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# The theory of autoimmunity in Meniere's disease is lacking evidence

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## ABSTRACT

The role of immunological factors in the pathophysiology of Meniere's disease (MD) has been hypothesized. In order to evaluate the current level of evidence on autoimmunity in MD, original articles relevant to the matter (1970–2016) were reviewed. The following has been considered to support the theory of autoimmunity in MD (1) the increased prevalence of autoimmune diseases among MD patients, (2) the elevated levels of antibodies and immunocomplexes in MD patients, (3) the association of MD with HLA-types and genetic polymorphisms and (4) the positive corticosteroid-responsiveness detected in some MD patients. However, all studies have been small and lack positive replication. Studies concerning antibodies, HLA types and genetic polymorphisms have produced conflicting results and no single antibody, HLA type or polymorphism has been found in all or even in a significant subpopulation of MD patients. No convincing basic research evidence of autoimmunity in MD exists hence the field needs further study.

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## 1. Introduction

Meniere's disease (MD) is an inner ear disorder characterized by episodes of rotational vertigo, fluctuating sensorineural hearing and tinnitus [1]. Other symptoms may include aural fullness in the affected ear and drop attacks [2]. The etiology of the disease is unknown. Endolymphatic hydrops (EH), a reaction leading to a fluid overload of the inner ear [3], has been vigorously studied in recent years after the development of inner ear imaging techniques [4]. Although EH is the most consistent histopathological finding in patients with MD, the causal relationship between EH and MD has not been proven and the disease mechanism remains unknown.

There is evidence that the inner ear is immunologically active [5,6]. Immunoglobulin and white blood cell deposition in the region of the endolymphatic sac has been detected, and the endolymphatic sac is surrounded by a dense network of lymphatics [5]. Animal experiments have shown that the endolymphatic sac is capable of generating an immune response [7].

There has been a growing amount of research on the role of autoimmunity and immunological mechanisms in the development of MD. In autoimmunity, immune responses are directed against the host's own cells and tissues [8]. It has been hypothesized that structures of inner ear tissue could act as autoantigens, i.e., targets of the host's own immune system [9]. Immune responses may be cellular involving activation of phagocytes and antigen-specific T-lymphocytes, or humoral involving the production of antibodies by plasma cells derived from B-cells of the immune system in response to an antigen [9,10].

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The etiology of the loss of normal self-tolerance in an autoimmune disease is considered multifactorial with associated genetic, environmental, hormonal and immunological factors; all previously studied in MD. Stress has also been suggested as a triggering factor of autoimmune reactions [11]. Due to this theory of immunological background in MD, treatments involving the use of steroids and other immunosuppressants have gained popularity. The purpose of this review is to evaluate the current evidence of autoimmunity in Meniere's disease, and to summarize these findings.

## 2. Methods

In order to review the scientific evidence supporting autoimmunity in MD, PubMed, Ovid Medline and Cochrane reviews databases were searched using the following key words: Meniere's disease and autoimmunity/autoantigen/auto-antibodies. The search was limited to original articles; English language and publication date from 1970–November 2016. A total of 78 original articles published in international journals were included to this review. This review focuses on the findings of basic research. Studies on the effect of glucocorticoids in the treatment of MD are not reviewed in detail; although they are briefly mentioned.

## 3. Epidemiological evidence of autoimmunity in Meniere's disease

MD has been linked to autoimmune diseases in a few large epidemiological studies. Gazquez et al. reported an increased prevalence of systemic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis in a large cohort of 690 Spanish MD patients compared to the general population [12]. Tyrrell et al. observed an increased prevalence of autoimmune hypothyroidism, psoriasis and autoimmune diseases in general in a large cross-sectional data set from the UK Biobank including 1376 MD patients and over 500 000 controls [13]. An increased prevalence of autoimmune diseases has been observed in a smaller set of familial MD patients [14]. Immunoglobulin E mediated allergy has also been proposed as a possible cause in some MD cases since an increased frequency of allergy has been reported by several studies [15–17]. Derebery et al. have also reported improvement in symptoms of MD after treating

for inhalant and food allergens [18]. As autoimmune diseases have been observed to co-occur in individuals and families, the concomitant occurrence of immune-mediated diseases is considered to support the possibility of an immunological origin of MD [19]. Similarly to many known autoimmune diseases, MD has a fluctuating natural course, which results in a slow progressive deterioration of the affected organ [20]. However, negative results concerning autoimmunity, allergy and Meniere

disease have also been reported [21–23].

## 4. Antibodies and Meniere's disease

Antibodies, or immunoglobulins, are glycoproteins produced by plasma cells that are part of the humoral immune system. Antibodies identify and neutralize foreign objects and extracellular microorganisms, such as bacteria and viruses, by recognizing a certain part or molecular structure of the foreign target, called an antigen [10].

### 4.1. Collagens

Collagens are the main structural proteins in various tissues and the basement membranes [24]. Studies have shown that type II, IV and IX collagens are widely expressed in the inner ear and are considered as important components of ear tissue [25,26]. It has been hypothesized that an autoimmune reaction against inner ear antigens, such as type II collagen, could cause damage in inner ear tissues and lead to MD [9,27]. A number of studies concerning collagen autoimmunity and MD have been performed (Table 1).

In animal studies an idiopathic endolymphatic hydrops (EH) was induced with an immune response to type-II collagen [28]. However, another group was not fully able to reproduce these results [29] since less extensive changes in the threshold shift, and in the histopathological findings, such as endolymphatic hydrops, vasculitis and spiral ganglion degeneration, were reported. No pathology in the stria vascularis or in the organ of Corti was detected. However, evidence of possible immunoglobulin deposition in the inner ear structures was present [29].

**Table 1**  
Collagen antibodies in MD patients.

Reference	Subjects	Controls	Studied collagens	Main result	p-value
Yoo et al. [30]	12	10	II	IL of anti-CII	<0.025
	17	16	I, IV	negative	NM
Herdman et al. [34]	37	20	I, II	negative	>0.05
Tomoda et al. [9]	18	10	II	IL of anti-CII both in sera and endolymph	NM
Fattori et al. [35]	45	25	I, II, V, laminin	negative	NM
Yoshino et al. [27]	29	22	II	IL of anti-CII	<0.01
Lopez-Gonzalez et al. [33]	9	31	II	negative	NM
Yoo et al. [31]	108	28	II	IL of anti-CII	NM
Koo et al. [32]	41	46	II	IL of anti-CII	0.002

IL = increased levels, NM = not mentioned.

anti-CI, -CII, -CIV, -CV = collagen I, II, IV, V antibodies respectively.

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