorineural hearing loss and vestibular dysfunction [33, 34]. It has also been hypothesized that inflammatory mediators may lead to capillary vasodilation and complex aggregation in the inner ear capillaries due to the presence of various inner ear antigens such as type II collagen and heat shock protein 70 [35, 36]. More recent antibodies studied include MP0-antibodies, antiphospholipid antibodies, and sialyl-I ganglioside antibodies [37–39]. Conflicting studies on the role of circulating immune complexes have indicated further studies are necessary [40, 41]. With regard to genetics, polymorphic host cell factor 1 gene may affect herpes simplex virus reactivation based on the association between polymorphic host cell factor 1 gene and a reduced risk of MD [42]. MD has also been linked to the *PTPN22* gene 1858C/T polymorphism and may play a role in T-cell function [43]. Additionally, symptomatic improvement after oral and intratympanic glucocorticoids in MD suggests an autoimmune relationship; however, these therapies may only be effective in certain MD patients [44]. Although these studies together suggest a

possible immune etiology of MD, additional research efforts are necessary to determine the role of thyroid autoimmunity in the formation of endolymphatic hydrops.

Notable bias was introduced given that many studies lacked uniform standardization of diagnostic criteria and clinical data reporting. The lack of absolute guidelines for MD makes it challenging to compare studies over time. In addition, methodology between studies, including reporting serologic or metabolic laboratory tests, varied greatly when comparing MD patients to control groups. Thus, given the significant variability in the data collected from each study, meta-analysis was not able to be performed. Furthermore, the low sample size across studies was a consistent limitation of the included articles, which is a challenge when evaluating uncommon clinical disorders like MD.

Conclusion

It has been suggested that studies correlating autoimmune TD and MD lack replication and consistent identification of a single antibody or HLA complex. Although the studies included in this review suggest a possible autoimmune etiology of MD, additional clinical data are necessary to determine the role of thyroid autoimmunity and hypothyroidism in the development of endolymphatic hydrops. Moreover, further research efforts are needed to validate a common susceptibility factor in MD and autoimmune thyroid disorders and distinguish whether a relationship is secondary to a common immunologic agent or metabolic and hormonal derangements. Thus, it is possible that multiple etiologies of MD could be further classified into different subtypes such as spo-

radic, familial, autoimmune, and metabolic. Additional studies are necessary to delineate autoimmune and metabolic relationships in MD; however, it is possible that different etiologies of MD exist and further subtype classification may be necessary.

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Statement of Ethics

The authors have no ethical conflicts to declare as this is a systematic review.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study concept and design: Patel, Isildak, and Saadi. Acquisition and analysis of data: Patel, Isildak, and Saadi. Interpretation of data: Patel, Liaw, Hwang, Isildak, and Saadi. Drafting of the manuscript: Patel, Liaw, Hwang, Isildak, and Saadi. Critical revision of the manuscript for important intellectual content: Patel, Liaw, Hwang, Isildak, and Saadi. Study supervision: Isildak.

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