Title: Etidronate for the Neurotologic Symptoms of Otosclerosis: Preliminary Study. By: Brookler, Kenneth H., Tanyeri, Hasan, ENT: Ear, Nose & Throat Journal, 01455613, Jun1997, Vol. 76, Issue 6

Database: Academic Search Complete

Etidronate for the Neurotologic Symptoms of Otosclerosis: Preliminary Study

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Abstract

The efficacy of etidronate, a bisphosphonate, was assessed as a treatment for the inner ear symptoms of otosclerosis in a retrospective case review of 896 patients diagnosed with otosclerosis, with primary complaints of dizziness, hearing loss, tinnitus or Meniere's syndrome. The diagnosis of otosclerosis was based on small-pixel computed tomography of the temporal bones. Of the 896 patients placed on an etidronate protocol, 545 were followed for more than six months and were analyzed. The symptomatic response to etidronate, as well as audiologic and computerized rotary chair results were used in the assessment. Patients who were previously on sodium fluoride were separately analyzed. In this preliminary study etidronate appeared to be an effective treatment for the neurotologic symptoms of otosclerosis. Prospective blinded efficacy studies of the bisphosphonates in the treatment of otosclerosis should be undertaken.

Introduction

Otosclerosis has been implicated in patients with symptoms of sensorineural hearing loss, tinnitus, dizziness and Meniere's syndrome.(n1-n39) The histopathologic basis of otosclerosis leads to an understanding of how clinical neurotologic symptoms occur without evidence of the expected middle ear findings. Otosclerosis is an osseous dyscrasia of the labyrinthine capsule.(n40) Findings in the active or the "spongiotic" phase of disorganized bone, rich in osteocytes, include enlarged marrow spaces containing blood vessels and connective tissue, and multi-nucleated osteoclasts in the center of the lesion absorbing the disorganized bone. These lesions, found anywhere in the otic capsule and oval window, can spread to varying degrees. The healed or "sclerotic" phase is characterized by totally disorganized dense bone with small vascular spaces and no evidence of absorptive

activity. The hair cells appear to be normal.(n40) There are temporal bones with both otosclerotic lesions and endolymphatic hydrops.(n41-n43) The neurotologic symptoms appear to occur via the toxic suppression of hair cell activity by enzymes deposited into the inner ear fluid.(n40) The enzyme theory of inner ear symptoms was first proposed by Wolff and Bellucci in 1960(n44) and was further expanded by subsequent investigations.(n45-n47) This theory was further evaluated with the use of sodium fluoride by virtue of its effect on rapidly remodeling bone such as that seen in association with spongiotic lesions; reducing the enzymatic activity and thereby arresting the middle ear and inner ear lesions.(n2, n45-n60) Sodium fluoride has been the only recommended medical treatment for otosclerosis.(n49, n57-n59, n61-n68) In the past, the neurotologic symptoms of some patients have responded to the use of fluoride.(n1, n5, n7, n36, n45, n46, n48, n54, n57, n61, n62)

With the advent and availability of the bisphosphonates, etidronate (Didronel) has emerged as a possible treatment for otosclerosis. One paper was published on the agent's potential effect on the middle ear symptoms of otosclerosis,(n69) and another mentions the use of bisphosphonates with "surprisingly good" results, but without mentioning the clinical symptoms treated.(n59) There is experimental evidence suggesting that the bisphosphonates are useful in the treatment of the active phase of otosclerosis.(n70) The purpose of this study was to retrospectively evaluate the use of etidronate to treat the neurotologic symptoms of otosclerosis.

Etidronate is a bisphosphonate primarily indicated for the treatment of Paget's disease of the bone in a continuous dosing schedule. Since 1990,(n118-n120) it has been recommended for the treatment of osteoporosis in a pulsed-dosing schedule.

The bisphosphonates belong to a group of contemporary compounds developed to mimic the naturally occurring substance pyrophosphate.(n121-n123) Bisphosphonates are analogues of pyrophosphates that have a common phosphorus-carbon-phosphorus (P-C-P) chain, making them impervious to breakdown by pyrophosphatases.(n122-n126) They are resistant to cleavage by alkaline phosphate.(n123) Their structure reduces the membrane permeability which accounts for 1-10% of the absorption in the gastrointestinal tract.(n125) Approximately 20-60% of the absorbed bisphosphonate is concentrated in active bone(n122, n125) and the remainder is rapidly excreted unchanged in the urine.(n124) Their chemical structure causes the bisphosphonates to be avidly absorbed onto the surface of hydroxyapatite crystals in bone at sites of active remodeling.(n123, n124) This strong affinity for the calcium phosphate apatite surface inhibits both the formation and dissolution of the crystals(n122) by inhibiting the activity of the osteoclasts when they engulf bisphosphonate-containing minerals during the resorption process.(n122) This is accomplished by local effects and/or by ingestion into the cell, but without destroying the cell.(n124) Implied local effects include inhibition of acid production, lysosomal enzymes, pyrophosphatases and prostaglandin synthesis.(n121, n122) There is also evidence that bisphosphonates, when added to osteoblasts, inhibit osteoblast-stimulating activity.(n127, n128) The serum half-life is about two hours; the half-life in bone is considerably longer.(n122, n123) Etidronate is the only bisphosphonate that inhibits mineralization,(n122, n124) and this is the reason for using a pulsed-dosing schedule.

Methods

Patients

A total of 896 patients from a larger database of patients with otosclerosis-related diagnoses were included in this retrospective case review. There were 356 men and 540 women ranging in age from 18 to 89 years (average 53 years) [Table 1]. Patients presented with primary neurotologic symptoms of dizziness (n=426),(n7, n15, n23, n38, n50, n67, n129) tinnitus (n=152),(n6, n7, n50, n67) sensorineural hearing loss (n=265)(n2, n4, n7, n9, n12,

n15, n18, n19, n21, n28, n33, n35-n37, n71, n131-n133) and Meniere's syndrome (n=53).(n1, n5, n27, n31, n36, n134-n138)

There was a positive family history of hearing loss, tinnitus and dizziness in 55% of the patients. There was a family history of otosclerosis, a history of otosclerosis surgery or Schwartze's sign in 9%. Twenty-four percent of the women noted the onset of symptoms in relation to the menarche, the regular menstrual cycle, pregnancy, menopause or the use,of hormone replacement therapy. Tympanometry was shallow in 188 patients (21%). Reflexes were diphasic in 33 (4%) and absent in 43 (9%).

Diagnosis

A diagnosis of otosclerosis was suggested upon the basis of history, family history, physical examination and audiometric studies. A prior history of stapedectomy or fenestration strongly points to otosclerosis as the underlying etiology of the neurotologic complaint. Important for an otosclerosis diagnosis is the presentation or exacerbation of symptoms in women at puberty, during pregnancy, lactation and menstruation, during use of contraceptive pills or during menopause.(n47, n50, n59, n71-n74) A family history(n75-n84) of stapedectomy or fenestration will strongly point to otosclerosis while, in others, there may be a family history of only hearing loss, tinnitus or dizziness.(n6, n7, n85, n86) In some patients, Schwartze's sign can be seen on otoscopy, revealing the hyperemia of the promontory from the accumulation of blood vessels.(n7, n86) Audiometry may reveal a mixed hearing loss,(n7, n36) suggestive of a conductive component. Also important are the acoustic immittance findings. There may be tympanometry findings of markedly reduced compliance consistent with a stiff ossicular chain but without a conductive hearing loss.(n36, n62, n87-n92) The acoustic stapedial reflexes may show the on/off or diphasic findings pathognomonic of an otosclerotic fixed anterior pole of the stapes with a mobile posterior pole and no significant conductive component.(n40, n50, n59, n87, n90, n93, n94) Depending upon the middle ear anatomy, the reflexes may be totally absent rather than diphasic, with a sensorineural hearing loss and no conductive component. The most important and confirmatory finding of otosclerosis is in the imaging of the temporal bones. Since the lesions are bony it should be possible with current imaging techniques to visualize most bony changes with respect to density, size or distortion of the described histopathology(n17, n18, n32, n40, n43, n95-n105) The best modality is computed tomography (CT) of the temporal bones.(n86, n106-n117)

Prior to 1993, polytomography of the temporal bones was the imaging modality used to identify otosclerosis. Since 1993, small-pixel computed tomography of the temporal bones has been the only diagnostic procedure available to identify otosclerosis. With this resolution, the density of the basal turns of the cochlea, pericochlear lucency, plaques in the poles of the footplate and footplate thickness are easily identified.

For the purposes of this study a diagnosis of otosclerosis was based on the minimal imaging criteria of otosclerosis of the temporal bones. This is accomplished by viewing ultra-thin 1 mm slices of the temporal bone in the axial plane. The Siemens model HiQS scanner was used to evaluate the temporal bones in this study. This scanner uses an extended gray scale to 4000 Hounsfeld units (HU) with a pixel matrix of 1024. The exposure was 130 kVolts at 480 mAmps for four seconds. This produces a small pixel size of 0.07 mm and allows for excellent viewing of the oval and round windows, bony labyrinthine capsule and ossicles. The degree of resolution enables both stapes crura to be seen in the same slice in continuity with the footplate. There are three areas of the otic capsule in which to view the otosclerotic lesions, which may be sclerotic, spongiotic or mixed. First, the poles of the footplate are examined where there is an anterior focus(n18, n40, n41, n43, n94, n103) and, less often, a posterior focus. Extending from an anterior focus, there may be plaque formation on the basal

turn to the apex of the cochlea. Next, the footplate is assessed for thickness. It may be normal or thickened to varying degrees. Last, the bony capsule around the cochlea is examined. It may show normal or patchy demineralization or pericochlear lucency.(n13, n107) Previously reported pericochlear lucency seems to occur with thicker slices and/or a larger pixel size.(n117)

Treatment

Etidronate was introduced for use in our patients with a clinical diagnosis of otosclerosis in 1991. Treatment with etidronate was indicated for patients unable to tolerate fluoride preparations or for whom the fluoride preparations did not appear to be effective.

For this study there was no clear-cut dosing schedule for otosclerosis treatment. The Paget's disease protocol called for six months on and six months off the drug in the calendar year and the osteoporosis protocol called for two weeks on and 11 weeks off. The first dose of etidronate for otosclerosis was 400 ma. This was taken daily for two weeks followed by four weeks of supplemental calcium carbonate with vitamin D, and repeated once with the patient returning in three months. If the symptoms improved or stabilized, the duration of treatment with calcium carbonate and the vitamin D supplement was increased to six weeks and the eight-week cycle was repeated before the next visit. If the etidronate was continued beyond seven months, the cycle was changed to two weeks of etidronate and 11 weeks on the calcium carbonate and vitamin D. Some patients responded with an exacerbation of symptoms as the time between administrations of etidronate increased. To prevent the exacerbation, sodium fluoride was reintroduced into the 1 3-week cycle. The patients went on the etidronate for two weeks, and the calcium carbonate and vitamin D supplement for six weeks, followed by sodium fluoride orsodiummonofluorophosphate and calciumcarbonateforfive weeks. The patients were seen at six-month intervals thereafter. Depending upon the symptoms at two years, some dosing variation may be considered or the treatment suspended and the patient observed.

Etidronate was gradually introduced as the primary agent of treatment for the neurotologic symptoms of otosclerosis based on the response of those switched over from the fluoride treatment. This article will also report on those patients switched from the traditional fluoride treatment, and on the difference in the clinical effect achieved.

The objective measurements of improvement in neurotologic function include improvement in symmetry of the rotary chair-induced nystagmus(n139) and significant improvement in hearing (> 15 decibles in pure tones, >15 decibels in speech reception threshold, >16% in speech discrimination).

Results

There were 545 patients seen in follow-up at six months or longer (Table 2). Follow-up ranged from six to 57 months. Initially, the patients were divided into three groups. The first group had less than six months of follow-up and was excluded from analysis because of this short duration. The second group had six to 12 months of follow-up and the third was followed for longer than 12 months (Table 2). The six to 12-month group had 150 patients. The distribution of primary complaints and treatment response of that group was very similar to that of the group of 395 patients followed longer than 12 months, and the two groups were combined.

The response to treatment was divided into three possibilities for each of the presenting symptoms to allow for a spreadsheet analysis (Table 3).

Responses of the group presenting with dizziness were categorized according to the patients' assessment as no change, improved or asymptomatic. There were 19 patients (7%) who reported no change, meaning that the dizziness was the same or worse on the etidronate. Patients whose dizziness improved (145 [54%]) reported that symptoms were better, caused little or no disability and, while tolerable, dizziness was not completely gone. Asymptomatic patients were those with no dizziness symptoms (103 [39%]). There were 230 patients in whom computerized rotary chair testing was performed. Testing was performed at the three-month visit or sooner, unless normal symmetry was noted as part of an original vestibular evaluation. There was normal symmetry in 115 (59%) patients. Symmetry improved from abnormal to normal in 68 (35%) patients, and remained abnormal in 12 (6%). These percentages paralleled the patients' self-evaluations.

Patients assessed their hearing loss in three categories: no change, improved or normal. No change in a patient with progressive sensorineural hearing loss was an improvement over pretreatment status. There were 44 patients (27%) in this group, 114 (70%) in the improved group and two (4%) who improved to normal hearing. There were 103 patients for whom hearing results were available for comparison. Hearing was the same in 73 (71%), better in 28 (27%) and worse in two (2%).

The tinnitus response was categorized as no improvement, improved or asymptomatic. There were 22 (32%) patients in whom the tinnitus was uncharged, 36 (52%) in whom tinnitus was improved (still present but tolerable) and 11 (16%) in whom the tinnitus disappeared.

Response among the patients with Meniere's syndrome was assessed as no change, improved or asymptomatic. There were six patients (13%) with no change in symptoms. It is of note that when the "no change" group was analyzed the numbers fell from 23% in the six to 12-month follow-up group to 9% in the longer than 12-month follow-up group. An "improved" response was defined as less frequent episodes of shorter duration and lesser severity, producing a tolerable situation allowing near-normal functional status for work and social activities. There were 15 patients (32%) in this group. There were 26 (55%) patients who were asymptomatic. Computerized rotary chair testing was available in 35 patients. Normal symmetry was found in 24 (69%), improved symmetry in eight (23%), and abnormal symmetry in three (9%). Hearing tests were available in 46 of these Meniere's syndrome patients. Hearing was the same in 23 (50%) patients, improved in 14 (30%) patients, and worse in nine (20%) patients.

There were 186 patients who were switched from sodium fluoride alone to etidronate for whom there was follow-up of six months or longer (Table 4). These patients were switched because the fluoride failed to control the symptoms, because of adverse effects or to see if a better result could be achieved with etidronate. Of the 85 patients with a primary complaint of dizziness, 47 (55%) were improved and 32 patients (38%) were asymptomatic. Of the 61 patients with a primary complaint of sensorineural hearing loss, 17 (28%) had no change in hearing and 43 patients (70%) were improved. Of the 17 patients with a primary complaint of tinnitus, 10 were improved and tinnitus disappeared in three. Of the 23 patients with Meniere's syndrome, nine were improved and 11 were asymptomatic.

Discussion

The diagnosis of neurotologic disorders secondary to otosclerosis is controversial. Much of the controversy seems to stem from the perceived inability to make a diagnosis of otosclerosis without conductive hearing loss. Imaging technology advances with small-pixel computed tomography of the temporal bones now provide the resolution necessary to make a diagnosis of otosclerosis. The literature is replete with information supporting the

concept of inner ear disorders secondary to labyrinthine otosclerosis. Since experience revealed a beneficial response to the use of fluoride (n1, n4-n6, n47, n50, n59, n64, n92, n140) the concept of treating inner ear otosclerosis with a bisphosphonate seemed reasonable.

It was decided to analyze the data beginning at six months. As the data were being collected, there was a large group of patients (351) who were not seen at six months or beyond. Closer examination of this group revealed that many had returned at three months, as required in the protocol, and were significantly better or asymptomatic, possibly feeling that further follow-up was unnecessary. Included in this group were 83 patients with tinnitus, comprising 55% of all the tinnitus patients. The failure to follow-up in this tinnitus group may represent an inadequate subjective response to the treatment over this period of time.

The collated data for the patients who returned between six and 12 months were analyzed. It was apparent that this group of 150 patients was responding to the regimen in the respective diagnostic categories in similar numbers to those in the group with more than 12 months of follow-up. The only changes in response were the decreasing numbers of poor responders as the treatment duration increased.

The group of patients previously on fluoride treatment was examined. Analysis of this group is important because many of the patients treated with etidronate were also treated for concomitant metabolic disorders, possibly affecting the inner ear. This group of 186 patients, which was switched from fluoride to etidronate, acted as their own controls with respect to a concurrent treatment. The clinical results were similar to those of the larger group.

Conclusions

The results of this preliminary study support the theory that the etidronate effect reduces the osteoclastic activity in otosclerotic lesions, thus reducing the enzyme level in the inner ear fluids and the toxicity of the hair cells.

In 1991 etidronate was the only bisphosphonate available and papers were appearing in the literature describing its application for osteoporosis. (n119, n141, n142) The results of this preliminary study reveal that etidronate can effectively halt the decline and sometimes rapidly reverse the symptoms of abnormal inner ear function. As the pulsed-dosing schedule is lengthened the response of the inner ear may lessen, as seen in some of our patients. It is suggested that these otosclerotic lesions require the effect of an additional active agent such as fluoride to sustain the clinical effect of the etidronate. Fluoride salts affect bone by stimulating osteoblastic function.(n143, n144)

Summary

In patients with neurotologic complaints, ultra-thin, small-pixel computed tomography of the temporal bones should be performed to visualize otosclerosis. The bisphosphonate, etidronate, used in an appropriate dosing schedule, appears to be a more effective treatment for the neurotologic symptoms of otosclerosis than sodium fluoride alone. Future investigation on this subject should be centered on:

1. The minimum technical specifications required for the radiologic diagnosis of otosclerosis with high-resolution computed tomography scanners;
2. Evaluation of the subsequent generation of bisphosphonates and their potential role in the treatment of the symptoms of otosclerosis;
3. Development of blinded studies of the bisphosphonates in patients with appropriate clinical diagnoses; and

4. A detailed follow-up survey on the group of bisphosphonate-treated patients with less than six months of follow-up.

Acknowledgment

The authors wish to recognize Pamela Oh, BS of Neurotologic Associates, P.C., New York, NY, and Richard C. Brookler, MBA for their help in preparing this manuscript. Technical assistance with the imaging in formation was provided by Doreen Liebeskind, MD, and Peter Terzopoulos, EE of Park Avenue Radiologists, P.C., New York, NY.

Table 1. Initial Symptoms by Gender.

	Male	Female	Total
Dizziness	41%	52%	426
Hearing Loss	32%	28%	265
Tinnitus	20%	15%	152
Meniere's	7%	5%	53
Total	356	540	896

Table 2. Follow-up Breakdown.

	<6 Months	6-12 Months	>12 Months	Total
Dizziness	159	81	186	426
Hearing Loss	103	31	131	265
Tinnitus	83	26	43	152
Meniere's	6	12	35	53
Total	351	150	395	896

Table 3. Response by Initial Symptom.

	No Change	Improved	Asymptomatic	Total
Dizziness	19 (7%)	145 (54%)	103 (39%)	267
Hearing Loss	44 (27%)	114 (70%)	4 (2%)	162
Tinnitus	22 (32%)	36 (52%)	11 (16%)	69
Meniere's	6 (13%)	15 (32%)	26 (55%)	47
Total	91	310	144	545

Table 4. Response Compared to Fluoride.

	No Change	Improved	Asymptomatic	Total
Dizziness	6 (7%)	47 (55%)	32 (38%)	85
Hearing Loss	17 (28%)	43 (70%)	1 (2%)	61
Tinnitus	4 (24%)	10 (58%)	3 (18%)	17
Meniere's	3 (13%)	9 (39%)	11 (48%)	23
Total	30	109	47	186

Reprint requests to: Kenneth H. Brookler, MD, Neurotologic Associates, P.C., 111 East 77th Street, New York, NY 10021; Phone: 212/861-6900; Fax: 212/472-0134.

References

(n1.) Brookler KH. Meniere's disease: Role of otospongiosis and metabolic disorders. Acta Otolaryngol 1984; (Suppl 406):31-6.

(n2.) Causse JR, Chevance LG. Sensorineural hearing loss due to cochlear otospongiosis: Etiology. Otolaryngol Clin North Am 1978; 11:125-34.

(n3.) Causse JR, Causse JB, Bretlau P, et al. Etiology of otospongiosis sensorineural losses. Am J Otol 1989;10:99-107.

(n4.) Cody DTR, Baker HLJ. Otosclerosis: Vestibular symptoms and sensorineural hearing loss. Ann Otol Rhinol Laryngol 1978; 87:778-96.

(n5.) Cole JM, Funkhouser G. Meniere's disease and otosclerosis (without oval window treatment). Laryngoscope 1972; 82: 102-734.

(n6.) Freeman J. Otosclerosis and vestibular dysfunction. Laryngoscope 1980;90:1481-7.

(n7.) Freeman J. Progressive sensorineural hearing loss and cochlear otosclerosis: A prospective study. Laryngoscope 1979; 89:1487-1521.

(n8.) Gross CW. Sensorineural hearing loss in clinical and histological otosclerosis. Larygoscope 1969; 79:104-12.

(n9.) Gundersen T. Sensorineural hearing loss in otosclerosis. Scand Audiol 1973; 2:43-51.

(n10.) Gungovich VA, Rosenfeld LG. The diagnosis of cochlear otosclerosis. Arch Otolaryngol 1974;99:281.

(n11.) Gussen R. Labyrinthine otosclerosis and sensorineural deafness. Pathologic findings of the spiral ligament. Arch Otolaryngol 1975; 101:438-40.

(n12.) Hansen MC. Otosclerosis and sensorineural hearing loss. Arch Otolaryngol 1983; 109:598-600.

(n13.) Havriliak D, Parisier S. Cochlear otosclerosis presenting in children: A case report. Am J Otol 1991; 12(1):61-3.

(n14.) Hulk J, Jongkees LBW. Vestibular examiniation in cases of otosclerosis. J Laryngol 1950; 64:126-30.

(n15.) Igarashi M, Jerger S, Toshiaki O, et al. Fluctuating hearing loss and recurrent vertigo in otosclerosis: An audiologic and temporal bone study. Arch Otorhinolaryngol 1982; 236:161-71.

(n16.) Khrappo NS. Vestibular disorders in otosclerosis and their anatomical physiological bases. Vestn Oto-Rhino-Laryng 1964;26:228.

(n17.) Lindsay JR, Beal DD. Sensorineural deafness in otosclerosis. Observations on histopathology. Ann Otol Rhinol Laryngol 1966;75:436-57.

(n18.) Linthicum FHJ. Correlation of sensorineural hearing impairment and otosclerosis. Tr Am Otol Soc

1966;54:155-68.

(n19.) Linthicum FH, Filipo R, Brody S. Sensorineural hearing loss due to cochlear otospongiosis: Theoretical considerations of etiology. Ann Otol Rhinol Laryngol 1975;84:544-51.

(n20.) Linthicum FHJ, Lalani AS. Sensorineural impairment in unilateral otosclerosis. Ann Otol Rhinol Laryngol 1975; 84:11-5.

(n21.) Linthicum FHJ, Neely JG. Unrelated sensorineural hearing loss in patients with otosclerosis. A report of three cases. Laryngoscope 1977; 87:1746-52.

(n22.) Liston SL, Paparella MM, Mancini F, et al. Otosclerosis and endolymphatic hydrops. Laryngoscope 1984; 94: 1003-7.

(n23.) McCabe BF. Otosclerosis and vertigo. Trans Pac Coast Otoophthalmol Soc 1966; 47:37-42.

(n24.) Meurman O, Aantaa E, Virolainen E. Vestibular disorders in clinical otosclerosis. Arch Otolaryngol 1969; 90:756-8.

(n25.) Morales-Garcia C. Cochleovestibular involvement in otosderosis. Acta Otolaryngol 1972; 73:484-92.

(n26.) Naunton R, Valvassori G. Sensorineural hearing loss in otosclerosis. Arch Otolaryngol 1969; 99:281.

(n27.) Paparella MM, Mancini F, Liston SL. Otosclerosis and Meniere's syndrome: Diagnosis and treatment. Laryngoscope 1984; 94: 141417.

(n28.) Parahy C, Linthicum FHJ. Otosclerosis: Relationship of spiral ligament hyalinization to sensorineural hearing loss. Laryngoscope 1983; 93:717-20.

(n29.) Parahy C, Linthicum FHJ. Otosclerosis and otospongiosis: Clinical and histological comparisons. Laryngoscope 1984; 94:508-12.

(n30.) Rasmussen H. Vestibular function prior to and following operation for otosclerosis. Arch Otolaryngol 1949;49:402-13.

(n31.) Richards SS. Meniere's syndrome in otosclerosis. Brit Med J 1964; 2:1227.

(n32.) Ruedi L. Histopathology of sensorineural degeneration and other inner ear changes in otosclerosis, in Schuknecht HF (ed): Otosclerosis. London, Churchill Livingstone, 1962.

(n33.) Sataloff J, Farb S, Menduke H, et al. Sensorineural hearing loss in otosclerosis. Trans Am Acad Ophthalmol Otolaryngol 1964; 68:243-8.

(n34.) Schow RL. Tomography and sensorineural hearing loss in otospongiosis: New data on unresolved issues, in Shambaugh GE, Jas JJ (eds): Proceedings of the Shambaugh Fifth International Workshop on Middle Ear Microsurgery and Fluctuant Hearing Loss. Huntsville, AL, Strode Publishers Inc, 1977; 492-9.

(n35.) Shambaugh G. Sensorineural hearing loss due to cochlear otospongiosis: Pathogenesis, clinical

diagnosis, and therapy. Otolaryngol Clin North Am 1978; 11:135-54.

(n36.) Sismanis A, Hughes GB, Abedi E. Coexisting otosclerosis and Meniere's disease: A diagnostic and therapeutic dilemma. Laryngoscope 1986; 96:9-13.

(n37.) Valle V, Linthicum FJ. Proven cochlear otosclerosis: Sensorineural with conductive hearing loss. Ann Otol Rhinol Otolaryngol 1984; 93:105-11.

(n38.) Thomas JE, Cody DTR. Neurologic perspectives of otosclerosis. Mayo Clin Proc 1981; 56:17-21.

(n39.) Virolainen E. Vestibular disturbances in clinical otosclerosis. Acta Otolaryngol 1972; (Suppl 306):1-34.

(n40.) Linthicum F. Histopathology of otosclerosis. Otolaryngol Clin North Am 1993; 26:335-52.

(n41.) Johnsson LG, Hawkins JE, Linthicum FH. Cochlear and vestibular lesions in capsular otosclerosis as seen in microdissection. Ann Otol Rhinol Laryngol 1978; 87 (Suppl 48):1-40.

(n42.) Johnsson LG, Hawkins JE, Rouse RC, et al. Cochlear and otoconial abnormalities in capsular otosclerosis with hydrops. Ann Otol Rhinol Laryngol 1982; (Suppl 91):3.

(n43.) Sando I, Hemenway WG, Miller DR, et al. Vestibular pathology in otosclerosis temporal bone histopathological report. Laryngoscope 1974; 84:593-605.

(n44.) Wolff D, Bellucci R. The histopathology observed in fifty biopsied stapedes. Trans Amer Acad Ophth Otolaryngol 1960; (July-August):540-53.

(n45.) Causse JR, Chevance LG, Bretlau P, et al. Enzymatic concept of otospongiosis and cochlear otospongiosis. Clin Otol 1977; 2:23-32.

(n46.) Causse JR, Shambaugh GEJ, Causse JB, et al. Enzymology of otospongiosis and NaF therapy. Amer J Otol 1980; 1:206.

(n47.) Petrovic AG, Stutzmann JJ, Shambaugh GEJ. Experimental studies on pathology and therapy of otospongiosis. Am J Otol 1985; 6:43-50.

(n48.) Causse, Shambaugh GE, Chevance LG, et al. Cochlear otospongiosis: Etiology, diagnosis, and therapeutic implications. Adv ORL 1977; 22:23-32.

(n49.) Causse JR, Uriel J, Berges J, et al. Objective changes in trypsin, alantitrypsin, and a2-macroglobulin values as a result of sodium fluoride treatment in patients with otosclerosis. Am J Otol 1985; 6:38-42.

(n50.) Causse JR, Causse JB. Clinical studies on fluoride in otospongiosis. Am J Otol 1985; 6:51-5.

(n51.) Shambaugh GE, Causse JR, Petrovic A, et al. New concepts in management of otospongiosis. Arch Otolaryngol 1974; 100:41926

(n52.) Bretlau P, Hansen HJ, Causse JB, et al. Otospongiosis: Morphologic and microchemical investigation after NaF-treatment. Otolaryngol Head Neck Surg 1981; 89:646-50.

(n53.) Causse JR, Chevance LG. Sensorineural hearing loss due to cochlear otospongiosis: Etiology. Otolaryngol Clin North Am 1978; 11:125-34.

(n54.) Causse JR, Shambaugh, Jr. GE, Bretlau P. Cochlear otospongiosis: Etiology, diagnosis, and therapeutic implications. Adv Oto-RhinoLaryngol 1975; 22:43.

(n55.) Chevance LG, Causse JR, Bretlau P, et al. Hydrolitic activity of the perilymph in otosclerosis. A preliminary report. Acta Otolaryngol (Stockh) 1972; 74:23-8.

(n56.) Chevance LG, Causse JR, Berges J. Study of alpha 1 antitrypsin activity of the perilymph during the progression of otospongiosis. Arch Otol 1976; 102:363-4.

(n57.) Causse J, Chevance LG, Shambaugh GE. Clinical experience and experimental findings with sodium fluoride in otosclerosis (otospongiosis). Ann Otol 1974; 83:643-7.

(n58.) Bretlau P, Causse JR, Causse JB, et al. Otospongiosis and sodium fluoride. A blind experimental and clinical evaluation of the effects of sodium fluoride treatment in patients with otospongiosis. Ann Otol Rhinol Laryngol 1985; 94:103-7.

(n59.) Causse JR, Causse JB, Uriel J, et al. Sodium fluoride therapy. Am J Otol 1993; 14:482-90.

(n60.) Causse J, Uriel J, Berges J, et al. The enzymatic mechanism of the otospongiotic disease and NaF action on the enzymatic balance. Am J Otol 1982; 3:297-314.

(n61.) Causse JR, Shambaugh GE, Causse JB, et al. Enzymology of otospongiosis and (NaF) sodium fluoride therapy. Am J Otol 1980; 1(4):206-14.

(n62.) Forquer BD, Linthicum FHJ, Bennet C. Sodium fluoride: Effectiveness of treatment for cochlear otosclerosis. Am J Otol 1986; 7: 121-5.

(n63.) Kerr G, Hoffman G. Fluoride therapy for otosclerosis. Ear Nose Throat J 1989; 68:426-9.

(n64.) Shambaugh GEJ, Scott A. Sodium fluoride for the arrest of otosclerosis. Arch Otolaryngol 1964; 80:263.

(n65.) Shambaugh GEJ, Petrovic AG. Effects of sodium fluoride on bone: Application to otosclerosis and other decalcifying bone diseases. J Am Med Assoc 1968; 204:969-73.

(n66.) Shambaugh GE. Fluorides for otospongiosis and other osteoporotic states. Ann ORL 1973; 90:129-38.

(n67.) Shambaugh GEJ. Further experiences with moderate dosage sodium fluoride for sensorineural hearing loss, tinnitus and vertigo due to otospongiosis. Adv Oto-Rhino-Laryngol 1977;22:35-42.

(n68.) Shambaugh JEJ. Adult fluoride therapy for otosclerosis (otospongiosis). Arch Otolaryngol 1983;109:353.

(n69.) Kennedy D, Hoffer M, Holliday M. The effects of etidronate disodium on progressive hearing loss from otosclerosis. Otolaryngol Head Neck Surg 1992;109:461-467.

(n70.) Petrovic AG, Stutzman JJ. Diphosphonates: A potential medication for evolutive otospongiosis, in Donath

A, Courvoisier B (eds): Symposium CEMO, Centre d'Etude des Maladies Osteoarticulares de Geneve IV. Nyon, Switzerland, Editions Medicine et Hygiene, Geneve, 1982; 417-22.

(n71.) Elbrond O, Jensen JJ. Otosclerosis and pregnancy: A study on the influence of pregnancy on the hearing threshold before and after stapedectomy. Clin Otolaryngol 1979; 4:259.

(n72.) Gristwood RE, Venables WN. Pregnancy and otosclerosis. Clin Otolaryngol 1983; 8:205-10.

(n73.) Smith HW. Effect of pregnancy on otosclerosis. AMA Arch Otolaryngol 1948; 48:159.

(n74.) Walsh TE. The effect of pregnancy on deafness of otosclerosis. Trans Amer Acad Ophthalmol Otolaryngol 1954; 58:420.

(n75.) Causse JR, Causse JB. Otospongiosis as a genetic disease: Early detection, medical management and prevention. Am J Otol 1984; 5:211-23.

(n76.) Davenport CB, Milles BL, Frink LB. The genetic factor in otosclerosis. AMA Arch Otolaryngol 1933; 17: 135-70, 340-83,503-48.

(n77.) Gapany-Gapanavicius B. Otosclerosis: Genetics and Surgical Rehabilitation. Jerusalem, Keter, 1975.

(n78.) Gordon MA. The genetics of otosclerosis: A review. Am J Otol 1989; 10:426-37.

(n79.) Hall JG. Otosclerosis in Norway, a geographical and genetical study. Acta Otolaryngol 1974; 324:1-20.

(n80.) Henry KR, Chole RA. Genetic and functional analysis of the otosclerosis-like condition of the LP/J mouse. Audiology 1987; 26:44-55.

(n81.) Larsson A. Otosclerosis. A genetic and clinical study. Acta Otolaryngol 1960; (Suppl 154):1-86.

(n82.) Hernandez-Orozco F, Courtney GT. Genetic aspects of clinical otosclerosis. Ann Otol Rhinol Laryngol 1964; 73:632-44.

(n83.) Morrison AW. Genetic factors in otosclerosis. Ann R Coll Surg Engl 1967; 41:2.

(n84.) Schaap T, Gapany-Gapanavicius B. The genetics of otosclerosis. I. Distorted sex ratio. Am J Hum Genet 1978; 30:59-64.

(n85.) Graham AB. An audiological and otological investigation of normal hearing individuals with a family history of otosclerosis. Chicago, Northwestern University PhD Thesis, 1953

(n86.) Saunders JE, Dereberry MJ, Lo WWM. Magnetic resonance imaging of cochlear otosclerosis. Ann Otol Rhinol Laryngol 1995; 104:826-9.

(n87.) Bel J, Causse JR, Michaux P, et al. Mechanical explanation of the on/off effect (diphasic impedance change) in otospongiosis. Audiol 1976; 15:128-40.

(n88.) Causse JR, Causse JB. Otospongiosis as a genetic disease. Early detection, medical management and

prevention. Am J Otol 1984; 5:211-23.

(n89.) Forquer BD, Sheehy JL. Cochlear otosclerosis: Acoustic reflex findings. Am J Otol 1981; 2:297-300.

(n90.) Forquer BD, Sheehy JL. The negative on/off effect in cochlear and early stapedial otosclerosis. Ear Hear 1981; 2:256-9.

(n91.) Forquer B, Sheehy J. Cochlear otosclerosis: A review of audiometric findings in 150 cases. Am J Otol 1987; 8:1-4.

(n92.) Linthicum F, Forquer B. Sodium fluoride as a treatment for otosclerotic hearing loss. Am J Otol 1985;6:35-37.

(n93.) Vartiainen E, Virtaniemi J, Kemppainen M, et al. Hearing levels of patients with otosclerosis 10 years after stapedectomy. Otolaryngol Head Neck Surg 1993; 108:251-5.

(n94.) Causse JB, Causse JR. Cochlear otosclerosis. J Laryngol Otol 1983; 8:84.

(n95.) Altmann F. Histopathology and etiology of otosclerosis: A critical review, in Schuknecht HF (ed): Otosclerosis. Boston, Little, Brown and Company, 1962; 16-42.

(n96.) Sando I, Hemenway WG, Miller DR, et al. Vestibular pathology in otosclerosis temporal bone histopathological report. Laryngoscope 1974; 84:593-605.

(n97.) Ruedi L. Histopathologic confirmation of labyrinthine otosclerosis. Laryngoscope 1965; 75:1582-1609.

(n98.) Nager G. Histopathology of otosclerosis. Arch Otolaryngol 1969; 89:341-62.

(n99.) Nadol JBJ, McKenna MS. Histopathology of Meniere's disease and otosclerosis: Relevance of possible immune mediated pathogenesis, in Veldman JE (ed) : Immunobiology, histopathology , and tumor immunology in otolaryngology. Proceedings Second International Academic Conference, Utrecht, The Netherlands, August 26-29, 1986. Amsterdam, Kugler Publications, 1987; 165-84.

(n100.) Lindsay JR. Otosclerosis: Histopathology, in Paparella MM, Shumrick DA (eds): Textbook of Ear, Nose and Throat, Vol. 2. Philadelphia, WB Saunders, 1973; 205-30.

(n101.) Lindsay JR. Histopathology of otosclerosis. Arch Otolaryngol 1973; 97:24-9.

(n102.) Lindsay J. Histopathology in autopsy specimens after stapes surgery, in Shucknecht (ed): Otosclerosis HFH-iso. Boston, Little Brown & Co, 1962; 359-70.

(n103.) Li W, Schachern P, Paparella M. Extensive otosclerosis and endolymphatic hydrops: Histopathologic study of temporal bones. Am J Otolaryngol 1994; 15:158-61.

(n104.) Antoli-Candela F, McGill T, Peron D. Histopathological observations on the cochlear changes in otosclerosis. Ann Otol Rhinol Laryngol 1977; 86:813-20.

(n105.) Altmann F, Kornfeld M, Shea JJ. Inner ear changes in otosclerosis. Histopathological studies. Ann Otol

Rhinol Laryngol 1966; 75:129.

(n106.) Vignaud J, Marsot-Dupuch K, Pharaboz C, et al. Imaging of the vestibule. Otolaryngol Head Neck Surg 1995; 112:36-49.

(n107.) D'Achambeau O, Parizel P, Koekelkoren E, et al. CT diagnosis and differential diagnosis of otodystrophic lesions of the temporal bone. Eur J Radiol 1990; 11:22-30.

(n108.) Damsma H. CT of cochlear otosclerosis. Radiol Clin North Am 1984; 22(1):37-43.

(n109.) DeGroot JAM, Huizing FW, Damsma H, et al. Labyrinthine otosclerosis studied with a new computed tomography technique. Ann Otol Rhinol Laryngol 1985; 94:223-5.

(n110.) Mafee MF, Henrikson GC, Deitch RL, et al. Use of CT in stapedial otosclerosis. 1985; 156(3):709-14.

(n111.) Mafee M, Valvassori G, Deitch R, et al. Use of CT in the evaluation of cochlear otosclerosis. Radiol 1985;156:703-708.

(n112.) Swartz J, Faerber E, Wolfson R, et al. Fenestral otosclerosis: Significance of preoperative CT evaluation. Radiology 1984; 151:703-7.

(n113.) Swartz J, Mandell D, Berman S. Cochlear otosclerosis (otospongiosis): CT analysis with audiometric correlation. Radiol 1985; 155:147-50.

(n114.) Swartz J, Mandell D, Wolfson R, et al. Fenestral and cochlear otosclerosis: Computed tomography evaluation. Am J Otol 1985; 6:476-81.

(n115.) Valvassori G, Dobben G. CT densitometry of the cochlear capsule in otosclerosis. AJNR 1985; 6:661-7.

(n116.) Valvassori GE. CT densitometry in otosclerosis. Adv Oto-RhinoLaryngol (Baser) 1987; 37:47-9.

(n117.) Valvassori G. Imaging of otosclerosis. Otolaryngol Clin N Am 1993; 26(3):359-71.

(n118.) Harris S, Watts M, Jackson R, et al. Four year study of intermittent cyclical etidronate treatment of postmenopausal osteoporosis: Three years of blinded therapy followed by one year of open therapy. Am J Med 1993; 95:557-67.

(n119.) Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990; 322:1265-71.

(n120.) Watts N, Harris S, Genant M, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990; 323:73-9.

(n121.) Fleisch H. Bisphosphonates--History and experimental basis. Bone 1987; 8(Suppl 1): S23-S28.

(n122.) Fleisch H. Bisphosphonates: Pharmacology. Sem Arth Rheum 1994; 23:261-2.

(n123.) Ott S. Clinical effects of bisphosphonates in involutional osteoporosis. J Bone Min Res 1993; 8(Suppl

2):S597-S606.

(n124.) Watts N. Treatment of osteoporosis with bisphosphonates. Rheum Dis Clin N Am 1994; 20(3):717-34.

(n125.) Rodan G, Balena R. Bisphosphonates in the treatment of metabolic bone disease. Ann Med 1993; 373-8.

(n126.) Gennari C, Nuti R, Agnusdei D, et al. Management of osteoporosis and Paget's disease. Drug Safety 1994; 11: 179-95.

(n127.) Khoker M, Dandona P. Diphosphonates inhibit human osteoblast secretion and proliferation. Metabolism 1989; 38: 184-7.

(n128.) Sahni M, Guenther H, Fleisch H, et al. Bisphosphonates act on rat resorption through the mediation of osteoblasts. J Clin Invest 1993; 91:2004-11.

(n129.) Paparella MM, Chasin WD. Otosclerosis and vertigo. J Laryngol Otol 1966; 80:511-19.

(n130.) Balle V, Linthicum FHJ. Histologically proven cochlear otosclerosis with pure sensorineural hearing loss. Ann Otol Rhinol Laryngol 1984; 93:105-11.

(n131.) Browning G, Gatehouse S. Sensorineural hearing loss in stapedial otosclerosis. Ann Otol Rhinol Laryngol 1984; 93:13-6.

(n132.) Linthicum FH, Reunes R, Belal A. Histologic and polytomographic correlations in cochlear otosclerosis, in Shambaugh GE, Shea JJ (eds): Proceedings of the Sixth Shambaugh and Third Shea International Workshop on Otomicrosurgery and Shea Fluctuant Hearing Loss Symposium, 1980. Huntsville, AL, Strode Publishers, 1981; 468-71.

(n133.) Ruedi L, Spoendlin H. Pathogenesis of sensorineural hearing loss in otosclerosis. Ann ORL 1966; 75:525-52.

(n134.) DeGroot J, Huizing E. Computed tomography of the petrous bone in otosclerosis and Meniere's disease. Acta Otolaryngol (Stockh) 1987; (Suppl 434):1-135.

(n135.) Ishibe T, Yoo TJ, Shea JJ, et al. Immunohistochemical studies in Meniere's disease, otosclerosis, and tympanosclerosis. Assoc Res Otolaryngol 1985; 92.

(n136.) Issa TK, Bahgat MA, Linthicum FHJ, et al. The effect of stapedectomy on hearing of patients with otosclerosis and Meniere's disease. Am J Otol 1983; 4:323-6.

(n137.) Yoo TJ, Stuart JM, Kang AH, et al. Type II collagen autoimmunity in otosclerosis and Meniere's disease. Science 1982; 217:1153-5.

(n138.) Yoon TH, Paparella MM, Schachern PA. Otosclerosis involving the vestibular aqueduct and Meniere's disease. Otolaryngol Head Neck Surg 1990; 103:107-12.

(n139.) Rubin W. Harmonic acceleration tests as a measure of vestibular compensation. Laryngoscope 1982; 91:489-92.

(n140.) Brookler K, Glenn M. Meniere's Syndrome: An approach to therapy. Ear Nose Throat J 1995; 74:534-42.

(n141.) Mallette L, LeBlanc A, Pool J, et al. Cyclic therapy of osteoporosis with neutral phosphate and beef, high-dose pulses of etidronate. J Bone Min Res 1989; 4: 143-8.

(n142.) Heaney R, Saville P. Etidronate disodium in postmenopausal osteoporosis. Clin Pharm Therapeut 1976; 20:593-604.

(n143.) Lafage M, Balena R, Battle M, et al. Comparison of alendrolate and sodium fluoride effects on cancellous and cortical bone in minipigs. J Clin Invest 1995; 95:2127-33.

(n144.) Reginster J. Treatment of bone in elderly subjects: Calcium, vitamin D, fluor, bisphosphonates, calcitonin. Horm Res 1995; 43:83-8.

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By Kenneth H. Brookler, MD, Neurotologic Associates, P.C., New York, New York and Hasan Tanyeri, MD, Clinical Fellow, Department of Otolaryngology, Lenox Hill Hospital, New York, New York

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