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Association between osteoporosis and otosclerosis in women

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Abstract

Similarities between osteoporosis and otosclerosis have been noted, including a similar association with the COL1A1 gene. Herein, the authors explore the possible clinical relationship between these two common disorders of bone.

In this retrospective study, the medical charts of 100 women aged 50 through 75 years who had undergone stapedectomy for otosclerosis were reviewed and the prevalence of osteoporosis in these women was noted. Similarly, the prevalence of osteoporosis was determined in a control group of 100 women aged 50 to 75 years with presbycusis.

Fifteen of 100 women with otosclerosis had a concomitant diagnosis of osteoporosis as compared with four of 100 women with presbycusis, yielding a significant clinical association ($p = 0.007$) between otosclerosis and osteoporosis.

This study suggests an association between otosclerosis and osteoporosis, providing impetus and justification for future prospective clinical studies and related research.

Key words: Otosclerosis; Osteoporosis; Collagen Type 1; Genes

Introduction

Otosclerosis is a bone disease that is unique to the human temporal bone.[1] One of the most common causes of acquired hearing loss, otosclerosis has a well-established hereditary predisposition, with approximately 50 per cent of affected individuals having other known affected family members. Otosclerosis occurs within the endochondral layer of the temporal bone, usually in certain sites of predilection that are associated with globuli interossei or so-called 'embryonic rests.' These globuli interossei are areas of the embryonic otic capsule that fail to undergo secondary remodelling during embryogenesis and contain a relatively primitive population of cells nestled within the original cartilaginous framework of calcified type II collagen. Unlike all other bones, the otic capsule does not actively remodel following development. The most common site of occurrence of otosclerosis is just anterior to the oval window.[1,2] Histopathologically, the otosclerotic process is characterized by a wave of abnormal bone remodelling, resulting in the replacement of otic capsule bone with a hypercellular woven bone, which may undergo further remodelling resulting in a mosaic sclerotic appearance. As the lesion enlarges and spreads, it encroaches on the stapes footplate and produces a conductive hearing loss ('clinical' otosclerosis). In some cases, the lesion may spread to involve the cochlea and result in irreversible sensorineural hearing loss. However, the majority of lesions do not encroach on the footplate or cochlea; such lesions remain small and asymptomatic ('histological' otosclerosis).[3–5] The small histological foci are 10-fold more common than the larger lesions that result in clinical manifestations. Despite intensive investigation, the factors that serve to prevent otic capsule remodelling and those which lead to the development of otosclerosis remain unknown.

Most genetic studies on families with otosclerosis support an autosomal dominant mode of inheritance with incomplete penetrance in the range of 20–40 per cent.[6–14] Linkage analysis of three large and unrelated families with multiple affected family members yielded three separate genetic loci,

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indicating that otosclerosis is heterogenetic.[15–19] The authors have previously reported a highly significant association between otosclerosis and polymorphic markers within the COL1A1 (collagen 1A1) gene.[20] The association was equally significant for familial and sporadic cases. The most statistically significant association found thus far has been with polymorphisms in the first intron Sp1 binding site. A significant association has also been reported between the COL1A1 first intron Sp1 binding site and osteoporosis, a common heterogenetic metabolic bone disorder that results in a gradual reduction in bone density and strength, predisposing affected individuals to fractures. The allelic frequencies reported in osteoporosis are practically identical with what has been found in cases of otosclerosis.[21] The association between these two common diseases of bone and a transcription factor binding site in the COL1A1 gene suggests that aberrant expression of the COL1A1 transcript might play a role in the pathogenesis in some cases of otosclerosis and osteoporosis. Additional evidence that such a mechanism may play a role comes from studies of type 1 osteogenesis imperfecta. Low bone mass and fragility fractures are common in patients with type 1 osteogenesis imperfecta, and approximately 50 per cent of these patients develop clinical otosclerosis.[22] The majority of patients with type 1 osteogenesis imperfecta have defects in COL1A1 transcription from mutations in the COL1A1 gene that result in reduced or null expression of the mutant allele.[23,24] Although this exact mechanism has been shown not to be the cause of the majority of cases of otosclerosis and osteoporosis,[21,24–6] it does demonstrate a relationship between abnormalities in COL1A1 expression and the development of both osteogenesis imperfecta and otosclerosis.

Osteoporosis is a major public health problem. The prevalence of osteoporosis is 30 per cent among postmenopausal Caucasian women over the age of 50 years in the United States, based on World Health Organization criteria (bone density more than 2.5 standard deviations below the mean for young-adult women).[27] The incidence of fractures increases with age and women have a more than twofold increased incidence of osteoporotic fractures compared with men. Common risk factors for osteoporosis, in addition to age and female gender, include Caucasian ethnicity, family history, sex hormone deficiency, corticosteroid use, low calcium intake, smoking and alcohol. Historically, a diagnosis of osteoporosis was made due to its clinical presentation with fractures. However, during the last 10 years there has been a dramatic increase in screening for osteoporosis using bone densitometry. With increased physician awareness and improved options for treatment, there has been an increase in the diagnosis and treatment of osteoporosis. The current FDA approved treatments for osteoporosis include alendronate, risedronate, raloxifene (a selective oestrogen receptor modulator), calcitonin and teriparatide (recombinant human parathyroid hormone). Etidronate, a first-generation bisphosphonate, was often used during the 1990s prior to the development of the newer bisphosphonates, alendronate and risedronate.

The clinical association between otosclerosis and osteoporosis has not yet been closely examined although there have been reports that patients with osteoporosis have a significant increase in hearing loss compared with the general population.[28,29] In this study, a retrospective analysis of clinical cases of otosclerosis and controls was performed to determine if there was evidence of an association between otosclerosis and osteoporosis. If so, it might serve to justify a more systematic prospective investigation of the potential association between these two common diseases.

Methods

This retrospective study was approved by the institutional review board at the Massachusetts Eye and Ear Infirmary. Using a computerized database, 1100 patients who had a stapedectomy performed for otosclerosis by one of five staff otologists between January 1990 and June 2003 were identified. Of these, 100 women aged between 50 and 75-years-old at the time of their first office visit at the Infirmary and whose charts were available were chosen randomly. This age range was chosen to select for a cohort of patients likely to have undergone evaluation for osteoporosis. Patients with osteogenesis imperfecta were excluded.

The same computerized database was used to identify 744 patients who had been given the diagnosis of presbycusis at their initial visit between January 1990 and June 2003. Presbycusis was defined as the presence of a bilateral sensorineural hearing loss with the characteristic audiological findings seen with ageing, namely progressively increasing thresholds with increasing frequency, without other evidence of an underlying cause, such as noise exposure or a familial or personal history of early-onset hearing loss. From this group, 100 women aged between 50 and 75-years-old were randomly selected to serve as controls. Patients with osteogenesis imperfecta, past otological surgery and mixed hearing loss were excluded.

The medical charts were reviewed, and the following data recorded for each patient: age at first visit, medical and surgical history, medications, allergies, and family history of hearing impairment or otosclerosis. For purposes of this study, patients were assigned a diagnosis of osteoporosis if a diagnosis of osteoporosis had been made by their primary care physician or if the patient was taking one of the following medications: alendronate, risedronate, etidronate, raloxifene, calcitonin or teripararatide. Hormone replacement therapy or calcium supplementation alone was not considered indicative of osteoporosis.

The diagnosis of the patient was not known prior to obtaining the original medical history upon initial presentation to this clinic, from which all data for this study were drawn. In the authors' clinic, the medical

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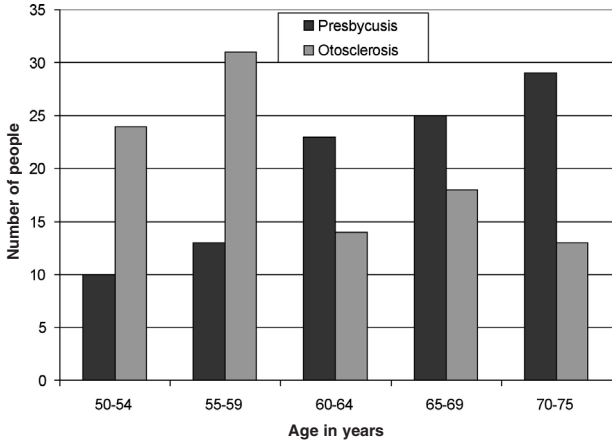

FIG. 1
Distribution of age between patients with presbycusis and otosclerosis.

history is performed with equal rigour, irrespective of the ultimate diagnosis, and always includes the history of the patient's otological problems, the past medical and surgical history, medication, allergies, social history, and family history.

The otosclerosis and presbycusis populations were grouped in five-year intervals based on age (Figure 1) for the purpose of analysis using the statistical programme for social science (SPSS) version 8.0. *P* values less than 0.05 were considered significant. A comparative analysis using the chi-squared test, odds ratio and a 95 per cent confidence interval was performed. A logistic regression was computed to adjust for age of patient at first consultation and year of first consultation yielding a second chi-squared with associated odds ratio. This controlled for the increased prevalence of osteoporosis with age, as well as for the progressively increasing awareness of osteoporosis as a treatable condition among US physicians.

Results and analysis

The mean age of the otosclerosis group was 60 years and that of the presbycusis group was 65 years. The age distribution of the two populations is shown in Figure 1, and a summary of the results in Table I. In the otosclerosis group, 46 patients underwent stapedectomy on the right ear and 54 patients on the left ear, confirming the diagnosis. Fifteen patients had been diagnosed as having concomitant osteoporosis, of which 12 were on alendronate, and three had a diagnosis of osteoporosis but were not on any therapy. Fifty-five out of 100 women reported a family history of hearing loss; 22 of these specifically reported a family history of otosclerosis. In the presbycusis group, four women had osteoporosis, of whom three were taking a bisphosphonate and one was taking raloxifene.

Chi square analysis of the two populations showed a statistically significant (p = 0.0063) association between otosclerosis and osteoporosis, corresponding to an odds ratio of 4.24 with a 95 per cent confidence interval of (1.35, 9.79). When the data were adjusted for age of the patient and the year in which the history and physical examination was performed, Chi square analysis showed a significant (p = 0.0068) association between otosclerosis and osteoporosis. The corresponding odds ratio was 5.39 with a 95 per cent confidence interval of (1.60, 18.15). Statistical analysis showed that adjusting for age at history and physical examination demonstrated a stronger association between osteoporosis and otosclerosis. However, the calendar year of diagnosis had no effect.

Discussion

The results of this study provide suggestive evidence for an association between clinical otosclerosis and osteoporosis. Because of the retrospective design and its focus only on women, the study falls short of being conclusive. It does, however, provide impetus and justification for a systematic and prospective study to investigate the clinical relationship between otosclerosis and osteoporosis, and to determine whether or not some cases of otosclerosis are a local manifestation of a more generalized disorder of bone. Although genetic studies have demonstrated a similar association between the COL1A1 Sp1 binding site in otosclerosis and osteoporosis, and similar allele frequencies between the two diseases, it is possible that a clinical relationship could result from a variety of different susceptibility alleles that impact bone metabolism, leading to both osteoporosis and otosclerosis.

The prevalance of osteoporosis in women over the age of 50 years of 15 per cent in the otosclerosis group and four per cent in the presbycusis group in this study falls well below the known prevalence of 30 per cent, probably due, at least in part, to under-diagnosis of osteoporosis by patients' general medical physicians; the disease is notoriously undertreated.[27] Nevertheless, this bias should fall equally on the otosclerosis and presbycusis groups since each patient's initial clinic history, from which the data for this study were drawn, was performed with equal thoroughness, regardless of ultimate

TABLE I
SUMMARY OF DATA

	Number of patients	Being treated for osteoporosis or established diagnosis of osteoporosis	Mean age of patients in each group (years)
Otosclerosis	100	15	60
Presbycusis	100	4	65

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diagnosis. Such documentation is not only good medicine but, in the United States, also required for third-party reimbursement for clinic visits.

- **Similarities between osteoporosis and otosclerosis, including an association with markers of the collagen gene COL1A1, have been previously reported**
- **This paper compares the prevalence of osteoporosis in 100 women with otosclerosis and in a parallel group of patients with presbycusis**
- **The prevalence of osteoporosis in otosclerosis was higher than in the control group and the study suggests that there is an association between these two conditions**

At present, there is no effective treatment for the sensorineural hearing loss that results from cochlear otosclerosis. Sodium fluoride has been used for decades to treat otosclerotic sensorineural hearing loss without robust data to support its efficacy.[30] In contrast, significant advances have occurred in the medical management of osteoporosis, including the development of potent bisphosphonates, selective oestrogen receptor modulators, and the use of recombinant human parathyroid hormone.[31] If otosclerosis and osteoporosis are indeed the result of similar underlying pathologic mechanisms in some cases, the management of otosclerotic sensorineural hearing loss could be improved by similar therapeutic means.

Summary

This is a retrospective review examining the prevalence of osteoporosis in women between the ages of 50 to 75 years with and without otosclerosis. There is a significant association between otosclerosis and osteoporosis in this subgroup of patients. This study provides impetus and justification for prospective randomized trials examining the link between otosclerosis and osteoporosis.

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