Otosclerosis, clinical long-term perspectives

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To Christer, Anna and Josefin

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ABSTRACT

This thesis has assessed medical, technical and health-related aspects of otosclerosis from a long-term perspective. A retrospective clinical study was performed where 65 subjects who had previously undergone stapedectomy (1977-1979) were assessed. Twenty-eight - Thirty years later a follow-up was conducted. In Paper I, hearing thresholds were studied. Thirty years after surgery the mean hearing impairment was comparable with the preoperative level. The hearing deterioration was mainly caused by sensorineural hearing loss which was significantly worse compared to an age and sex matched control population (ISO 7029). In Paper II, hearing aid use and satisfaction were analyzed. Almost all subjects (95%) would have benefitted from hearing aid rehabilitation, however only 54 % had been fitted with hearing aids. Subjects who had received hearing aids were generally everyday users (94 %) and were very satisfied with their hearing aids. In Paper III, hearing disability and health-related quality of life was assessed. The subjects experienced hearing problems, especially in complex listening situations and in localization of sounds. Health-related quality of life showed results comparable to that of the reference population. In Paper IV, 20 of the subjects were analyzed by multi-slice and cone-beam CT (MSCT, CBCT) to assess the applicability of CBCT in the assessment of otosclerosis. The study showed that CBCT was valid in the assessments and in many ways was equivalent to MSCT.

Keywords; Otosclerosis, hearing loss, conductive, stapedectomy, hearing aid, health-related quality of life, hearing disability, SF-36, SSQ, IOI-HA, MSCT, CBCT

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Redfors Y.D & Möller, C.

Otoclerosis: Thirty-year follow-up after surgery

Ann Otol Rhinol Laryngol, 2011;120, 608-614.

II. Redfors Y.D., Hellgren, J, Möller, C.

Hearing-aid use and benefit: A long-term follow-up in patients undergoing surgery for otosclerosis

Int J Audiol, 2013;Early online;1-6

III. Redfors YD, Olaisson S, Karlsson J, Hellgren J, Möller C.

Health-Related Quality of Life in patients who have undergone otosclerosis surgery: A long-term follow-up study

In manuscript

IV. Redfors YD, Gröndahl HG, Hellgren J, Lindfors N, Nilsson I, and Möller, C

Otosclerosis: Anatomy and Pathology in the Temporal Bone Assessed by Multi-Slice and Cone-Beam CT.

Otology & Neurotology, 2012;33,922-927

CONTENTS

ABBREVIATIONS

ABG	Air bone gap
AC	Air conduction
ALARA	As low as reasonable achievable
BC	Bone conduction
CBCT	Cone-beam computed tomography
dB	Decibel
FB	Fonetiskt balanserade ord
HL	Hearing level
HI	Hearing impairment
HRQL	Health-related quality of life
Hz	Hertz
ICRP	International Commission on Radiation Protection
IOI-HA	International Outcome Inventory for Hearing Aids
ISO	International Organization for Standardization
MCS	Mental Component Summery
MSCT	Multi-slice computed tomography
PB	Phonetically balanced words
PCS	Physical Component Summery
PTA	Pure tone average
S/N	Signal-to-noise ratio

SF-36	Short Form 36 Health Survey
SSQ	Speech Spatial and Quality
VGA	Visual grading analysis

1 INTRODUCTION

Otosclerosis – do we have a problem?

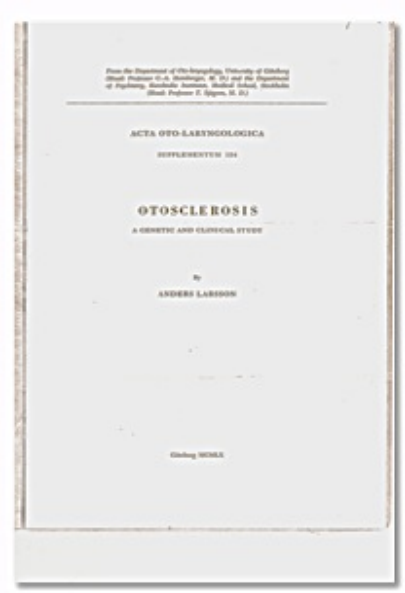
In a scene from a famous TV series, one of the doctors looks at a CT scan of a temporal bone and says, "It's otosclerosis! I can fix it!"

Fact or fiction?

Today, it is possible to bypass the fixated stapes with a stapedotomy or a stapedectomy – but what happens in the long term? Surgery bypasses the mechanical obstruction but does not cure otosclerosis. A majority of individuals with otosclerosis acquire the disease at a young age and consequently live with otosclerosis for many years.

My interest in otosclerosis started in genetics. Professor Claes Möller had in his office a couple of small brown boxes containing small white cards with cryptic writings. The boxes and cards were materials from Anders Larsson's extensive research in otosclerosis genetics. Anders Larsson was one of the pioneers in the field. Anders Larsson's son, and fellow ENT, had found the material in his attic and had given it to Claes for potential use in further research. In his research Anders Larsson aimed to calculate the heredity of otosclerosis. Individuals admitted to the Sahlgrenska University Hospital, Gothenburg (1949-57) with a diagnosis of otosclerosis were included in the research. Field investigations in which the relatives of the subjects were assessed followed. In all, 1740 individuals were included. As a result of this study Anders Larsson concluded that the mode of inheritance probably was autosomal dominant with a reduced penetrance of 25-40%, this figure is used even today (1).

Our genetic research in otosclerosis started in search of large families with many affected family members for linkage analyses. We, like many other researchers, found that these families are very rare. This research is still ongoing. My interest in otosclerosis was piqued! A common clinical experience is that many patients with otosclerosis suffer from a progressive severe hearing loss. When they visit the clinic, they wonder why their hearing is deteriorating. Yes, they have had otosclerosis, but that should have been taken care of, as they have had surgery. The present work started with a search for old surgical records, which were found in a tiny closet behind the secretariat.


ACTA OTO-LARYNGOLOGICA

SUPPLEMENTUM 124

OTOSCLEROSIS

A GENETIC AND CLINICAL STUDY

By

ANDERS LARSSON

Figure 1. Front page of Anders Larsson's thesis, Otosclerosis a genetic and clinical study

In our studies we aimed to assess the medical, technical (hearing aid uptake) and functional (HRQL) aspects of otosclerosis from a long-term perspective.

2 BACKGROUND

2.1 The auditory system

The auditory system is involved in the perception of sounds and is divided into two major parts: the ear and the central auditory system. You hear with the ear but listen with the brain. The purpose of the ear is to convert mechanical sound waves into nerve impulses, and the purpose of the central auditory system is to process the neural signals and finally to perceive sounds. The human auditory system is extremely sensitive and has an amazing ability to extract sounds from a background of noise. A listener with a healthy auditory system can "tune in" to a special conversation and quickly switch his or her attention if something more interesting turns up.

2.1.1 Anatomy

The ear consists of three major parts: the outer, middle and inner ear. The auricle and the external ear canal make up the external ear. The middle ear consists of the tympanic cavity and the osseous parts of the Eustachian tube. The tympanic cavity is an air-filled cleft within the temporal bone bounded laterally by the tympanic membrane and medially by the osseous labyrinth, the promontory, the basal turns of the cochlea and the oval and round windows (fig. 2). The tympanic cavity contains the three ossicles (malleus, incus and stapes), the tympanic segment of the facial nerve, the chorda tympani, the stapes and the tensor tympani muscles and its tendons.

The posterior wall of the tympanic cavity is complex and contains several important anatomical landmarks. It contains, for instance, the pyramidal eminence, a bony elevation that transmits the tendon of the stapedial muscle, and the chorda tympani entering the middle ear lateral to the pyramidal process. The facial recess is situated between the pyramidal process and the chorda tympani.

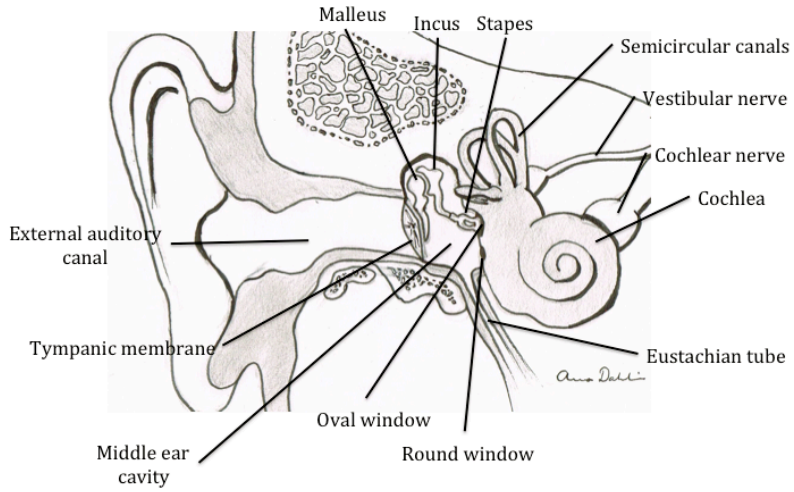


Figure 2. Schematic drawing of the outer- middle- and inner ear

The inner ear is situated within the temporal bone, in the otic capsule, and is made up of the cochlea and the peripheral parts of the vestibular system: the semicircular canals, utricle and saccule. The inner ear contains fluid-filled labyrinths: the osseous labyrinths (filled with perilymph) and the internal membranous labyrinth (filled with endolymph). These chambers are best visualized in the cochlea, where three channels are arranged in a spiral. The oval window leads into the scala vestibule, which continues to the apex of the cochlea, where it communicates with the scala tympani via the helicotrema. The scala tympani then extend to the round window at the base of the cochlea. Between these two scales is the scala media, with the organ of Corti and the sensory-receptor cells. The organ of Corti is situated at the basilar membrane of the scala media and contains one row of inner hair cells and three rows of outer hair cells. The sensory hair cells are connected via neurons that, in the modiolus form the auditory nerve (n. VIII). The auditory nerve extends medially through the inner ear canal and extends to the cochlear nucleus in the cerebellopontine-angle area.

The central auditory system extends from the cochlear nuclei to the cerebral cortex. The pathways are interconnected, with several nuclei at different levels. From the cochlear nucleus the pathways continues both ipsi- and contralateral to the superior olivary complex, further on through the lateral lemniscus, to the inferior colliculus and to the medial geniculate body. The primary auditory cortex is located in the temporal lobe (fig. 3).

The projection of audible frequencies is tonotopical, from the cochlea to the auditory cortex.

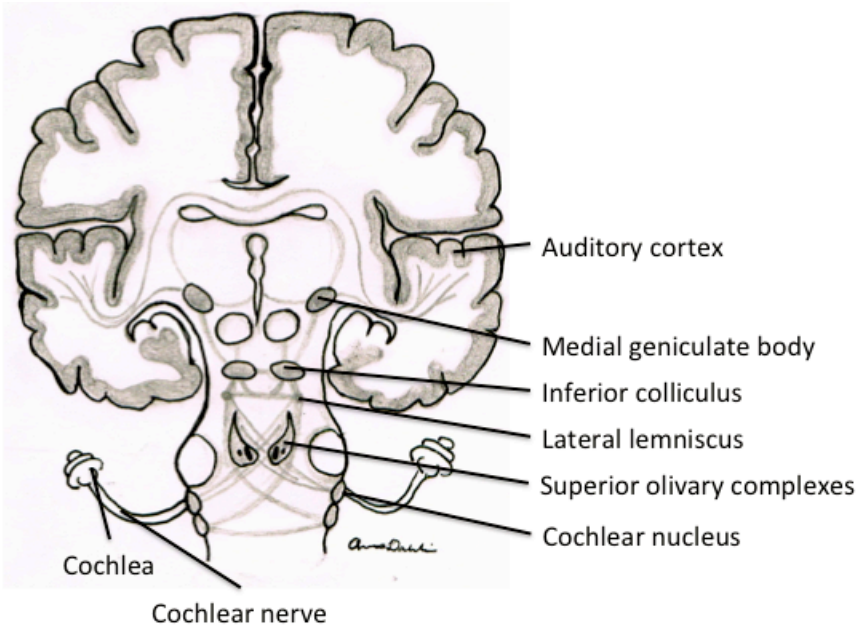


Figure 3. Schematic drawing of the central auditory pathways.

2.1.2 Physiology

Sound is acoustic energy produced by a moving object creating pressure waves. Hearing can be described as the transformation of airborne mechanical energy to electrically coded energy specified by frequency, amplitude and temporal resolution. The function of the outer and middle ear is to transfer sound energy to the inner-ear fluids. To make this work, the middle ear components must be intact, including a normal tympanic membrane, an air-filled tympanic cavity and intact ossicles with normal mobility. The transmission of pressure waves through the middle-ear ossicles transfers the sound energy to the inner-ear fluids via the stapes footplate and the oval window. Vibration of the stapes footplate produces a compressional wave in the inner-ear fluids. This wave creates a pressure difference across the cochlear scala media, producing a travelling wave in the basilar membrane. The travelling wave starts in the stiffest parts (the base) and propagates to the least stiff part (the apex). The travelling wave stimulates the hair cells and nerve impulses are created and progress to the auditory nerve and cochlear nucleus.

The physiology of hearing by bone conduction is not yet fully understood. Five major factors contributing to the hearing have been identified; 1) sound radiating into the ear canal, 2) inertia of the middle-ear ossicles, 3) inertia of the inner-ear fluid, 4) compression of cochlear walls, and 5) pressure from the cerebrospinal fluids. The inertia of the cochlear fluid has been considered as the most important factor (2).

In individuals with conductive hearing loss due to stapes fixation, the importance of the ossicle inertia in bone conduction hearing becomes evident, creating a false poorer bone-conduction threshold. This effect was first recognized by Carhart (1950) and has since been called the Carhart effect. The Carhart effect is most prominent at 2 kHz (2-4).

The central auditory system is complex with both sequential and parallel processing. “Sequential processing” means that the information is transferred from one center to the next in a hierarchical manner and is influenced and modified on the way to the auditory cortex. “Parallel processing” means that there is an increasing number of separate auditory pathways further up in the central auditory system, with increasingly more parallel processing. There are both ascending (afferent fibers) and descending pathways (efferent fibers), with the efferent pathways acting as a feedback system. The superior olivary complex receives information from both cochleas, the base for auditory binaural listening, with interaural time difference (ITD) being most important at lower frequencies and interaural level difference (ILD) being most important at high frequencies. Frequency specificity is coded by tonotopical organization throughout the auditory pathways.

2.1.3 Pathophysiology

The most common type of hearing loss is caused by inner-ear deficiencies (sensory hearing loss). The etiologies of sensory loss can be genetics, infections, noise, drugs, age, circulatory problems or a combination of these factors. The most common causes are probably genetic and age related. The hearing loss is in most cases due to hair cell loss where the hair cells at the base of the cochlea seem to be most vulnerable, causing a high frequency loss. Hearing loss caused by auditory neuropathy and central disturbances are not as common and in many cases are combined with other neurological deficiencies. Hearing loss caused by pathophysiology in the middle ear is often due to infections (acute otitis media, chronic otitis media), ventilation problems (serous otitis media, cholesteatoma), congenital malformations or trauma.

2.2 Hearing assessments

2.2.1 Pure tone audiometry

Pure tone audiometry assesses hearing thresholds for air and bone conduction over a range of pure tone frequencies. The results of the assessment are used to diagnose normal or abnormal hearing sensitivity and to evaluate the degree and type of hearing loss.

For reliable test results, the assessments must be carried out in a soundproof booth and with regularly calibrated audiometers (ISO 389). In air conduction, the test-retest reliability is 5 dB, while with pure tone bone conduction, the test-retest variability can be 10-15 dB (5, 6).

To be able to test the auditory function of each ear independently, masking of the non-test ear is necessary. Regarding bone conduction, the inter-aural attenuation (the amount of energy lost during the transmission of sound across the skull) is 0-10 dB, and thus, masking is necessary so that each ear can be tested separately. Regarding air conduction, the inter-aural attenuation varies and depends on for instance, skull anatomy and the frequencies tested; to prevent cross-signals to the non-test ear, masking should be applied if the inter-aural difference exceeds 40 dB (5).

When evaluating bone conduction thresholds in individuals with otosclerosis, inner-ear function is underestimated owing to the Carhart effect, (see page 6, physiology).

2.2.2 Speech audiometry

Speech audiometry is an important component in auditory diagnostics as well as in hearing aid fitting and rehabilitation. Many tests have been used to evaluate speech, which can be presented either monaurally or binaurally, at the threshold or supra-threshold level. The speech can be sentences, words or nonsense words, against a background of quiet or competing noise. In Sweden, phonetically balanced monosyllabic words presented at a supra-threshold level are the most commonly used test material (PB, in Swedish FB). The word list can be presented against a background of quiet or speech-weighted noise at a fixed signal-to-noise ratio (+4dB S/N) (7). The result is presented as the percentage of correct words at a certain presentation level.

2.2.3 Impedance measurements; Stapedial reflexes

In a normal ear, the stapedial reflex is elicited if sound of sufficient intensity (70 – 90 - 100 dB HL) reaches the inner ear. The contraction of the stapedial muscle results in the movement of the ossicular chain and as a consequence, the stiffening of the tympanic membrane. Stapedial reflexes are usually tested with pure tones at 0.5, 1, 2, and sometimes also 4 kHz. At least two frequencies must be tested to enhance the reliability of the test. The test can be performed with contralateral and ipsilateral stimulations. The standard probe-tone frequency today is 226 Hz, in contrast to the probe-tone frequency used in the 1970s, which was 625 Hz or even higher (5).

To be able to elicit and record a stapedial reflex, certain conditions must be fulfilled. First, the sound stimulus must be at a significant level above the pure tone threshold at the specific frequency tested. In 95% of individuals with normal hearing, the reflex threshold will vary between 70 and 100 dB. If sensorineural hearing loss greater than 45 dB (or 55 dB due to recruitment) is present in the stimulated ear, no reflex would probably be elicited (8). If the hearing loss in the stimulated ear were conductive, no reflex would probably be elicited if the hearing loss exceeded 30-40 dB. Second middle-ear disorders, such as otosclerosis with a fixated stapes or a disrupted ossicular chain, will obstruct the reflex. Finally, disturbed neural function in the brainstem and/or in the facial nerve would impair the acoustic reflex.

2.3 Otosclerosis

Otosclerosis has confused and interested clinicians and researchers for centuries (9).

• 1704	Valsalva	found a stapes fixated by ankylosis in postmortem examination on a dead patient.
• 1857	Tonybee	linked stapes fixation to hearing loss.
• 1893	Polizeer	described the fixated stapes as a specific disease with hearing loss. Earlier the hearing loss had been described as nervous deafness and the fixated stapes had been described as a consequence of catarrhal inflammation of the middle ear.
• 1902	Polizer	proposed the name otosclerosis.
• 1912	Siebermann	showed that the lesions begins as a spongification of the bone and named the disease otoscpongiosis.

Figure 4. Overview of the historical background of otosclerosis (9).

2.3.1 Clinical presentation

Otosclerosis is a common form of adult-onset hearing loss, with prevalence among Caucasians estimated to be 0.3-2.1%. The estimated prevalence varies depending on how the studies have been performed. Clinic-based studies (estimates from known patient populations) have show results varying between 0.1-0.3% (10-12), whereas population-based studies yielded 2.1 and 1.3 % (13, 14). Calculations from histological studies of clinical otosclerosis (defined as fixation of stapes) have shown results of approximately 0.3 % (in contrast to histological otosclerosis with results of 3-15%) (15). The average age of onset is in the third decade of life, with a range from late teenage years to the 6th decade and with a male-to-female ratio of 1:2 (1, 10, 14).

It has been debated whether pregnancies and oral contraceptives have any effect on the development of otosclerosis (16-18). One retrospective study showed that the risk of subjective hearing deterioration with bilateral otosclerosis increased with increasing number of pregnancies (18). In contrast, another retrospective study showed that no significant correlation was found between number of children and hearing loss in women prior to and after (3 years) stapedectomy (16). Possible effects of oral contraceptives have also been discussed, however a study including 17032 women with oral contraceptives did not demonstrate any increased risk of ear disease including otosclerosis (17). Preliminary, and so far unpublished data, from our cohort, demonstrated a significant correlation between number of children and PTA_4 AC and BC preoperatively but not at follow-up. The same correlation could not be demonstrated for men.

Clinical otosclerosis causes progressive hearing loss, primarily conductive and later mixed hearing loss. Studies reporting follow-up periods after surgery exceeding approximately 5-10 years have demonstrated progressive sensorineural hearing loss, which have been interpreted to be age related in the majority of cases (19-21). In contrast, recent studies have demonstrated sensory hearing loss disproportionate to age both pre- and postoperatively (22, 23). Pure sensorineural hearing loss due to cochlear otosclerosis has also been encountered both in histological studies and in the preoperative assessments of cochlear-implant candidates with computed tomography (24, 25).

In a majority of patients the hearing loss is of moderate-severe severity; however, a small number of patients (1.6%) develop a profound sensorineural hearing loss according to Shea (1999) (26). Ramsey et al. reported a significantly higher frequency, with 8.9% developing a sensorineural hearing loss exceeding 65 dB (BC) 25 years after surgery (range 15-44 years)(21). No relevant references regarding clinical bilateral disease have been found. Bilateral radiological otosclerosis has been reported in 85% and histological in 70-80% (27, 28). The classical pure tone audiometric configuration is the conductive hearing loss type most prominent at 500-1000 Hz, in combination with a notch in the BC threshold at 2000 Hz (the Carhart notch) and a sensorineural loss at 4000 Hz (fig. 5).

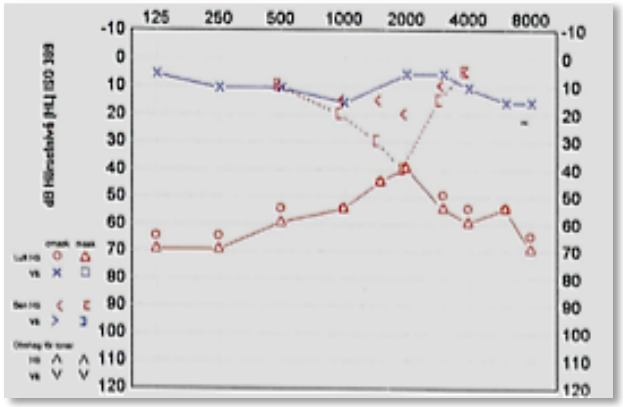


Figure 5. A pure tone audiogram in an otosclerosis subejct with typical Carhart's notch.

Tinnitus is a common symptom in clinical otosclerosis, with a reported frequency of 65-75% (1, 29). It can even be the presenting symptom before hearing loss is evident. Surgery has been demonstrated to alleviate the tinnitus in 50-80% of subjects in some studies, whereas in other studies, a postoperative tinnitus prevalence of 52% has been reported, with improvement in 33% and worsening in 11 % of subjects (30, 31).

Vertigo is infrequently encountered in otosclerosis subjects outside the immediate postoperative period, with a frequency similar to that in the general population according to Grayeli et al. (32): however, a recently published study of patients with non-operated otosclerosis and dizziness demonstrated an abnormal BC-VEMP (bone conduction- vestibular evoked myogenic potential) indicating saccular dysfunction. Immediate postoperative vertigo is significantly more common, with about 25% prevalence (19). Associations with endolymphatic hydrops and superior canal dehiscence syndrome have been discussed. The association between endolymphatic hydrops and otosclerosis is not clear; one possible explanation is obstruction of the endolymphatic duct by otosclerotic foci, which has been demonstrated in a histological study (33). Superior-canal-dehiscence syndrome has been reported after surgery, as a "third window" has been opened during surgery, and the symptoms of superior-canal dehiscence becomes clinical (34).

Otosclerosis is suspected if a patient shows progressive conductive hearing loss in combination with a normal otoscopy and with no previous history of ear disease. Impedance measurements indicating stapes fixation in at least

two frequencies strengthen the diagnosis, which can be confirmed via surgery or with CT. A diagnosis of 100% certainty requires histology for confirmation.

2.3.2 Histopathology

Otosclerosis is exclusively a disease of the bony labyrinth and the stapes, in the temporal bone and is only known to affect humans (35). In the otic capsule, the ossification process is enchondral and is completed at 1 year of age. Once ossified, the bone turnover in the otic capsule is significantly lower compared to all other parts of the human skeleton. The bone remodeling is centripetally inhibited with the lowest turnover rate closest to the perilymphatic space (0.1% per year compared to 10% in other parts of the human skeleton), most likely through the anti-resorptive action of the cytokine osteoprotegerin (OPG) (36). The significance of the special features of the otic capsule in the development of otosclerosis is not known.

In otosclerosis, the bony labyrinth is affected by abnormal bone remodeling, with lesions of bone resorption followed by new bone formation. The development of an otosclerotic lesion has been described as follows: 1) destruction of the enchondral bone with formation of resorption spaces characterized by high cellularity and vascularization, 2) production of immature bone, 3) repetition of the remodeling process with production of more mature bone and 4) formation of highly mineralized bone with irregular patterns. In addition an otosclerotic focus can have regions with both active and inactive stages of the disease. Predilection sites for otosclerotic lesions are anterior to the oval window, in the round window niche and in the peri-cochlear space (27, 37) (fig. 6).

Otosclerosis foci encountered in the temporal bone have been defined in three distinctive forms:

a) histologic otosclerosis; otosclerotic foci in the temporal bone without causing stapes fixation.
b) clinical otosclerosis; an otosclerotic foci engaging the stapes footplate and thus leading to a fixated stapes.
c) cochlear otosclerosis; an otosclerotic lesion replacing parts of the endosteal layer of the cochlea.

Histologic otosclerosis is approximately ten times more common than clinical otosclerosis. Histological otosclerosis does not exhibit sex differences like the clinical otosclerosis does, but the cause of the difference

is not known (27, 38). There have been conflicting results regarding the correlation between cochlear otosclerosis and sensorineural hearing loss and the mechanism is unclear (39). Diffusion of hydrolytic enzymes into the perilymph resulting in degeneration of the hair cells is one of the proposed mechanism (40).

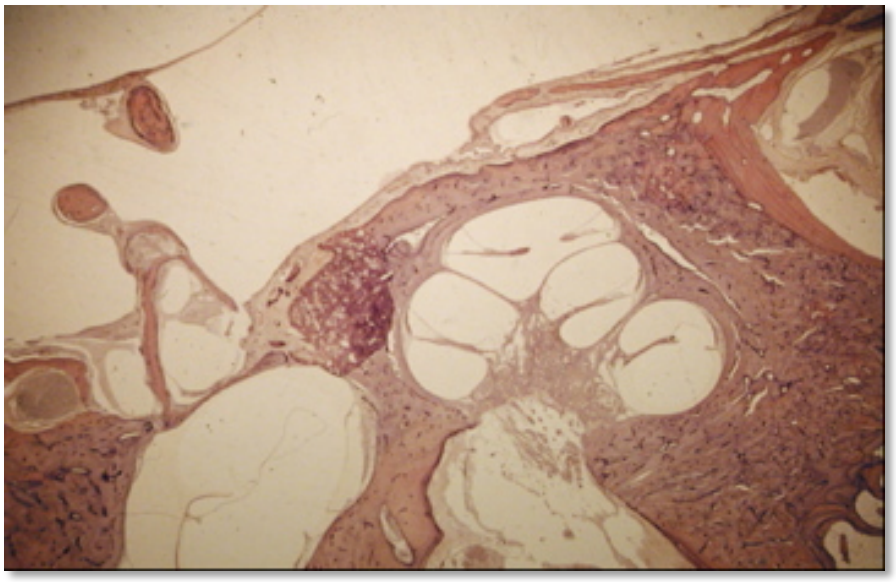


Figure 6. A histological view of an otosclerotic lesion adjacent to the stapes footplate and cochlea. (P. Bretlau by permission).

The term cochlear otosclerosis (previously only used to describe histologic otosclerosis with the replacement of the endosteal layer in the cochlea) has subsequently been used in conjunction with clinical otosclerosis to refer to sensorineural hearing loss, that is presumably caused by otosclerosis in contrast to age-related hearing loss. In this thesis the term cochlear otosclerosis refers to sensorineural hearing loss disproportionate ta age in subjects with otosclerosis.

2.3.3 Etiology

The etiology of otosclerosis remains unknown. Several hypotheses, including genetic, viral, autoimmune and hormonal factors, have been postulated. Today, the disease is considered complex, with both genetic and environmental factors of importance.

Genetics

The hereditary pattern recognized so far is autosomal dominant with reduced penetrance (40%)(1). Approximately 50% of individuals with otosclerosis have an affected family member; however, the families are rarely large enough for linkage analyses to be performed. Linkage analyses performed in large families with autosomal dominant otosclerosis have so far identified 10 possible genetic loci (OTSC 1-10) (41-48). Case-control studies have analyzed the association between otosclerosis and specific candidate genes. Interesting genes include COL1A1, TGF-β1, BMP2 and BMP4, all of which have a role in bone and /or otic-capsule development and remodeling (49-52). Genome-wide association studies (GWA) identified the RELN gene (produces reelin) in two independent otosclerosis populations; furthermore confirmed in additional families. RELN plays a role in neuronal migration however; its role in otosclerosis is unclear (52-54).

Viral

One of the hypothesized environmental factors in otosclerosis is persistent measles-virus infection. An association between measles virus and otosclerosis has been demonstrated; filamentous structures similar to Paramyxovirus have been detected by electron microscopy in otosclerotic osteoclasts (55). Measles-virus-specific IgG in otosclerotic perilymph, as well as measles-virus-specific proteins and RNA (using PCR technique), have been detected in otosclerotic stapes (56, 57). Furthermore, vaccination against measles appears to be associated with decreasing numbers of stapes surgeries and increasing age at surgery (58, 59).

Autoimmunity and inflammation

Another possible etiologic factor is an autoimmune reaction against type II collagen in the otic capsule (60). The inflammatory cytokines TGF-β1, BMP (2 and 4), TNF-α and the osteoprotegerin (OPG)-RANK-RANKL system have also been proposed to play a role in the pathogenesis (61). (RANK=receptor activator of nuclear factor κB, RANKL= RANK ligand). The OPG-RANK-RANKL system appears to be a determinant in bone metabolism with RANKL as a potent osteoclast activator, RANK as its receptor located on osteoclast precursors and OPG as a decoy receptor capable of inhibiting the maturation and activation of osteoclasts and promoting their apoptosis. OPG-knockout mice have been shown to develop osteoporosis and changes similar to otosclerosis (62).

Hormonal and metabolic factors

Clinical otosclerosis is twice as prevalent in females as in males, giving rise to the hypothesis that sex hormones may contribute to the development of

disease. Prolactin has an inhibitory effect on osteoblast function and enhances bone resorption by increasing the RANKL/OPG ratio. Estrogen has a protective role in bone metabolism but on the other hand estrogen and progesterone stimulates prolactin release (63). This interaction might explain why pregnancies, lactations and oral contraceptives may contribute to increased risk of otosclerosis.

2.3.4 Treatment and rehabilitation

Surgical treatment

Surgery for otosclerosis has not always been the safe way to improve hearing as it is today.

1878	Kessel	Found that a fracture through the horizontal semicircular canal (trauma) improved hearing in a deaf boy.
1842	Ménière	Stapes mobilization was considered dangerous, as many died in meningitis.
1923	Holmgren	Created a fistula in the horizontal semicircular canal and covered it by a mucoperiosteal flap (fenestration).
1929	Nylen	Developed the binocular microscope.
1930	Lempert	Developed the one-stage fenestra technique.
1953	Rosen	Renewed the technique of mobilization.
1958	Shea	Removed the stapes, covered the oval window with vein graft and attached an artificial stapes from the incus to the oval window (stapedectomy).
1962	Robinson	Introduced the piston / prosthesis.

1970	Meyers	Changed the large fenestra to small fenestra (stapedotomy).
Many modification by several surgeons		

Figure 7. The evolution of otosclerosis surgery (64).

The main goal of stapes surgery is to normalize hearing by bypassing the fixated stapes to transmit sound waves into the inner ear.

The main principles of stapedectomy are: the stapes footplate is removed; the oval window is sealed with a vein graft, fascia or perichondrium; and a prosthesis is installed from the incus to the oval- window niche.

The main principles of stapedotomy are: a fenestration is made in the footplate by a drill or laser, and a prosthesis is fitted from the incus into the fenestration in the footplate.

In both techniques, the stapes tendon is usually cut, the incudo-stapedial joint is divided and the supra structures of the stapes is removed. The surgery is mostly performed under local anesthesia. There are several variations in exactly how the surgery is performed (65).

Numerous studies have found that both stapedectomy and stapedotomy are successful surgical methods to improve hearing, in the short and longer-term perspective (66). Successful surgery has often been described in studies as ABG closure, with ABG <10 dB as the main goal (67). Gatehouse and Browning added the important parameters; AC improvement of >10 dB and BC not worsened by >5 dB (3). In comparison, stapedectomy has shown better gains at lower frequencies, while stapedotomy has shown better results at higher frequencies (4-6 kHz) (68-71). Long-term follow-up studies have not demonstrated any major differences between the methods (19, 66).

Medical treatment

Medical treatment in otosclerosis has been used in patients with progressive sensorineural hearing loss, with the intention of slowing down and/or stopping the progression of bone resorption. There is currently little evidence for the benefit of sodium-fluoride treatment (72, 73). A major limitation on treatment with sodium fluoride is the adverse effects (renal, liver, heart failure) at doses that may be effective (40-60 mg/day). Bisphosphonates may be an alternative, but further studies are required (74).

Hearing aid rehabilitation

Hearing aid rehabilitation in otosclerosis may be the sole treatment of choice or the treatment of choice during periods with deteriorated hearing, conductive, mixed or sensorineural.

With hearing impairment caused by otosclerosis, different hearing aid technologies can be used, depending on type and degree of hearing loss: a hearing aid placed behind the ear, in the ear-canal, a BAHA (bone anchored hearing aid) or an cochlear implant. In pure conductive hearing loss, the inner ear is intact, with normal speech recognition and dynamic range; hence, the goal of the hearing aid amplification is to overcome the conductive component with a favorable outcome (75). In patients with an ABG exceeding 45 dB, de Wolf and co-workers showed a benefit in speech recognition with BAHA compared to a behind the ear hearing aid (HA) (76).

For most individuals, bilateral amplification is beneficial with improved intelligibility in noise and sound localization (77-79). Unilateral hearing aid amplification may also cause an auditory deprivation, with decreased speech recognition in the unaided ear (80).

2.4 Computed tomography

The evolution of computed tomography (CT) has revolutionized diagnostic radiology during the last 30 years, making it central in diagnostics and management of different diseases, as well as in the care of otosclerosis patients. In otosclerosis, CT is used in cases with uncertain diagnosis, post surgery if the patient hearing has deteriorated, to evaluate prosthesis positioning, cochlear otosclerosis, vertigo, suspect superior-canal dehiscences an so forth. (34, 81).

2.4.1 Multi slice computed tomography (MSCT)

The standard computed tomography technique today is the so-called third-generation computed tomography, multi slice computed tomography. In MSCT, a wider fan-shaped x-ray system connected to a detector circles round the patient producing cross sectional images. In a 16-Slice (or more) scanner, a multiple-detector array (multiple parallel rows of detectors) enables simultaneous acquisitions of 16 thin slices per rotation. The innermost detector elements allows for 16 thin slices (from 0.5 mm to 0.75 mm thick, depending on the model). MSCT with half-second rotation times and

simultaneous acquisition, a near-3-dimensional volume with sub-millimeter sized voxels is well suited to advanced 3D reconstructions (82).

The rapid expansion of CT has expanded the numbers of examinations to the extent that CT now has a substantial impact on patients' and populations' exposure to medical x-rays. Limiting radiation dose is a growing concern (European Guidelines on quality criteria for computed tomography) (83) and as a consequence, two basic principles have been advocated by the International Commission on Radiation Protection (IRCP) (84). These principles include a policy of justification, including indication for and choice of imaging technique and optimization in the terms of ALARA (as low as reasonable achievable), meaning keeping the dose as low as possible to meet clinical requirements.

2.4.2 Cone beam computed tomography (CBCT)

Cone beam computed tomography, a new technique with advantages such as lower radiation dose and with the ability to examine a limited volume, might be the new technology in the evaluation of middle and inner ear. CBCT is increasingly being used in otology; however when new techniques are being introduced, one must make certain that the new technique is better than or at least as good as the technique that it replaces.

CBCT was originally developed at the Mayo Clinic Biodynamics Research Laboratory in 1982, with an emphasis on applications relating to cardiac and pulmonary function (85). In 2001, the CBCT system became commercially available for maxillofacial imaging (86) but its use for temporal bone imaging has also attracted interest. Studies of cadaver temporal bones have shown that CBCT is as accurate as (87, 88) or even better than MSCT (89) for revealing clinically and surgically important anatomical structures. Clinical studies in humans have so far focused on the use of the technique for imaging cochlear implants, implantable hearing aids and implants for bone-anchored epistheses and hearing aids (90, 91).

In the CBCT technique, a cone-shaped x-ray beam, together with a detector positioned on the opposite side, makes a circular movement around the patient. The x-ray beam and the detector are connected with a gantry. The center of the circle is positioned in the midpoint of the region of interest. Image data are recorded in a single rotation (200°-360°), during which sequential planar projections are acquired. The collected images are then

reconstructed to create a volumetric data set (primary reconstruction). From the volumetric dataset, voxels are extracted. The dimensions of the voxels in CBCT are isotropic and are dependent on the pixel size of the detector area (92) (figures 8,9 and 10).

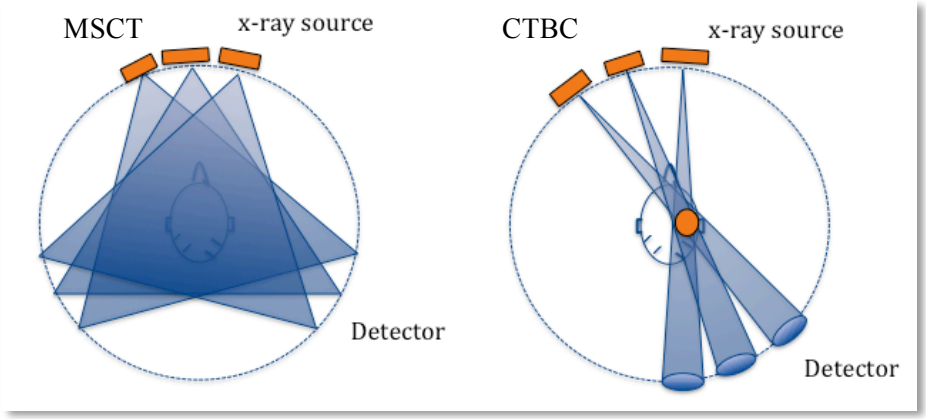


Figure 8. The principles of CBCT in comparison to MSCT.

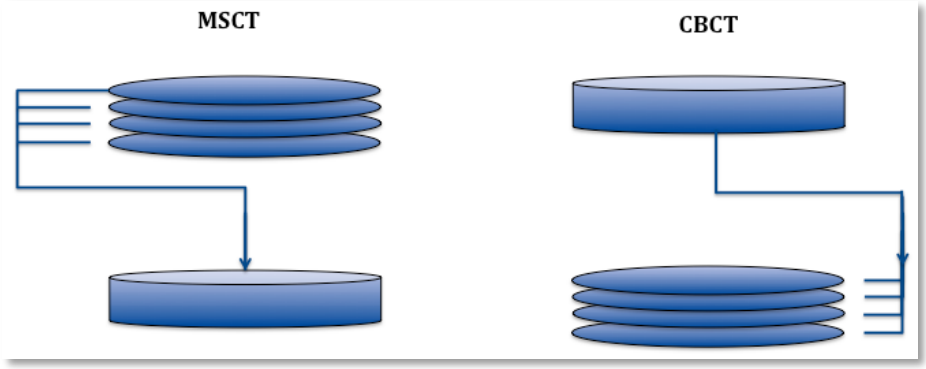


Figure 9 The principles of CBCT in comparison to MSCT.

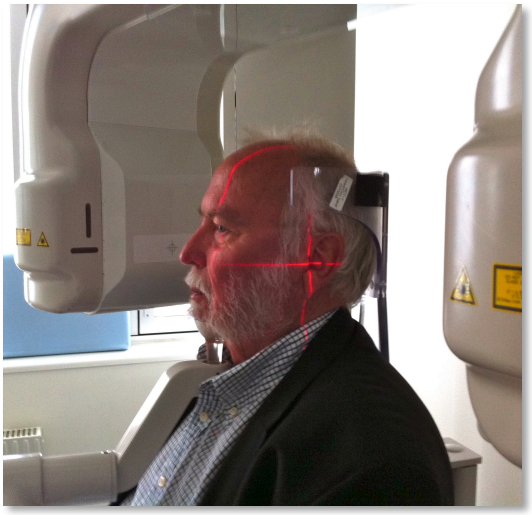


Figure 10. CBCT with a horizontally placed gantry with the X-ray tube and the flat panel (CMOS) detector positioned on opposite sides. During the examination, the patient is seated, and the head is fixed in place with a chin and forehead strap (not demonstrated in this picture). Laser light lines indicate the x, y and z planes. (Presented by permission)

Image quality, and thus the ability to visualize minor structures are influenced by several parameters. In CBCT, spatial resolution, contrast resolution and noise are factors of importance. Spatial resolution is the ability to discriminate objects of different attenuation at small distances and is influenced by the voxel size. High spatial resolution is possible with smaller voxel sizes, however, smaller voxel sizes requires higher radiation dose, as it otherwise results in increased quantum noise. Contrast resolution is a measure of the ability to distinguish between tissues with slightly different attenuation. Contrast resolution depends on the amount of gray-levels (bit-depth) that each voxel can attain and is also affected by limiting factors such as x-ray scatter and quantum noise. Small FOVs (fields of view) reduces the amount of scatter radiation and enhance the image quality. As each voxel only can attain one gray level, objects smaller than the voxel can be averaged out since the gray level is the result of an average of the densities in the voxel. This is called partial volume averaging and is reduced by smaller voxel size (93-95). Image quality is also dependent on patient factors, such as movement during exposure; minimized by short exposure time, supine positions or as in the machine we used, a forehead and chinstrap.

Image quality assessments can be divided into four main groups: physical methods, psychophysical methods, observer performance and evaluation of

diagnostic performance. Evaluation of diagnostic performance is focused on patient diagnosis and includes methods such as preference studies and visual grading analysis (VGA). VGA is the preferred method, according to Månsson (2000) when evaluating image quality by focusing on pre-defined anatomical structures (96).

2.5 Patient Reported Outcome

Although approximately 10% of the population in western countries has hearing loss affecting daily life, the consequences of hearing loss are often underestimated. Hearing loss gives rise to a variety of disabilities, such as the inability to recognize speech, especially in background noise, and the inability to identify and localize sounds. To be able to pick up speech and sounds, an individual with hearing impairment must concentrate much harder than an individual normal hearing. This extra work gives rise to fatigue, an additional consequence of hearing loss. Tinnitus, which is more frequent in individuals with hearing loss, can also be a factor enhancing the fatigue. These disabilities lead to limitations on activity and restrictions in participation, which might result in reduced social and intellectual stimulation and passivity. The consequences of hearing loss alone cannot be captured and measured by traditional quantitative data. This difficulty has led to the development of patient-outcome-report studies, studies on health-related quality of life and measurements of disease and disability.

The concept "disability" is a complex phenomenon that has been defined by WHO: an umbrella term covering a) impairments (eg. hearing impairment), b) activity limitations (difficulties encountered by an individual in executing a task) and c) participation restrictions (problems experienced by an individual in involvement in live situations). (www.who.int/topics/disabilities/en/)

2.5.1 Quality of Life – Health-Related Quality of Life (HRQL)

In medical research, "quality of life" has been restricted to a person's perception of quality of life related to health and disease. Additionally, "health status" has in the literature increasingly been referred to as "quality of life" or more correctly "health-related quality of life". Questionnaires

measuring health status are named generic questionnaires (eg. Short Form-36; SF-36) and are usually used in medical care and research together with disease-, symptom- or disability-specific questionnaires (eg. SSQ, HAD) (97, 98).

Generic instruments are intended for general use, regardless of condition or disease and are valid in healthy people. Generic instruments are frequently used as an outcome measure in the evaluation of different treatments, as well as in chronic diseases, to evaluate the burden of the disease on health status.

2.5.2 Patient-reported outcomes and hearing loss

Studies analyzing the impact of hearing loss on HRQL using the generic instrument SF-36 have shown impaired scores indicating poorer HRQL on both mental and physical scales in large population-based studies (99, 100) while other studies found no decline in HRQL (101). It has been argued that generic instruments lack the sensitivity needed to measure the effects of hearing loss (102); on the other hand, there is an ongoing debate as to whether generic instruments should reflect health and not functional limitations (103).

In otosclerosis, all patient report outcome studies performed to date to our knowledge have evaluated surgery (104-106). Hearing loss in otosclerosis is predominantly mixed and is often asymmetric, influencing disability and differentiating the hearing loss from other types of hearing loss, such as age-related hearing loss. Localization of sounds may be more difficult for patients with otosclerosis with asymmetric hearing loss compared to individuals with symmetric sensorineural hearing loss; this difference is probably caused by the greater degree of asymmetry (107, 108).

In this thesis one generic (Short Form 36; SF-36v2), one disability specific (Speech, Spatial and Quality; SSQ) and one hearing aid rehabilitation specific (International Outcome Inventory for Hearing Aids; IOI-HA) questionnaire were used.

2.5.3 Short Form 36 (SF-36v2)

The Short Form 36 (SF-36) is one of the most widely used generic questionnaires; it is a multipurpose survey comprising 36 questions covering both physical- and mental- health aspects of HRQL (109). The Swedish version has been thoroughly validated, and the psychometric properties are comparable with the original data (110-112). The second version of the SF-36, the SF-36v2, is a further modification of the first version. The most

important change was in the functional scales RP and RE, which were changed from a dichotomous to a five-step format. The new format has improved the psychometric properties of the questionnaire without disturbing the structure of the original SF-36 (113).

The questionnaire measures 8 domains of health: physical function (PF), role physical (RP = problems with work or daily activities due to physical health), bodily pain (BP), general health (GH = evaluates personal health), vitality (VT), social function (SF = interference with normal social activities due to mental or physical health), role-emotional (RE = problems with work or other daily activities as a result of emotional problems) and mental health (MH). These eight domains are summarized into summary scores: the Physical component summery (PCS) and the Mental component summery (MCS) (114). The scale scores range from 0 to 100 with 100 as the most favorable outcome.

2.5.4 Speech Spatial and Quality (SSQ)

SSQ was initially developed and validated by Gatehouse and Nobel (2004) to enhance the measurement of auditory disability, with special emphasis on the benefit of binaural hearing (115-117). The SSQ addresses a range of aspects of hearing and covers three main domains: speech, spatial perception and quality of sounds. The questionnaire has shown good reliability with Crohnbachs $\alpha = 0.88$ (118).

The questionnaire contains 50 items that measures three main aspects of hearing: I) speech, II) localization and III) quality of sounds.

Further studies have divided the domains into 10 pragmatic subgroups (119): A. speech: 1) speech in quiet, 2) speech in noise, 3) speech in speech contexts and 4) processing and switching among multiple speech streams, B. spatial: 1) localization and 2) distance and movement, C. quality: 1) sound quality, 2) identification of sound and objects, 3) segregation of sounds and 4) listening effort. The questionnaire uses a 0-10 rating scale, where 0 is minimal ability and 10 is complete ability. The mean score and standard deviation were calculated for each item, subgroup and domain.

An increasing number of studies have used SSQ as an evaluation of hearing disability in different populations as well as to measure outcomes in rehabilitation (HA, BAHA, CI) (120, 121).

2.5.5 International Outcome Inventory for Hearing Aids (IOI-HA)

The questionnaire was initially developed to assess hearing aid outcomes in adults in a research context (122, 123). IOI-HA is a validated questionnaire with good psychometric properties and has been translated into many languages, including Swedish (124). The questionnaire has also been validated in Swedish (125).

The IOI-HA comprises seven different domains with seven questions: 1) hearing aid use, 2) hearing aid benefits, 3) residual activity limitations, 4) satisfaction, 5) residual participation limitations, 6) impact on others and 7) quality of life. Factor analysis has indicated that the outcome measures can be divided into two subscales: Factor 1 (items 1, 2, 4 and 7) and Factor 2 (items 3, 5 and 6). Factor 1 represents hearing aid satisfaction and Factor 2 represents participation restriction (126, 127). Each item is scored from 1 to 5; a higher score indicates a more favorable outcome. The interpretation of the questionnaire is based on the mean score from each item, a total global score, and sub-scores for Factors 1 and 2.

3 AIMS

The study was performed to assess long-term outcomes in individuals with surgically treated otosclerosis.

Specific aims were;

- To assess hearing impairment 30 years after surgery with stapedectomy.
- To assess hearing-aid rehabilitation, hearing aid acquisition and benefit 30 years after stapedectomy.
- To assess health-related quality of life and hearing disability 30 years after stapedectomy.
- To compare CBCT with MSCT in the assessment of otosclerosis.

4 MATERIALS

4.1 Study population

The study population was identified through surgical registers. The studies started with retrieval of the old surgical registers, from the years 1977-79, at the Department of Otorhinolaryngology, Sahlgrenska University Hospital. The surgical records were sorted according to operation code and included diagnosis code, personal identification number and date of admittance and discharge from the hospital. The Department of Otorhinolaryngology at Sahlgrenska University Hospital is a tertiary referral center and was at the time the only hospital in the region performing stapedectomy. In all, 224 stapedectomies were performed during the period.

The inclusion criteria were: subjects born in 1930 or later undergoing stapedectomy in 1977-1979 due to otosclerosis (n=115). Otosclerosis was defined as a preoperative progressive hearing loss, impedance measurements indicating stapes fixation and per-operative findings of stapes fixation. The exclusion criteria were: subjects, who had moved from the region, were deceased or "missing" (fig. 11). Ninety-three individuals were invited to participate and 65 agreed to enter the study after giving their informed consent.

The study population consisted of 42 (65%) females and 23 (35%) males, all Caucasian. The mean age at surgery was 36 years, with a standard deviation (SD) of 6.6 and range of 20-48 years. At follow-up, the mean age was 65 years (± SD 6.6, range 48-77); for female subjects, the mean was 66 (48-77), and for men the mean was 64 (54-73). The participants came from the region of Västra Götaland, in the western Sweden, (table 1).

The subjects' ears were classified and analyzed according to surgery (Paper I-IV) and hearing sensitivity (AC) (paper II-III):

1. Surgery; a) study ear (operated in 1977-79) and b) control ear
2. Hearing sensitivity at follow-up; a) ear with best hearing and b) ear with worst hearing

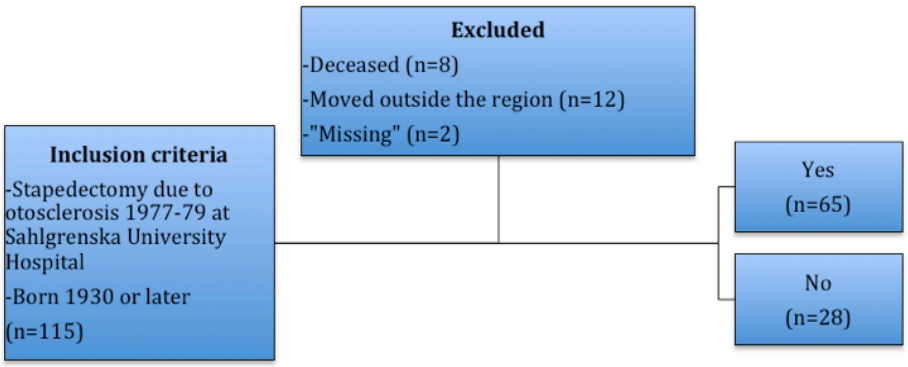


Figure 11. Inclusion and exclusion criteria.

Table 1. Baseline study population

Variables		At surgery	At follow-up
Sex	**Female (%)**		**65**
Age	**Years (mean)**	**36**	**65**
Otosclerosis	**Bilateral (%)**		**88**
Study ear	**(n)**		**65**
Control ear	**Otosclerosis / surgery (%)**		**52**
	Otosclerosis / no surgery (%)		**35**
	No otosclerosis (%)		**12**
Living arrangements	**With others**		**44%**
Education	**≤ 9 years** **10-12 years** **≥ 13 years**		**42%** **23%** **26%**
Co-morbidity	**Yes**		**72%**
Familiar otosclerosis	**Yes**		**46%**
Tinnitus	**Yes**		**51%**

Co-morbidity: chronic disease such as cardiovascular disease, diabetes, etc.

Surgery

Stapedectomy was the primary form of surgery for the study ear, in 62/65 of the subjects. Three subjects had had a stapes mobilization prior to

stapedectomy. A wire prosthesis and fascia to cover the oval window niche were used in the majority of cases. A Teflon wire prosthesis and perichondrium were used in 7/65 of the cases. Eleven surgeons performed the surgeries. At follow-up, revision surgeries had been performed in 30% of the study ears (including the stapes mobilizations; 18% with one, 6% with two and 6% with three revisions).

Study population in Paper IV

In the fourth study, a subsample of the otosclerosis cohort was selected for radiological examination. The subjects were stratified according to their bone conduction in the study ear at follow-up (mean of frequencies 0.5, 1, 2 and 4 kHz) and consecutively drawn from the best (A; normal hearing to moderate hearing loss) and worst (B; severe to profound hearing loss) groups. In total, twenty patients underwent radiological examinations (fig. 12). Both groups consisted of 7 women and 3 men. The mean age was 65 years (61 years in Group A and 68 years in Group B). Bilateral otosclerosis was found in 17/20 of the subjects and bilateral surgery had been performed in 10/17 of the subjects.

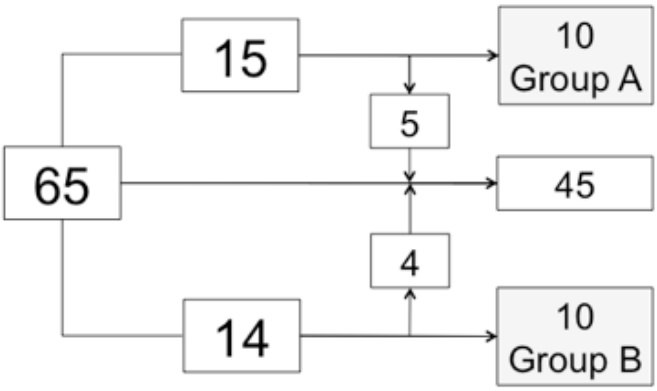


Figure 12. Inclusion in Paper IV; Group A consisted of subjects with the best bone conduction values at follow-up, while Group B consisted of subjects with the worst BC at follow-up.

4.2 Reference populations

ISO 7029 (Paper I)

The hearing outcome was compared to a reference population from the ISO 7029 according to age and sex (128). Database A (ISO 7029) describes the normal hearing distribution for each frequency (0.125, 0.25, 0.5, 1, 1.5, 2, 3,

4, 6 and 8 kHz; AC) as a function of age and sex in an otologically normal population. As the reference population was otologically normal, it was assumed that their air conduction equaled their bone conduction.

Swedish reference population SF-36v2 (Paper III)

The outcome of SF-36v2 was compared with an age- and sex- matched reference group selected from a Swedish population study (113). Normative data were collected in 1998-99 by sending the questionnaire SF-36v2 to a non-stratified, random national sample of 3000 (selected from the population register) 18- to 75-year-old Swedish residents; 2185 answered the questionnaire. From this study population, an age- and sex- matched reference population (n=236) was selected. The mean age was 64.4, with a standard deviation of 6.7 (range 40-78). Thirty-five percent of the reference population was men; 65% were women.

4.3 Non-responders

Forty-six preoperative and 41 postoperative audiograms were identified and analyzed for non-responders (n=50) and compared with the study group. No major differences were found regarding sex, age, gender or pre- and postoperative hearing outcomes (table 2). Reasons for not participating were given by most of the non-participants; in a majority, the cause was poor health of the subject or the subject's spouse. One individual was dissatisfied with the surgery and did not want to participate in the study.

Table 2. Study-ear compared with non-responders. Non-responders analyses are based on 46/50 preoperative and 41/50 postoperative audiograms. The mean values, SD and range are presented.

Varibles	Study group		Non-responders	
Sex, F/M	42/23		37/13	
Age at surgery Years ± SD, range	36 ± 6.6	20-48	38 ± 7.6	17-49
PTA_4 Pre op				
AC	53 ± 10.8	30-84	51±10.6	36-83
BC	27 ± 10.0	11-54	24 ± 8.6	9-51
ABG	26 ± 8.8	6-49	26 ± 7.8	12-42
PTA_4 Post-op				
AC	32 ± 12.6	15-60	30 ± 10.8	14-61
BC	22 ± 8.9	9-51	19 ± 8.0	7-43
ABG	10 ± 7.2	0-35	9.0 ± 5.6	0-26
dB HL/ dB ± SD, range				

5 METHODS

5.1 Audiological tests

Pre- and postoperative audiometry 1977-79

Pure tone audiometry (Paper I-IV)

Medical records were reviewed. Pure tone audiometry had been performed in a soundproof booth with monaural presentation, using a clinical audiometer (OB-70 Madsen Electronics©, Canada), calibrated according to the International Standards Organization (ISO) standard. The audiogram included frequencies of 0.25-8 kHz for air conduction (AC) and frequencies of 0.5-4 kHz for bone conduction (BC). Preoperative pure tone audiometry had been performed less than a month preoperatively, except in two subjects (6 and 14 months). Postoperative pure tone audiometry had been performed, on average, 6 month postoperatively (mean value 6.5, SD 5.8, range 1-34 months). Pure tone average (PTA_4) values (0.5, 1, 2 and 4 kHz) were calculated regarding AC and BC thresholds, as well as the Air-Bone Gap (ABG). The guidelines from the Committee on Hearing and Equilibrium regarding the four-tone pure tone average (0.5, 1, 2 and 3 kHz) could not be followed, as 3 kHz was not included in pre- and postoperative testing (129).

Speech recognition (Paper II-III)

Preoperative speech audiometry was carried out, monaurally, in the same clinical setting as pure tone audiometry. A Swedish speech discrimination test was used with phonetically balanced monosyllabic words (the results are not reported in this thesis.)

Impedance audiometry (Paper I-IV)

Tympanometry and stapedial reflexes were tested with a clinical-impedance analyzer. Stapedial reflexes were tested preoperatively with contralateral stimulation at frequencies 0.5, 1 and 2 kHz. The maximum stimulation was 115 dB HL and the probe tone frequency was 625 Hz or 800Hz.

Follow-up audiometry, 2007-08

Pure tone audiometry (Paper I-IV)

Pure tone audiometry was performed in a soundproof booth with monaural presentation, using a clinical audiometer (AC 30, Interacoustics©, Denmark), calibrated according to the International Standards Organization (ISO) standard. The audiogram included frequencies of 0.25-8 kHz for AC and frequencies of 0.5- 4 kHz for BC. In cases with severe mixed or sensorineural hearing loss resulting in an inability to establish an air-conduction threshold, 110 dB HL was noted; in subjects with an inability to establish the bone-conduction threshold, 70 dB HL was noted. Pure tone average (PTA_4) values (0.5, 1, 2 and 4 kHz) were calculated regarding AC and BC thresholds, as well as ABG. Hearing impairment was defined as a pure tone average (0.5, 1, 2 and 4 kHz) > 25 dB HL.

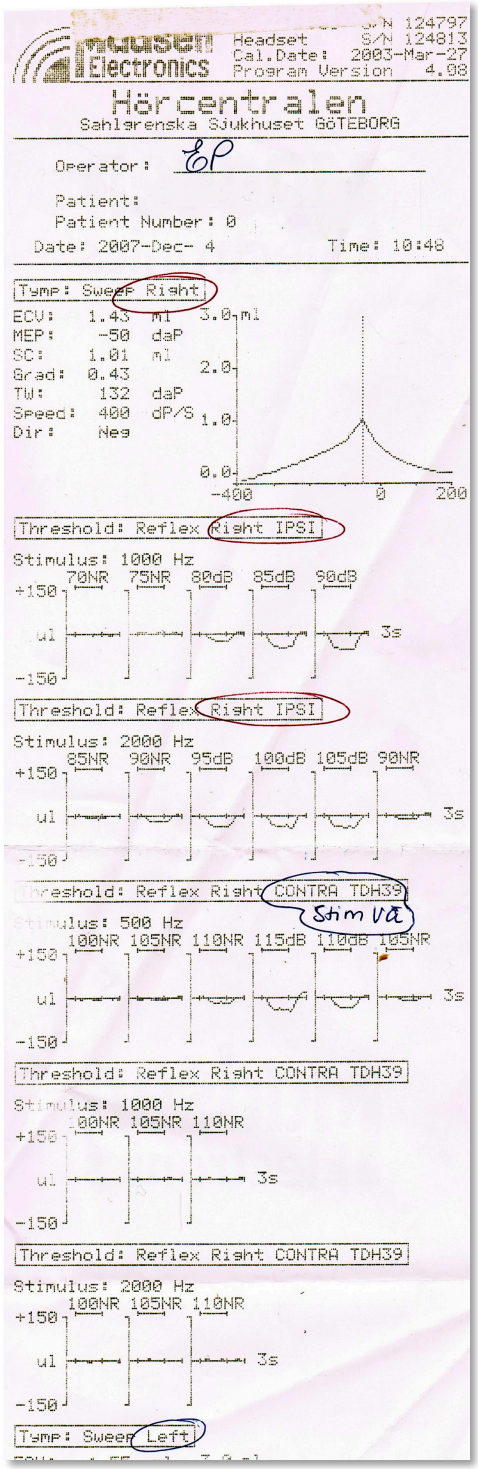
Bone conduction in the otosclerotic ears that had not undergone surgery (23/65) was corrected according to the Carhart effect (5 dB at 0.5 kHz, 10 dB at 1 kHz, 15 dB at 2 kHz and 5 dB at 4 kHz) in the comparison with the study ears (4, 20). (Paper I)

Speech Recognition (Paper II-III)

Speech audiometry was carried out in the same clinical settings as pure tone audiometry, monaurally. As test material, a Swedish speech in noise test was used as well as a Swedish speech in quiet. The words were phonetically balanced monosyllabic words in both tests. In the speech in noise test the words were pre-mixed with a speech-weighted noise in a fixed signal-to-noise ratio (+4dB S/N) (7).

Impedance audiometry (Paper I-IV)

Tympanometry and stapedial reflexes were tested with a clinical-impedance analyzer (Madsen Electronics©, Canada). Stapedial reflexes were tested in the non-operated ears with ipsi- and contralateral stimulation. The frequencies tested were 0.5, 1 and 2 kHz, with a maximum stimulation of 110 dB HL and a probe tone frequency of 226 Hz (fig. 13).



The stapedial reflexes were considered pathological if no reflexes could be measured, provided that the hearing loss did not exceed 30-40 dB HL (if conductive) and 50 dB HL (if sensorineural on the stimulus side or if a biphasic reflex pattern was noted; (130).

At follow-up, a "control ear" that had not undergone surgery was considered to have otosclerosis if the audiogram showed conductive or mixed hearing loss with a significant air bone gap (≥10 dB at two or more frequencies or ≥15 dB at one frequency) or pathologic stapedial reflexes at 2-3/3 test frequencies (0.5, 1, and 2 kHz).

Figure 13. An impedance audiometry protocol with stapedial reflex measurements ipsi and contralateral in the right ear.

5.2 Medical visit

At follow-up, structured interviews and an oto-microscopic examination were performed. Two audiologists performed a short structured interview concerning hearing aid rehabilitation while the otolaryngologist (YDR) performed an interview dealing with questions concerning medical history, tinnitus, heredity for otosclerosis and so forth.

5.3 Patient Reported Outcomes

In this thesis, the generic questionnaire SF-36v2 (Paper III), a shortened version of the hearing disability specific questionnaire SSQ (Paper III) and the hearing aid rehabilitation specific questionnaire IOI-HA (Paper II) were used (Appendices I-II). All participants answered SF-36v2 and SSQ, while only those having a hearing aid answered IOI-HA.

In addition to these questionnaires, all subjects answered a questionnaire concerning demographic data such as living relations, education, yearly income, smoking habits, occupation and employment (see Appendix III; Papers I-IV). Data regarding income, occupation and early retirement were questions, which many of the subjects were reluctant to answer, for that reason these results were not included in the analyses.

SSQ (Paper III)

A shortened Swedish version of the questionnaire SSQ was used (Appendix II). After completing the study, we discovered that some questions had reversed scales and that some of the anchoring phrases had been altered in relation to the English version. These questions were removed from the analysis (Questions; II; 14, 15, 16 and III; 2, 14, 15, 17). An additional four questions were removed because of a high percentage of missing answers (>20%; Questions; I; 8, 9 and II; 17 and III; 1). Two subjects were excluded due to >50% of the items were missing. Because of the excluded questions, two of the ten “pragmatic subscales” have not been calculated; segregation of sounds and listening effort. The subjects were asked to answer the questions as if they were using their hearing aids, if appropriate. All questionnaires were delivered to the otosclerosis subjects by ground mail in advance of the visit to the clinic. At the clinic, the subjects delivered the questionnaires to the research coordinator prior to the examinations.

5.4 Computed tomography

Multi-Slice Computed tomography (MSCT)

MSCT of the petrous bones was performed with a standardized protocol using a 16-slice CT scanner, LightSpeed Pro 16 (GE Medical Systems®, Milwaukee, WI, USA), voxel size 0.218 mm³, 120 kV, 120 mA, with 0.625 mm section thickness and coronal reformations to 0.6 mm layer thickness and 0.5 mm layer distance.

Cone-Beam Computed tomography (CBCT)

CBCT of the petrous bone was performed on a 3D Accuitomo FPD (J. Morita Co®, Tokyo, Japan) with a 60 x 60 mm cylindrical volume, 360° rotation and exposure parameters of 17.5 seconds, 80 kV and 6-8 mA, depending on the subject size. The voxels are isotropic and of size 0.125 mm^3. Primary data reconstructions were made by i-Dixel-3DX, 3D, Version 1.691, acquisition software at the Accuitomo workstation. Secondary reconstruction was made using the i-Dixel software to obtain a slice thickness and an interval of 0.5 mm. A workstation with Sectra IDS5 (Sectra Imtec AB®, Sweden) PACS Multi Planar was used.

Radiological evaluation

Anatomical structures in the temporal bone were analyzed by visual grading analysis (VGA) with a four-grade scale (96). The visibility of each structure was scored as; 1 = not visible, 2 = poorly reproduced, 3 = adequately reproduced and 4 = very well reproduced. The anatomical structures analyzed are listed in table 3. To evaluate critical reproduction and the clinical applicability of CBCT, the scores of 1-4 were dichotomized (83). The first category comprised 1 and 2 (not visible and poorly reproduced), and the second category included 3 and 4 (adequately and very well reproduced). The otosclerotic changes were graded according to Rotteveel et al. (25) where Type 1 represents fenestral lesions (thickened footplate and/or narrowed or enlarged windows), and Type 2 represents retrofenestral lesions (with or without fenestral involvement). Type 2 is further subdivided into 2a) double-ring effect, 2b) narrowed basal turn and 2c) double ring and narrowed basal turn. Type 3 is a severe retrofenestral lesion (unrecognizable otic capsule) with or without fenestral involvement.

Two senior radiologists performed the evaluations independently. Evaluator 1 was a senior specialist in neuroradiology, and Evaluator 2 was a senior specialist in maxillofacial radiology. Evaluator 1 had extensive experience

with MSCT but no prior experience with CBCT. Evaluator 2 had experience with both techniques. Both had previous experience with temporal-bone imaging and analysis.

Table 3. Anatomical landmarks in the middle and inner ear analyzed by visual-grading analysis

Scutum	**Incudo malleolar joint**
Incus	**Malleus**
Petrotympanic fissure	**Modiolus**
Vestibular aqueduct	**Cochlear aqueduct**
Vestibular saccules	**Semicircular canals**
Cochlea	**Round window**
Sinus tympani	**Oval window**
Eminentia pyramidalis	**Facial recess**

5. 5 Statistics

Paper I

Patients with otosclerosis were compared to an otologically normal population (Acoustics - Statistical distribution of hearing thresholds as a function of age, ISO 7029, second edition 5/1/2000) (128). For each variable reflecting hearing deviation, a z-score was calculated. The z-scores were based on the 10th, 25th, 50th, 75th and 90th percentiles presented for the normal material for each frequency and age at 10-year intervals. The 90th percentile was assigned the value of 1.28 (according to the normal distribution); the 75th percentile was assigned 0.67; the median was 0; the 25th percentile was -0.67, and the 10th percentile was -1.28. To obtain z-scores between and beyond the given percentiles, a linear-regression model was used to interpolate and extrapolate the association between the z-score and the variable of hearing deviation. These linear regressions were piecewise linear, with breakpoints in the medians for each age and frequency. A z-score described how the values for the hearing-deviation variables for patients with otosclerosis were related to the normal population of the same age, gender and frequency (fig. 14).

To test whether the difference between z-scores postoperatively and at follow-up was not zero, Fisher's test for paired comparisons were used, to test for a difference between scores. Fisher's test for paired comparisons was also used to test whether there was a statistical difference between the preoperative and follow up PTA_4 regarding AC and BC. Statistical analysis

comparing study ears and otosclerotic control ears was performed in 23 patients with bilateral otosclerosis, who only underwent surgery on the study ear, using Fisher's test for paired comparisons.

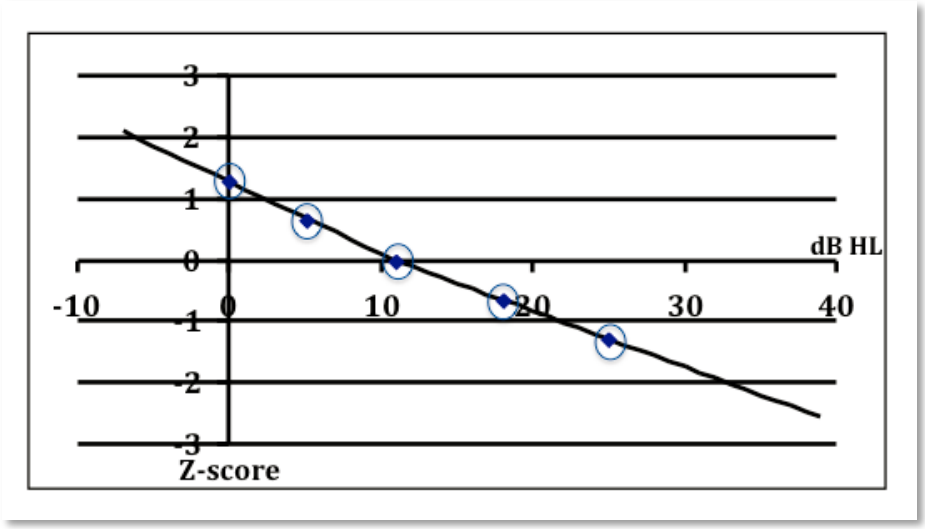


Figure 14. An example of a linear-regression model for females, 70 years of age and hearing distribution at 1 kHz. The squares marked with circles represents the 90th, 75th, 50th 25th and 10th hearing distribution.

Paper II

Univariate analyses were performed, comparing subjects with and without hearing aids using the non-parametric Fisher's permutation test. The variables included were age, sex, co-morbidity, PTA_4 better ear, education, living arrangements, uni or bilateral otosclerosis and heredity. A multiple logistic-regression analysis was then performed with the same variables included.

A spline logistic-regression model was fitted using knots at the 10th and 90th percentiles to study the association between PTA_4 in the best ear and hearing aid uptake. The splines were second-order functions between the breakpoints and linear functions at the tails, resulting in a smooth curve. To analyze the probability of not having a hearing aid in relation to time after surgery, a time-event (Kaplan Meier) analysis was performed. Furthermore, an extension of the Poisson regression model (131) was used to analyze the

association between age and sex and the "risk" of getting a hearing aid. In contrast to logistic regression, the Poisson regression uses the length of each individual's follow-up period.

Paper III

To test whether there was a difference regarding the scores on the SF-36v2 (the eight domains and the two component scores) between the study group and the reference population, the Mann-Whitney U-test was used. Correlation analyses were performed between the summery component scores (PCS and MCS) on the SF-36v2 and SSQ (speech, spatial and quality) using Pitman's test. Pitman's test was furthermore used for univariate analyses of the correlation between the sub-scores on the questionnaires' and; age, sex, hearing sensitivity (better and worse ear), speech recognition, conductive hearing component (ABG), asymmetry in hearing sensitivity, hearing aid uptake (yes/no), co-morbidity (yes/no) and tinnitus (yes/no). Statistical significance was set at $p<0.05$, and a two-sided value was used. A multiple linear-regression analysis was performed for multivariate testing, with the statistically significant variables included and with forward testing set by the p-values.

Subgroup analysis was performed using the Mann-Whitman U-test, comparing the sub-scores (PCS, MCS, speech, spatial, quality) for hearing aid users with those of non-users and comparing unilateral with bilateral hearing impairment.

Paper IV

Assessing images using a visual grading scale produces ordinal categorical data; non-parametric methods were therefore used. In this study, we used frequency tables for the analysis of paired ordinal data, which identify and measure agreements and systematic disagreements. A within-group sign test was used. The p-value was calculated for tests of systematic differences between the methods. For agreement between evaluators, weighted kappa with a 95% C.I. was calculated.

Ethical approval

The studies included in this thesis, were approved by the Regional Ethical Review Board in Gothenburg.

6 RESULTS

6.1 Paper I

Study ears

The pure tone audiometry results for the study ears (AC, BC, PTA_4 and ABG) regarding pre-, postoperative and follow-up values are presented in table 4 and fig. 15. The postoperative improvement in air conduction (mean PTA_4) was 21 dB and the improvement was most pronounced in the lower frequencies of 500-1000 Hz. The mean postoperative ABG was 10 dB. The mean improvement in bone conduction was 5 dB.

Table 4. Summery of audiometric mean data for study ears by frequency.

		0.5 kHz	*1 kHz*	*2 kHz*	*4 kHz*	*6 kHz*	*8 kHz*	*PTA*
Preoperative	AC (dB HL)	57	54	50	50	58	50	53
	BC (dB HL)	25	24	33	27			27
	ABG (dB)	32	30	17	23			26
Postoperative	AC (dB HL)	28	26	31	42	54	54	32
	BC (dB HL)	20	18	25	26			22
	ABG (dB)	8	8	6	16			10
Follow-up	AC (dB HL)	41	44	52	67	77	88	51
	BC (dB HL)	26	26	43	48			36
	ABG (dB)	15	18	9	19			15
Difference*	AC (dB HL)	13	18	21	25	23	35	19
	BC (dB HL)	6	8	18	22			14
	ABG (dB)	7	10	3	3			5

*Difference between postoperative and follow-up values.

At follow-up, the air conduction (PTA_4) had deteriorated 19 dB compared with the postoperative value (from 32 to 51 dB HL), and the bone conduction had deteriorated 14 dB (from 22 to 36 dB HL). The 30-year air-conduction PTA_4 showed no significant difference compared with the preoperative value ($p>0.30$). The bone conduction (PTA_4) demonstrated a significant increase in threshold compared with preoperative values ($p<0.0001$) (fig. 16).

At the time of follow-up, 66% of the study ears showed a moderate-to-profound hearing loss, calculated as PTA_4

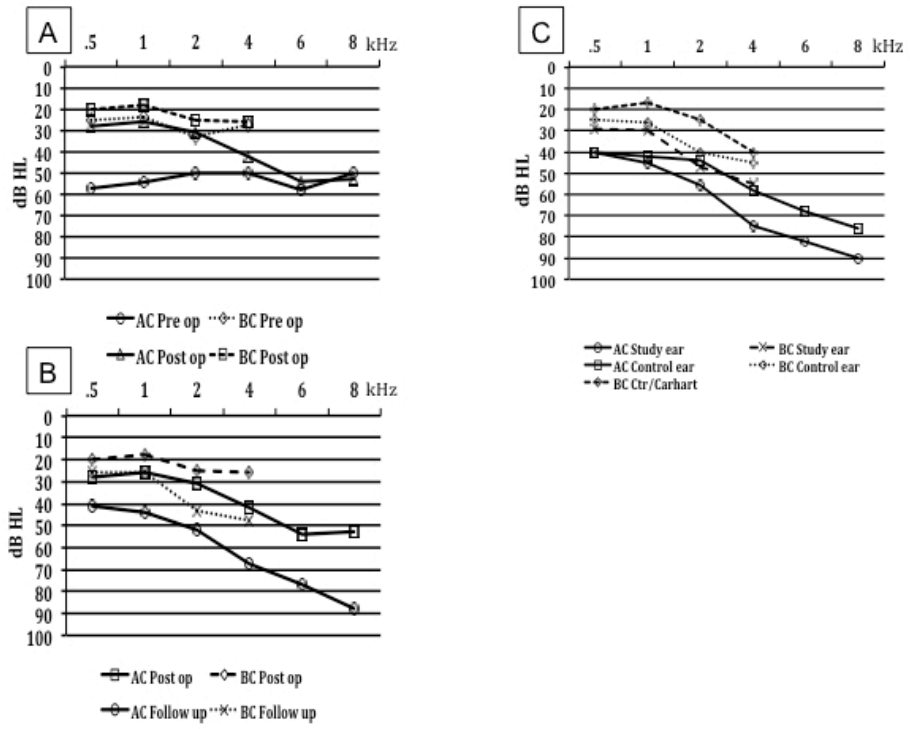


Figure 15. Audiograms comparing AC and BC. The mean values for each frequency are presented. A) Pre- and postoperative study ears B) Postoperative and follow-up study ears C) Follow-up study ears are compared with control ears with otosclerosis not operated on (n=23). The control ears are presented both with and without correction according to Carhart (4).

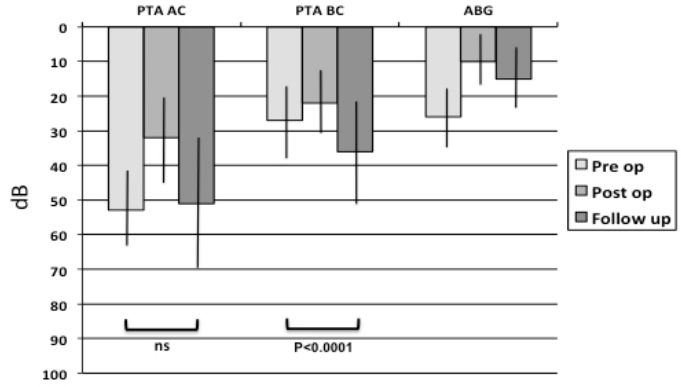


Figure 16. Summery of pure tone audiometry (AC, BC, ABG) in the study ears, Pre-, postoperative and follow-up. Mean values and SD are presented.

Control ears

The control ears with untreated otosclerosis at follow-up had a mean PTA_4 of AC 23 dB HL and a mean BC of 20 dB HL preoperatively; at follow-up they had a PTA_4/AC of 46 dB HL and a BC of 34 dB HL. After correction according to Carhart, the corresponding threshold was BC 25 dB HL (4).

At follow-up, there were no significant differences between the study ears and the untreated otosclerotic control ears (n=23) in terms of either AC or BC. After correction according to Carhart (BC in not operated otosclerosis control ears), a significant difference was noted, with a significantly better bone-conduction threshold for the otosclerotic ears without surgery ($p<0.001$).

Reference population

The mean values for postoperative and follow-up AC and BC for each frequency were compared in terms of age and gender with a reference population (ISO 7029), with no history of ear diseases, by calculating z-scores. Both AC and BC, postoperatively and at the 30-year follow-up, were significantly worse compared with the reference population ($p<0.001$). The differences were significantly larger for AC than for BC and for post-operative values compared with follow-up ($p<0.001$). The mean z-score was significantly lower for the untreated otosclerotic control ears than for the normal population, for both AC and BC with Carhart correction.

No sex differences were noted in PTA_4 pre- or postoperatively or at follow-up and, as a result, all subjects were analyzed as one group.

6.2 Paper II

At follow-up, 98% of the subjects had hearing loss, 75% had bilateral hearing loss, and 23% had unilateral hearing loss. Hearing sensitivity, speech recognition, ABG and hearing aid use in relation to I) study and control ears and II) best and worst ears are presented in Table 5.

Table 5. Hearing sensitivity, ABG, speech recognition in noise and hearing aid use presented in relation to study and control ears and in relation to best and worst ears.

		Number	*PTA_4*	*ABG*	*Speech recognition*	*Hearing aid*
		n	*dB HL± SD*	*dB ± SD*	*Mean % ± SD*	*n (%)*
1: a	Study ear	65	51 ± 18.9	15.2 ± 9.3	46 ± 26.2	28 (43%)
b	Control ear	65	44 ± 20.2	10.9 ± 9.6	54 ± 26.5	25 (39%)
	No otosclerosis	8	29 ± 11.6	0.3 ± 3.5	72 ± 10.5	1 (12%)
	Otosclerosis, no surgery	23	46 ± 21.0	11.7 ± 11.3	51 ± 24.8	10 (46%)
	Otosclerosis surgery	34	47 ± 20.1	12.9 ± 7.8	51 ± 28.8	14 (46%)
2: a	Best ear	65	39 ± 17.2	7.7 ± 7.1	57 ± 23.4	25 (39%)
b	Worst ear	65	56 ± 18.8	17.8 ± 8.9	43 ± 27.7	28 (43%)

Observed hearing aid use related to hearing sensitivity is presented in table 6. In all, 46% of the subjects had no hearing aid amplification, while 26% had unilateral and 28% had bilateral hearing aids. In subjects with bilateral hearing loss exceeding 40 dB, approximately 50% had bilateral HA amplification; 25% had unilateral amplification, and 25% had no amplification at all.

Table 6. Observed hearing aid (HA) uptake in relation to hearing sensitivity based on PTA_4 AC.

Observed	**No HA**	**Unilateral HA**	**Bilateral HA**	**Total**
Normal hearing, mild HI (n)	**(2) 67%**	**(1) 33%**	**(0) 0%**	**(3) 100%**
Unilateral HI (n)	**(15) 75%**	**(4) 20%**	**(1) 5%**	**(20) 100%**
Bilateral HI (n)	**(13) 31%**	**(12) 29%**	**(17) 40%**	**(42) 100%**
Total (n)	**(30) 46%**	**(17) 26%**	**(18) 28%**	**(65) 100%**

Normal hearing = bilateral $PTA_4 \leq 25$ dB HL, Mild HI with no "theoretical need" for HA = >25, <30 dB HL, Unilateral HI = ≥ 30 dB HL worst ear and < 30 dB HL best ear, Bilateral HI = ≥30 dB HL bilateral.

When analyzing possible explanatory variables for hearing aid uptake in the otosclerosis cohort, significant differences were seen regarding PTA_4, speech recognition and co-morbidity. (Table 7, page 44, presents the included variables.) The group without hearing aids had a mean $PTA_{4\ \text{better ear}}$ of 30 dB HL, whereas the group with hearing aids had a mean $PTA_{4\ \text{better ear}}$ of 47 dB HL ($p<0.001$). The subjects without a hearing aid had a mean speech-

recognition score of 65%, whereas the subjects with a hearing aid had a mean score of 53% ($p<0.05$). A significant difference was also seen regarding co-morbidity (health problems such as cardiovascular disease and diabetes), where the subjects without hearing aids had a lower co-morbidity compared with the subjects with hearing aids (57% vs. 86%, $p<0.05$). When analyzing the explanatory variables between subjects with uni- or bilateral hearing aid uptake, the only significant difference was hearing sensitivity (unilateral HA=40 dB HL (better ear), bilateral HA=54 dB HL (better ear), $p<0.05$). The subsequent multiple logistic regression analysis demonstrated that only $PTA_{4\ \text{better ear}}$ had a statistically significant value for the probability of having a hearing aid.

The spline logistic regression model demonstrated that the probability of hearing aid use increased with increasing PTA_4. With a PTA_4 of 36 dB HL, in the best ear, the probability of having a hearing aid was 53%, while, with a PTA_4 of 66 dB HL, the probability was 91%.

Thirty-three (33/35) subjects with hearing aids completed the IOI-HA questionnaire. Nineteen of the patients with hearing aids (54%) were full-time users (> 8 hours/day), and 94% were everyday users. Eighty percent estimated that their hearing aid(s) helped very much or quite a lot, and 77% judged their hearing aid(s) to be very much worth the trouble. The patients reported a fairly high degree of residual activity limitations; 39% reported very much/quite a lot of limitation, and an additional 23% reported moderate limitations. The patients assessed the impact on others as bothering others "very much/quite a lot" (15%), moderately (27%) and slightly or not at all (58%). A summary is presented in figure 18. The global score was 28.2, (Factor 1, 17.4 and Factor 2, 10).

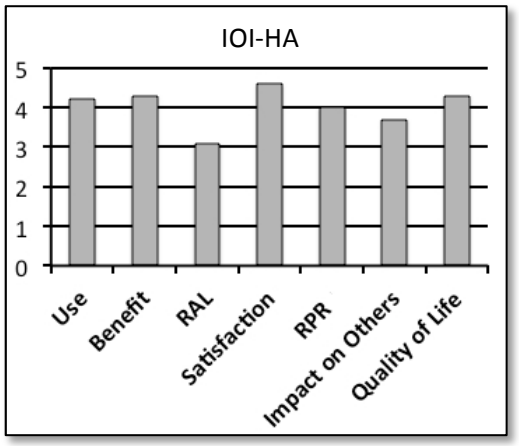


Figure 17. Mean score for each IOI-HA item; max score = 5; use = hearing aid use, benefit = hearing aid benefit, RAL = residual activity limitations, RPR = residual participation restriction, QoL = quality of life.

Table 7. Subjects' characteristics included in explanatory analyses. BE = better ear, WE=worse ear.

Paper	Variables		
II	**Living arrangements**	**With others**	**44%**
II	**Education**	**≤ 9 years** **10-12 years** **≥ 13 years**	**42%** **23%** **26%**
II, III	**Co-morbidity**	**Yes**	**72%**
II	**Familiar otosclerosis**	**Yes**	**46%**
II, III	**PTA_4** **(dB HL ± SD)**	**BE** **WE**	**39 ± 17.2** **56 ± 18.8**
II, III	**Speech recognition** **(% ± SD)**	**BE** **WE**	**57 ±23.4** **43 ± 27.7**
II, III	**ABG** **(dB ± SD)**	**BE** **WE**	**8 ± 7.1** **18 ± 8.9**
III	**Asymmetry**	**>15 dB difference in $PTA_{4\ BE/WE}$**	**42%**
III	**Tinnitus**	**Yes**	**51%**

6.3 Paper III

Health-related quality of life, as measured by the eight domains in the SF-36-v2, revealed no differences between the subjects with otosclerosis and an age- and sex-matched reference population; moreover, no differences in the physical component summery were observed between the groups. However, the mental component summery score was significantly higher compared with that of the reference population ($p<0.05$). The 8 domain scores in relation to the reference population are shown in fig. 18.

Figure 18. The scores of the SF36v2 eight domains. The otosclerosis cohort is presented in relation to the reference population. PF = physical functioning, RP = role physical, BP = bodily pain, GH = general health, VT = vitality, SF = social functioning, RE = role emotional, MH = mental health.

Hearing disability was analyzed using a shortened version of the SSQ hearing-specific questionnaire. The subjects had minor problems with speech in quiet, sound quality and identification of sounds (scores 7.1, 7.3 and 7.2). More difficult speech contexts, such as speech against a background of noise, speech in speech contexts, multiple speech-stream processing and switching attention obtained considerably lower scores (4.4, 4.8 and 4.0) as did localization of sounds and judging the distance and movements of sounds (5.0 and 4.4). The subgroups, domains and overall global scores are shown in figure 19.

Subgroup analysis, comparing SSQ domain scores in hearing aid users to subjects with no hearing aids revealed significantly poorer scores in hearing aid users, especially in the spatial and quality-of-sound sub-scores. Subgroup analyses comparing uni- and bi-lateral hearing loss showed a higher degree of disability in the group with bilateral hearing loss in terms of speech in quiet, distance and movement and sound quality and identification of sounds.

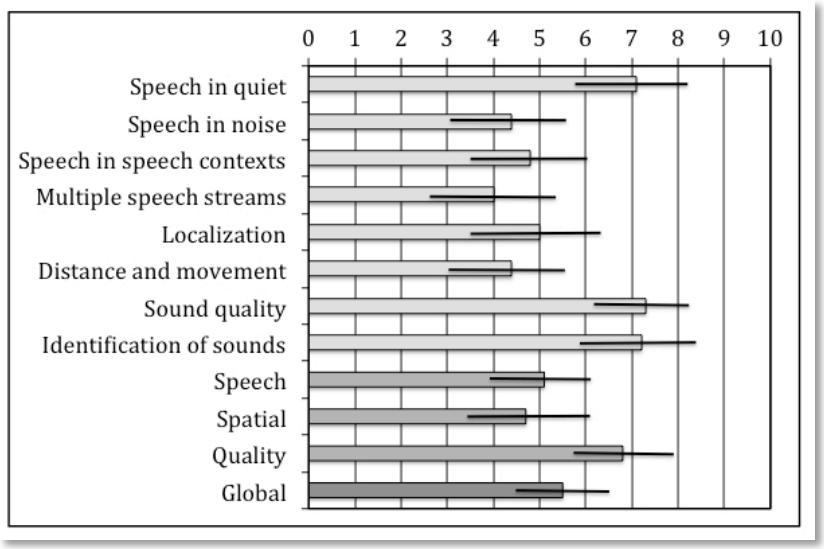


Figure 19. The SSQ scores for the eight subgroups, the three domains (speech, spatial and quality) and finally the global score (mean value of all questions). The mean values and SD are presented.

Physical-component summery score (PCS) correlated significantly with age and co-morbidity. In the multiple-linear-regression analyses, both age and co-morbidity remained as explanatory factors; increased age and co-morbidity were correlated to worse scores. The PCS and MCS correlated significantly with the speech and spatial domains in the SSQ. The mental-component score also showed a statistically significant correlation with the quality domain, but did not correlate with any of the other evaluated factors, such as hearing sensitivity or hearing aid uptake.

The scores for the SSQ domains of speech and spatial correlated significantly with the PTA_4 in the better and worse ear, speech recognition in the better and worse ear, hearing aid uptake and co-morbidity. After multiple-linear-regressions analysis, the PTA_4 in the worse ear alone remained as an explanatory factor. The variables of PTA_4 in the worse ear and co-morbidity were explanatory factors for the spatial scores.

The domain "Quality" showed significant correlations with PTA_4 in the better and worse ears, speech recognition in the worse ear, hearing aid uptake and co-morbidity. The degree of conductive component, asymmetry, and tinnitus did not significantly correlate with any of the scores. Following the multiple-linear-regression analysis, hearing sensitivity in the better and worse ears remained as explanatory factors.

6.4 Paper IV

Characteristics of the otosclerosis subjects, Groups A and B are presented in table 6.

Table 6. Patient characteristics.

Variable	Group A (n = 10)	Group B (n = 10)	Total (n = 20)
Sex			
Female	7	7	14
Male	3	3	6
Age (yr)	61 (48–67)	68 (63–76)	65 (48–76)
Hearing thresholds			
Pure tone average/air conduction, dB HL	33 (19–56)	72 (59–101)	
Pure tone average/bone conduction, dB HL	19(6–35)	56 (46–65)	
Control ear			
Healthy	1	2	3
Otosclerosis, operated	7	3	10
Otosclerosis, not operated	2	5	7

Analysis of temporal bone structures

All 16 anatomical structures were clearly visible using both MSCT and CBCT. Critical reproduction was obtained in 12/16 anatomical structures in 75% of study ears scored by evaluator 1 and in 16/16 anatomical structures in 85% of the ears scored by evaluator 2. Evaluator 1 rated in favor of MSCT in 16/16 of the anatomical structures ($p<0.05$) and gave systematically lower scores for CBCT. Evaluator 2 found no significant differences between the techniques in 14/16 of the structures. The petrotympanic fissure was best visualized by CBCT, while the modiolus was best visualized by MSCT

(evaluator 2). An example of a visualization of the oval window is shown in figure 20.

Agreement between evaluators was found in 80-100% (for the oval window, 30%) of the assessments in MSCT and to a considerably lower degree in CBCT, 30-70%, (for the oval window, 0%).

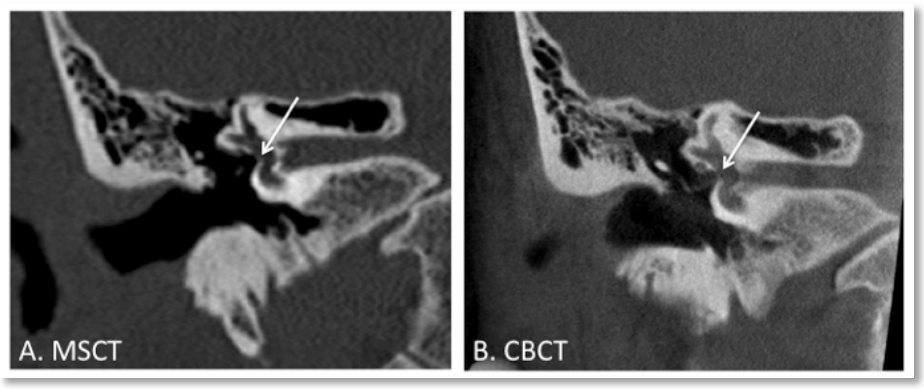


Figure 20. Frontal view. Normal oval window in the same patient visualized by MSCT (A) and CBCT (B).

Analysis of otosclerosis

Otosclerotic lesions (fenestral/retrofenestral) were identified in the majority of the studied ears – in MSCT 80% (Evaluator 1) and 95% (Evaluator 2) and in CBCT 50% (Evaluator 1) and 85% (Evaluator 2). Only fenestral lesions were diagnosed to a higher degree by MSCT compared with CBCT - 60% and 30% (Evaluator 1) and 85% and 65% (Evaluator 2), respectively. Retrofenestral lesions were diagnosed in 20% (4/20) by both modalities (Evaluator 1) and in 15% by MSCT and 20% by CBCT (Evaluator 2), see figure 21. In the studied ears, all lesions but one were graded as a double ring effect. In control ears, one severe retrofenestral lesion and one narrowed basal turn were noted (CBCT, Evaluator 2). Retrofenestral lesions were present in 5/20 of the patients, all from Group B, with severe hearing loss (mean BC 53 dB HL, AC 64 dB HL). The same result was found in the control ears, where the retrofenestral lesions were exclusively present in Group B (PTA_4 BC 57 dB HL, AC 71 dB HL). In the vast majority of cases, both CBCT and MSCT were able to adequately visualize the prosthesis and its position.

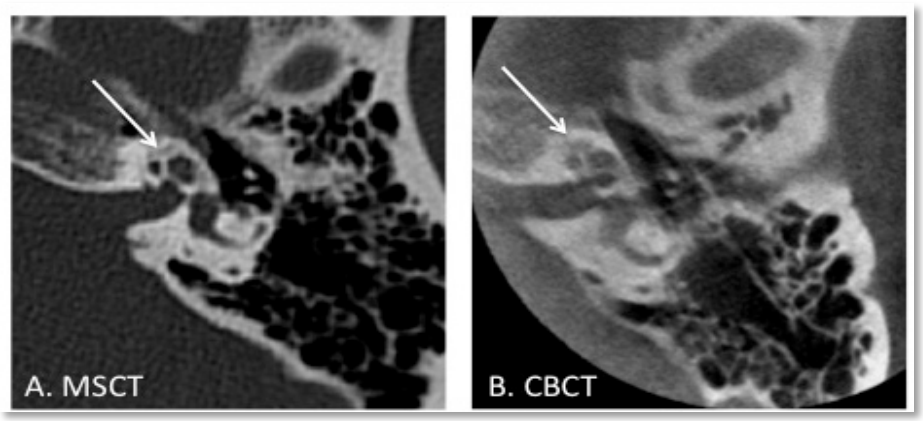


Figure 21. Axial view, otosclerotic cochlear demineralization in the same subject using MSCT (A) and CBCT (B).

7 DISCUSSION

This thesis has assessed medical, technical (hearing aid uptake) and functional (HRQL) aspects of otosclerosis.

The results show that the hearing loss is progressive, with a substantial inner-ear component demonstrated in the audiometric and radiological exams. Rehabilitation is insufficient, given that hearing aid uptake is relatively low, especially in subjects with bilateral otosclerosis. The results also show that the HRQL is as good as it is in a normal population.

Previous long-term studies have studied air bone gap (67), or pure tone audiometry with conductive and sensory hearing loss (132). In this study, our subjects were evaluated regarding hearing function, audiological rehabilitation, health-related quality of life and radiological findings.

The results from the different studies show that subjects with operated otosclerosis have benefitted from a good primary surgical outcome, but the sensory loss becomes more prominent with time. Hearing loss both after surgery and after 30 years is more severe compared to that seen in age-matched cohorts. The sensory component in the ears subjected to surgery was not better compared to otosclerotic ears without surgery. Retrofenestral, cochlear otosclerosis was present in subjects with worse BC thresholds. The lesions were equally well visualized by CBCT and MSCT. The hearing aid uptake should be significantly higher, considering the fact that these subjects suffer from a chronic and progressive hearing impairment.

Otosclerosis: Thirty-year follow-up after surgery (Paper I)

The first study aimed to evaluate hearing sensitivity 30 years after surgery. We also wanted to assess hearing sensitivity in relation to age-related hearing loss and to compare ears subjected to surgery, to ears that were not operated on. We found that 30 years after surgery, the majority had a moderate-to-profound hearing loss (66%) and that the hearing loss in ears subjected to surgery was comparable to (AC) and worse (BC) than seen in ears not subjected to surgery; furthermore, the hearing loss was more pronounced than age-related hearing loss (both postoperatively and at follow-up).

The individuals in our cohort were included due to surgery 30 years ago and are partly reflecting the situation that prevailed at the clinics in the late 1970s.

In the 1970s, the otosclerosis surgeries were centralized to the region hospitals in Sweden, and the standard surgical technique was stapedectomy. Many surgeries were performed by many different surgeons (11), both experienced and in training. Successful surgery have been measured as the percentage of individuals with a postoperative ABG <10 dB and AC gain >10 dB and by the percentage of individuals with BC not worsened by >5 dB (3). In this study the postoperative values were; ABG ≤10 dB 65%, AC gain ≥10 dB 82% and BC not worsened by ≥5 dB 97%. These data are comparable to those seen in Sweden today (unpublished data from the Swedish Quality Register; otosclerosis surgery) (133) indicating that the results of the primary surgery were good.

In 1977-79, the standard surgical method was stapedectomy, while the standard surgery of today is stapedotomy. When comparing the hearing outcome between these two techniques postoperatively, no major differences have been shown (134, 135). In some studies, stapedectomy has shown a better postoperative result in the lower frequencies (68, 134). In the higher frequency range, a significant improvement has been reported from stapedotomy postoperatively and at shorter follow-up periods. (70, 135, 136). From longer-term perspective, no difference between the techniques has been reported (19). The long-term hearing deterioration after surgery in our study is probably valid even today in ears undergoing stapedotomy.

In this study, 18% of the subjects had one, 6% had two and 6% had three revision surgeries. These frequencies are fairly high relative to other studies, in which frequencies of about 10-15% have been reported (19, 68, 137, 138). Possible explanatory factors could be the longer follow-up period, the number of surgeons performing the surgeries (11), the inclusion of both experienced surgeons and surgeons in training and local traditions with a high revision rate. As no major differences were seen regarding bone or air conduction preoperatively or at follow-up, we believe that the higher revision rate in this study did not affect the final hearing outcome in a major way.

The main method for hearing assessment used in this thesis was pure tone audiometry. Assessments from the 1970s were compared with assessments of today. There should be no systematic errors caused by the time interval, as equipment, methodology and calibration norms have not changed during this time period.

In the long-term, we found that the hearing gained from surgery was mainly maintained but that the hearing sensitivity deteriorated to the preoperative level. The deterioration was mainly due to a loss of sensorineural function,

where the mean ABG had only deteriorated by 5 dB during the 30-year period. We found that 6.2% of subjects in our cohort had a BC threshold >65 dB which was in accordance with the study by Ramsay who reported a frequency of 8.9% for the development of sensorineural hearing loss exceeding 65 dB (BC) 25 years after surgery (range 15-44 years) (21). Three of the subject in our study (4.6%) had bilateral hearing loss exceeding 70 dB and were close to the indication for a cochlear implant; however with speech discrimination scores in quiet still "to good". On the other extreme one individual with bilateral otosclerosis and bilateral surgery had at follow-up still bilateral normal hearing thresholds!

To analyze whether the deterioration in sensorineural hearing function could be explained by age-related hearing loss, a comparison was made to the International Standardized Database, ISO 7029, Database A (128). Estimates of hearing thresholds distribution depends on the reference population screened. Today, there are two international standardized databases for hearing-threshold levels as a function of age, Database A (ISO 7929) and Database B. Database A describes hearing distribution in an otologically normal population (otologically screened), while Database B describes a non-screened population. Non-screened populations such as that in Database B, are used to evaluate hearing thresholds in, for example populations exposed to occupational noise. Screened populations such as that in Database A are commonly used in assessing hearing thresholds in hereditary hearing loss. The reference population has been exposed to normal environmental factors but is screened for and is free from otologically disease. The intention is that the studied population only will differ in regard to the otologically studied disease/hereditary hearing loss (128). ISO 7029 has been criticized for being outdated and maybe too restricted (139, 140)(141). New attempts have been made to form new and more reliable databases, most of them from unscreened populations (139, 142). In our study we partly used analyses from the 1970s when some of the analyses of ISO 7029 were gathered and the difference between the otosclerosis cohort and ISO 7029 is far greater than that between the screened Norwegian, the unscreened Swedish population and that of ISO 7029. One disadvantage of ISO 7029 is the lack of data for older individuals. In our study, these individuals were omitted from the analyses and creating a limitation in the study. Despite the criticism, ISO 7029 was used in our study, as it is still the most valid and frequently used screened standard database.

The statistical analysis comparing the study ear and the ISO control group with regard to both AC and BC based on the described z-score revealed a highly significant difference both postoperatively and at the 30-year follow-

up. Thus, the otosclerosis patients had a significantly more pronounced hearing loss, compared with a normal hearing population, measured by both AC and BC and both postoperatively and after 28-30 years. Our results are in agreement with the study by Topsakal et al., (22) who compared preoperative bone conduction thresholds (after correction according Carhart) in otosclerosis patients with ISO 7029. Z-scores decreased between the post op values and the follow–up values, indicating that the normal population "caught up" during the 30-year follow-up, although the otosclerosis populations still had highly significantly worse scores both regarding bone conduction and air conduction than did the reference population at follow-up. When age-related hearing loss progresses with age in the normal population, the differences decrease.

The cochlear component in otosclerosis has been investigated using different approaches (39). One approach was to compare the otosclerotic ears undergoing surgery with the other non-operated control ears (20, 143, 144). In our study, 23 patients had an otosclerotic ear that had not undergone surgery at follow-up. The hearing result revealed no statistical differences in air conduction compared with the operated ears and the same thing applied to the bone conduction until correction for the Carhart effect was made. With the correction according to Carhart, the bone-conduction threshold was significantly better in the otosclerotic ears that did not undergo surgery.

This result must be interpreted with caution, as there are several factors affecting the analysis. The audiometric definition of clinical otosclerosis is one factor. An audiometric definition of a non-operated otosclerosis ear is lacking in almost all studies (143, 145). Browning and Gatehouse set their audiometric criteria for otosclerosis to ABG $\geq$15 dB (averaged frequencies 0.5, 1 and 2 kHz) and absent stapedial reflexes (frequencies were not defined) (13, 20). Our criteria were, a significant conductive component and/or absent stapedial reflexes in 2-3/3 frequencies, and hence, our criteria were stricter regarding stapedial reflexes but less strict regarding the conductive component. We wanted to include all possible otosclerosis rather than to exclude possible otosclerosis cases.

A second issue affecting the analysis was the magnitude of Carhart correction. Initially the Carhart correction was calculated from bone conduction in fenestration operations. However, the magnitude of the Carhart correction was re-evaluated by Gatehouse and Browning 1982, (3) and they came to the conclusion that the magnitude of the Carhart correction corresponds well to their correction figures after stapedectomy. The estimates

are probably underestimates, however, because the mechanics of the middle ear still are altered after surgery.

Another aspect is the rule in ear surgery that you choose the worse ear for surgery, never the best. The results could therefore be biased by selection. At the time of surgery only 39% of the analyzed non-operated-on otosclerosis ears had otosclerosis (in the whole group 60% of the subjects had bilateral otosclerosis compared to 88% at follow up); however, this selection was made 28-30 years earlier and at the time of the present analyses, air conduction was equal between the study and control ears.

The bone-conduction thresholds were significantly better in the non-operated ears compared to the operated ears. This finding is in contrast to the theory that surgery enables sounds to reach the cochlea and thus protects it from premature degeneration due to inactivity (143). On the other hand surgery could also affect the cochlea negatively by surgical trauma or by noise because the stapedial tendon was cut making the ears more sensitive to noise-induced trauma. Finally, bone conduction is an estimate of sensorineural function, both in the operated and in the non-operated ears.

In the first paper hearing outcome was calculated as mean values rather than as the more proper median values. This calculation was chosen to enable us to compare our result to other long-term follow-up studies (19, 21, 132). In the multiple-linear-regression analysis median values and percentiles were used. There were no major differences between the mean and median values. Analyses of non-responders from the study population showed no major differences regarding pre- or postoperative data or sex and age at surgery. Nevertheless, the analysis was not complete, as some of the pre- and postoperative audiometric data from non-participants were missing (pre-op 7/50, post-op 12/50).

The true nature of the sensorineural hearing-loss progression seen in the otosclerotic subjects can be and has been the subject of considerable debate. In our opinion, the sensorineural hearing loss seen in the otosclerotic subjects is mainly due to otosclerosis in combination with age-related hearing loss. Maybe, otosclerosis causes premature ARHL with cochlear degeneration.

Hearing-aid use and benefit: A long-term follow-up after surgery (Paper II)

Thirty years after surgery, 98% of the otosclerosis subjects had hearing loss (75% bilateral and 23% unilateral, mixed in the majority of subjects). Hearing aid uptake was poor. Overall, we found that 46% of the individuals did not have a hearing aid despite a theoretical need in 95% of the individuals. Those with a hearing aid reported a high level of satisfaction and benefit and were in high percentage full-time users (>8h/day); however, they also reported residual activity limitations.

The theoretical need for hearing rehabilitation was in our study based on pure tone average in the best ear. A reasonable threshold for hearing aid rehabilitation has been estimated to be 30 dB HL (146, 147); however, theoretical need is really a simplification of reality. HA prescription should also be based on additional factors, such as the patient's motivation, expectation and experience of disability, participation restriction and activity limitations, as well as speech discrimination and type of hearing loss (148). At the clinic, different instruments can be used in conjunction with the audiogram in the assessment process prior to hearing aid fitting. Examples of such instruments are COSI (Client Oriented Scale of Improvement) (149) and the questionnaire HHI- E, -A (The Hearing Handicap Inventory for the – Elderly, -Adult) (150, 151).

In the group with bilateral moderate-to-profound hearing loss who were eligible for bilateral hearing aids, only 50% had bilateral hearing aids; 25% had unilateral hearing aids, and 25% had no hearing aids at all. In the group with moderate hearing loss (40-49 dB HL) in the better ear, only approximately 50% were using a hearing aid at all, despite a comparatively low mean age of 65 years and 50% being still of working age. Additionally, 75% of individuals with unilateral hearing loss and a theoretical need of a hearing aid had no hearing aid. In a long-time follow-up study by Aarnisalo (2003), the figure was even worse; only 37% had hearing aids, despite hearing impairment comparable to that in our study (19). Smyth and Hassard estimated, based on their surgical results, that a majority if not all of their patients would eventually need hearing aid amplification (152).

Only 40% of those with bilateral hearing loss were fitted with bilateral aids. The frequency of bilateral versus unilateral hearing aid fitting varies in different countries, in different populations and over time. However, there is evidence that bilateral hearing aid fitting has benefits, such as improved intelligibility in noise and sound localization, for most patients (77-79, 153). Unilateral hearing aid amplification may also cause an auditory deprivation

effect with decreased speech recognition in the unaided ear and in the binaural listening situations (80).

Given that uncorrected hearing loss has great impact on speech perception, detection and localization of sounds and affects social life as well as cognitive and physical functions and quality of life, hearing aid rehabilitation is an important issue in the care of otosclerosis patients (154). Furthermore, there is ample evidence of the benefits of hearing aid rehabilitation (155-157). Despite the psychosocial benefits of hearing aid use, internationally it has been estimated that only 20-25% of individuals with age-related hearing impairment who would benefit from a hearing aid are actually provided with hearing aids (99). The Swedish Council on Health Technology Assessment (2003) presented an estimate of Swedish figures. Their report was based on a systematic review of the scientific literature (1990-2002), and from the ULF study (Living Condition Survey, Statistics Sweden). They came to the conclusion that only approximately 50% of adults who would benefit from hearing aids were fitted and of those fitted with hearing aids approximately 50% used their aids (156).

Our study reports hearing aid uptake that correlates with the report from the Swedish Council on Health Technology; approximately 50% of individuals with theoretical need have a hearing aid. This figure must be regarded as a failure in the care of otosclerosis patients. These subjects have had a well-known ear disease for many years, and the disease is progressive in the vast majority of subjects. When fitted, hearing aid users showed a high level of satisfaction and benefit, as shown by IOI-HA in our study. The hearing aid users also were highly likely to be every day (>4h/day) or fulltime (>8h/day) (94% and 54% respectively, a finding usually linked to high satisfaction). If the expected benefit of a treatment is high the indication for that treatment increases (156).

One important factor affecting hearing aid outcome is an individual's ability to discriminate speech. Evaluation of speech discrimination is a valuable complement to pure tone audiometry and in hearing aid assessments. In the 1970s speech recognition test in quiet were used. These tests discriminated poorly among individuals with conductive or sensorineural hearing loss, as they could still score close to 100% despite considerable hearing loss. Since then, speech recognition tests in competing noise have been developed to increase the degree of difficulty and thereby minimize the ceiling effect and enhance the discriminative power. In this thesis, we used the Swedish Speech recognition test in noise at follow-up, even though it was not used in the 1970s (7). The speech-discrimination scores were high considering the

degree of hearing loss, with speech in noise scores achievable in 88% of the subjects. The median scores were 52% and 62% in study and control ears, respectively.

Several possible predictors of hearing aid uptake were evaluated in this study, and the only statistically significant predictive variable was hearing sensitivity in the better ear. At a PTA_4 of 36 dB HL in the better ear, the probability of having a hearing aid was only 53%, but, with a PTA_4 of 66 dB HL, the probability had increased to 91%, a hearing threshold with implications even for a conversation between two persons in a quiet room. For comparison, Lundman et al showed in a follow-up study (mean 5 years) after otosclerosis surgery, that individuals with severe social hearing disability had a mean PTA_4 in the better ear of 34 dB HL (158).

A tendency was encountered regarding sex, though, not statistically significant; women had hearing aids almost twice as frequently as men (OR 1.9). Either the finding has no statistical significance as indicated, or our study cohort was too small (Type II error). According to a power calculation the cohort should have been in the order of 494 individuals to achieve a power of 80%. It would be of interest to do further research in this area.

Possible explanatory factors for the low hearing aid uptake among otosclerosis subjects could be the option of surgery. Surgery has found to be central for many otosclerosis subjects, as it is associated with the hope of regained hearing. Hearing aids on the other hand, were associated with periods of deterioration in hearing function and disability and therefore had negative connotations (159). Lack of information for the patients about the risk of sensorineural hearing loss in the long run and the consequent need for audiological hearing rehabilitation could be another factor (152). The lack of awareness of the need for hearing aid rehabilitation is also evident when viewing the scientific reports focusing on surgical outcome.

Positive findings in our study related to benefit, satisfaction and hearing aid use. The otosclerosis subjects with hearing aids were in general satisfied and perceived benefits from their aids, and as many as 94% were everyday users. The high rate of hearing aid use is in contrast to other studies, where figures as low as 25 % and even worse have been reported (160). The high satisfaction and benefit scores could be due to mixed hearing loss with a varying proportion of conductive component, generally regarded as favorable for hearing aid fitting and benefit and as previously shown by Brännström and Wennerström (2010) (161). In pure conductive hearing loss, the cochlear

function is well preserved, and thus, speech recognition as well (as shown in our study); the hearing loss is more of a quantitative than qualitative issue.

Despite their high benefit and satisfaction scores, the otosclerosis population in this study who were using hearing aids still encountered residual problems with their hearing. Sixty-four percent estimated that they had "very large" to "moderate difficulty", despite using a hearing aid. The global score was comparable to other studies but the distribution within the questionnaire was somewhat different, with higher satisfaction and benefit scores (Factor1) and lower (=worse) scores regarding participation restriction and activity limitations (Factor 2) (125, 126, 162, 163). A finding also reflected in the significant correlations between Factor II and the mental component summery score in SF-36v2 as well as with worse speech scores in SSQ (unpublished data).

Our study reflects to some extent country-specific conclusions. Conditions and traditions regarding hearing aid prescription vary around the world and even among different regions in a country. Factors such as the organization of the health-care system and funding of hearing aids play a vital role.

This study, however, shows that there is an unmet need for hearing aid use in otosclerosis individuals from a long-term perspective. Additionally, studies of ARHL are not applicable to subjects with otosclerosis. Hence, larger studies with control groups are desired to improve audiological rehabilitation and hearing aid use in patients with otosclerosis.

Health-Related Quality of Life in patients who have undergone otosclerosis surgery: A long-term follow-up study (Paper III)

Hearing loss, and especially uncorrected hearing loss, causes hearing related disabilities such as difficulties in speech perception and in localizing sounds and has been shown to affect social life, cognitive- and physical functioning and quality of life (154).

This study has shown that subjects with otosclerosis had a generic health-related quality of life measured by the SF-36v2 that was better than or comparable to that of a Swedish reference population. On the other hand this study has also found different difficulties 30 years after stapes surgery. The problems were most pronounced in more complex listening situations, such

as listening in environments with competing sounds, and for spatial localization, as assessed by SSQ.

HRQL in the otosclerosis population was equivalent to that in the reference population in all domains and in terms of the physical component summery score (PCS). The mental component summery score (MCS) was significantly higher in the otosclerosis population compared to the reference population, contrary to our preliminary hypothesis. The difference was small but however statistically significant. The individuals have been living with their hearing loss and otosclerosis for a long time and have probably adjusted to their hearing loss using conscious or unconscious coping strategies, as well as choices of education, work, leisure-time activities and so forth. In the absence of coping strategies, challenging hearing situations and environments are deselected. The slow progression of the hearing loss in the majority of the studied subjects could facilitate these coping strategies, or alternatively, the lack of coping strategies. A slow progression can imply unawareness of deteriorating hearing and consequently a lack of coping.

One plausible explanation for why the MCS was slightly better than in the reference population could be the different contexts in which the questionnaire was delivered. The otosclerosis subjects answered their questionnaires as part of an audiological and medical follow-up, whereas the reference population was randomly selected from the Swedish population register. As a result, the otosclerosis subjects had positive connotations, while the reference populations did not. Another factor, albeit less likely, is the time span of 9 years between the investigation of the reference population and the study group.

In contrast to our study's findings, several population-based studies have shown a correlation between hearing loss and reduced scores on the SF-36. For example, the Blue Mountain Hearing Study (2007, 2012) showed an association between bilateral hearing impairment and poorer SF-36 scores in both physical and mental domains. Moreover, it also showed that poorer scores were associated with poorer hearing and that hearing aid use in a 10-year follow-up was associated with higher score (99, 100, 164). Other studies have found that generic HRQL measurements lack precision and sensitivity to the specific effects of hearing loss (101). One reason for the different results is probably the differences in sample size. In large population studies even small differences can show statistical significance.

The otosclerosis subjects had decreased scores in all sub-scores; the lowest scores and thereby the greatest disabilities were obtained in complex speech

contexts and in their ability to sustain attention to and to switch attention between multiple input streams (speech), as well as in spatial abilities. One of the rationales for developing the Speech Spatial and Quality questionnaire was to enhance the ability to assess different aspects of auditory functioning, rather than just speech (115). These areas are also those in which the greatest differences can be found between our cohort and the published studies on cohorts of normal-hearing individuals, see figure 22 (165, 166).

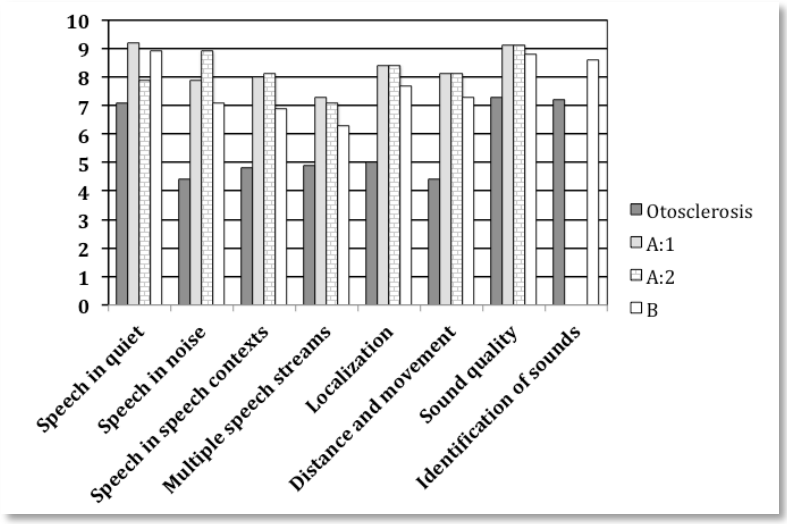


Figure 22. SSQ subscores; Otosclerosis subjects in relation to normal hearing populations presented in two different studies. (A) Noble et al. 2012, subjectively no hearing difficulties, A:1 age 50-64 years, A:2 age 65-80 years (165) *(B) Banh et al. 2012, mean age of 70 years. Subscale scores calculated from individual item scores presented in the article* (166)*. The mean values are presented, 10=maximal ability and 0=minimal ability.*

Compared with SSQ studies in cohorts with pure sensorineural hearing loss without hearing aids, our subjects obtained higher scores in all domains (mean differences 1 scale unit) but lower scores compared with the uni and bilateral-aided groups (mean difference 1 scale unit) (115-117, 119).

In the comparison with other studied cohorts, it is important to take into account, the complexity in our studied group in terms of severity and type of hearing impairment. The majority of subjects in our study had bilateral mixed hearing loss; 23% had a unilateral hearing loss and 42% had a PTA_4 asymmetry exceeding 15 dB HL. Approximately half the cohort had a corrected hearing loss with hearing aids, (approximately half the corrected subjects had bilateral HA acquisition and half had unilateral HA acquisition).

Furthermore, the probability of having a hearing aid increased with increased hearing loss.

In the correlation analyses, we wanted to assesse possible predictors of outcome scores on the SF-36 and SSQ. The MCS correlated significantly with hearing disability as measured by SSQ domains but not with the quantitative data, such as PTA_4, speech recognition, ABG or hearing asymmetry. In other words, experienced hearing disability therefore correlated better with mental health and HRQL than did the measured hearing impairment. This finding is in accordance with previous studies, and consequently, it forms one important rationale for using questionnaires in the care of individuals with hearing impairment and furthermore in research context (101).

Age and co-morbidity affected the PCS negatively. Increased age and co-morbidity were associated with significantly lower scores in the physical domains. Increased age and co-morbidity are well-known confounding factors when analyzing the burden of chronic conditions on HRQL (167).

Significant correlations with the SSQ domains were found for PTA_4, speech recognition, hearing aid use (yes/no) and co-morbidity (yes/no), but in the multiple linear regression analyses, hearing loss in the worse ear was the only remaining predictive variable. Regarding the quality domain, PTA_4 in the better ear was the most important predictor. Our interpretation is that binaural auditory function is more important in speech and spatial domains than in judging sound qualities and distinguishing sounds from one another.

Asymmetry, ABG or tinnitus had no correlation with the outcomes of the questionnaire. It is well known that unilateral hearing loss and asymmetric hearing loss affect the spatial hearing abilities, and, in other studies, asymmetry assessed by the SSQ was associated with disabilities, especially in the spatial domain (116). The previously mentioned corrected hearing loss (which equalizes the disabilities in relation to hearing thresholds) is important in interpreting the results. In the hearing aid study (Paper II) we showed that the sole predictor for hearing aid use was PTA_4. The subgroup analyses demonstrated poorer scores for hearing aid users and for individuals with bilateral hearing loss compared with unilateral loss in all sub-scores, and the multivariate analyses showed that this result was due to poorer hearing sensitivity.

This study is a descriptive cohort study and, as such has some limitations. First, as in paper II, the lack of control group. A control group would have

made it possible to perform comparative analyses. A second limitation was our use of the modified SSQ. The SSQ was not properly validated in Swedish, and a shortened version of the questionnaire was used. The SSQ was used, as no other questionnaires so extensively target different aspects of hearing disability. Our use of the shortened version of the SSQ could have affected the results, but as the original questionnaire is based on calculations of means from the outcome from 50 questions, we believe that the removal of some questions would not affect the result significantly.

Otosclerosis: Anatomy and Pathology in the Temporal Bone Assessed by Multi-Slice and Cone-Beam CT (Paper IV)

The aims of Paper IV were to evaluate the use of CBCT for imaging of the middle and inner ear in patients with otosclerosis and to compare the technique with MSCT. We found that, in the majority of cases, CBCT was able to visualize anatomical structures of interest in the middle and inner ear. Fenestral lesions were found to a higher degree by MSCT, whereas retrofenestral lesions were equally diagnosed by both techniques and were found only in the group with severe hearing loss. The stapedial prosthesis and its position were adequately visualized by both methods.

To our knowledge, this is the first study comparing the use of CBCT and MSCT in patients with otosclerosis. The study group did not differ from the original otosclerosis cohort in terms of age or sex and they were selected on the basis of their sensorineural hearing function at follow-up. Ten subjects with the best and ten with the worst BC were selected. Consequently, Group A had significantly better PTA_4 regarding both AC and BC than did Group B. The mean age was also different between the two groups; with a lower mean age in Group A compared with Group B.

Images with high resolution are mandatory for the visualization of small anatomical or pathological processes in the middle and inner ear MSCT has therefore become the most frequently used technique (81, 168). When selecting an appropriate imaging technique for each diagnosis or patient the ALARA principle (As Low As Reasonable Achievable) should be followed (84). CBCT has a principal advantage in the significantly reduced radiation dose compared to MSCT and has shown promising results in analyzing cadaver temporal bones. Middle- and inner ear structures have been accurately visualized with advantages over MSCT, such as reduced volume-averaging effects and less metal- and beam-hardening artifacts (87-89, 169). Based on these findings, CBCT was considered to be a suitable method for evaluating otosclerotic patients with small, sometimes difficult to diagnose, otosclerotic foci and middle-ear prostheses.

As previously mentioned, one important advantage of CBCT over MSCT is the significantly lower radiation dose. Effective doses from the type of CBCT machine that we used, when scanning a volume of 60 x 60 mm, are reported to be in the range of 52-166 μSv (i.e., up to more than 10 times lower than from MSCT; (170-172). Low-contrast resolution can be a problem in CBCT, partly because of X-ray scatter, but scanning smaller volumes, as in this study, reduces the amount of scatter radiation (93). There are large differences between different CBCT machines that must be considered when CBCT is compared to MSCT. We used a CBCT with a small voxel size (0.125 mm^3), which is important for high spatial resolution and thus for examining subtle structures (94). The small voxel size may be an important reason why the machine that we used was found to be superior to many other CBCT brands for identifying minor anatomical structures (173).

The 16 anatomical structures that were analyzed were chosen on the basis of their clinical and surgical relevance in middle- and inner ear diseases. These structures have also been used as anatomical landmarks in a previous temporal cadaver study (88). The anatomical landmarks studied were equally adequately well visualized by the two techniques in the majority of ears, with the exception of the modiolus, the petro-tympanic fissure, the vestibular aqueduct and the oval window in CBCT, according to Evaluator 1. As all study ears had undergone a stapedectomy, the oval windows were all affected by otosclerosis and surgery, which might explain the lower agreement for the oval window in both MSCT and CBCT compared to other analyzed structures. Evaluator 1 gave systematically lower visibility scores and, consequently, fewer diagnosed fenestral lesions with CBCT compared to MSCT. For comparison, cadaver temporal-bone studies have previously shown an advantage of CBCT compared to MSCT in visualizing anatomical landmarks; however, when whole-head specimens were analyzed, no significant differences could be demonstrated between the two techniques (174).

The discrepancies were highly dependent on the evaluator. Both evaluators were experienced in the use of MSCT, as demonstrated by the high level of agreement between the evaluators in MSCT (80-100%; with the exception of the oval window). Only Evaluator 2 had extensive experience in using CBCT, which might explain the discrepancies. CBCT images are different in appearance compared to the conventional MSCT (175). Inter-observer bias is a well-known problem in qualitative image studies, as the grading is subjective (174, 176). One temporal-bone study comparing CBCT and MSCT previously recognized this issue (189). In the evaluation of new

technologies it is important to analyse and take into account observer agreement and disagreement.

To our knowledge, no study of radiological evaluations in patients with otosclerosis 30 years after surgery has previously been conducted. Preoperative CT by Lagleyere et al. (2009; 88.5%) and by Shin et al. (2001; 74.5%) revealed a frequency of fenestral lesions that was similar to or higher than that shown in our study, while Rooteveel et al. (2004) found significantly fewer fenestral lesions (32%) in a pre-cochlear implantation study (25, 28, 168). Pre-operative fenestral lesions are not completely comparable to fenestral lesion, 30 years after surgery (or pre-cochlear implantation). A higher frequency of fenestral otosclerotic lesions and the surgical effect might be reasons for the reduced frequency.

Among our patients with pronounced sensorineural hearing loss (Group B), retrofenestral lesions were found in a total of 50% of the ears, while in those with best-preserved sensory function (Group A), no retrofenestral lesions were found. Our figure of 50% is slightly lower compared to pre- cochlear implant studies (77% and 75%, respectively) (25, 177). There appears to be a strong correlation between retrofenestral lesions and the degree of hearing loss. This is in accordance with several studies, radiological as well as histological, where a correlation has been shown between cochlear otosclerosis and degree of sensorineural hearing loss, whereas in other studies the correlation has not been verified (28, 39, 178, 179).

The stapedial prosthesis and its position were well visualized by both methods (80%), in accordance with Peltonen et al. (2009) but in contrast with Dalchow et al. (2006), who reported non-detectable stapedial prostheses in a clinical study (87, 180). These studies were performed on cadavers and were very small, however. One interesting finding, not reported in the results was that a dislocation of the stapedial prosthesis appears to be correlated to the ABG. The numbers in this study are, however, too small to perform a statistical analysis and further studies would be of great interest.

8 CONCLUSION

- Otosclerosis is not only a middle-ear disease, but also an inner-ear disease with progressive hearing impairment.

- Thirty years after stapedectomy sixty-six percent of the subjects displayed a moderate to profound hearing loss in the study ears.

- Hearing deterioration was mainly caused by sensorineural hearing loss and the sensorineural hearing loss was significantly greater compared with the ISO reference population, both in early and late stages of the disease. The difference in sensory function could not be explained by age alone.

- Almost all surgically treated subjects will eventually need hearing aid rehabilitation, however, this was obtained in only approximately 50% of our subjects.

- Patients who had undergone hearing aid rehabilitation were generally everyday users and were very satisfied with their hearing aids.

- The otosclerosis subjects experienced hearing disability, especially in complex listening situations and in localization of sounds, but nonetheless had a health-related quality of life comparable to that of the reference population.

- CBCT is suitable for temporal bone imaging in otosclerosis, with the advantage of considerable lower radiation dose compared with MSCT.

- Based on our findings, we recommend that health-care providers (otolaryngologists, surgeons and audiologists) inform patients that stapedectomy and possibly stapedotomy will not affect the progression of disease and that there is a strong likelihood that audiological rehabilitation and the use of hearing aids will eventually be needed, with good expected results.

9 FUTURE PERSPECTIVES

The main goal of future research in otosclerosis is, in my opinion, to solve the question about etiology aiming at developing better diagnostic tools and effective treatments. In approximately 9% of adult cochlear implant patients, the severe hearing loss is caused by otosclerosis (25).

One important aspect in genetics is to define the phenotype. Today linkage analyses are sparse and hard to perform, as most families only have a limited number of affected individuals. One reason could be that we don't recognize the affected individual. As an example; 26% of cochlear implant otosclerosis patients, had a pure sensorineural hearing loss and were not recognized as having otosclerosis until the time of pre-surgical assessments (25). Furthermore, histological otosclerosis is ten times more common than clinical otosclerosis; however the correlation sensorineural hearing loss is debated (39). In studies defining the otosclerosis phenotype, radiological assessments will be important. I think CBCT will be central in these assessments, as good as MSCT, but with advantages such as lower radiation dose, much cheaper and with the possibility of assessing only the target volume (the middle and inner ear), however further studies are needed.

Another important issue is to make individuals with otosclerosis and health-care providers (audiologists, otolaryngologists and surgeons) aware of the progressive nature of the hearing loss. Stapedectomy and possibly stapedotomy will not affect the progression of disease and there is a strong likelihood that audiological rehabilitation and the use of hearing aids, with good results, will eventually be needed. To improve the audiological rehabilitation in otosclerosis further studies are needed.

10 SAMMANFATTNING PÅ SVENSKA

Otoskleros är en relativt vanlig öronsjukdom som drabbar ca 0,3-1% av befolkningen i västvärlden. Sjukdomen är vanligast hos kvinnor och debuterar oftast i tidig vuxen ålder. Skelettet som omger örat drabbas av bennedbrytning, följt av bennybildning vilket leder till att stigbygeln i mellanörat växer fast. Detta innebär att ljud får svårare att passera in till innerörat med hörselnedsättning som följd. Även innerörat kan drabbas av varierande grad. I vilken grad innerörats hörselnedsättning beror på otoskleros eller åldersrelaterad hörselnedsättning är oklart. Svårighetsgraden av hörselnedsättningen varierar kraftigt, från lindrig till grav hörselnedsättning/dövhet.

Orsaken till otoskleros är komplex, multifaktoriell och är ännu oklar. Man vet att ärftlighet spelar roll, troligen även mässlingsvirus och autoimmunitet. Eftersom orsaken till otoskleros är okänd finns i nuläget ingen bot.

Otoskleros är en kronisk sjukdom med varierande förlopp, en av de diagnostiska möjligheter som står till buds är datortomografi, vilket kan bli aktuellt upprepade gånger. Kon-datortomografi (CBCT) är en ny teknik som har visat sig lovande i preliminära temporalbensstudier där de små strukturerna i mellan och innerörat har avbildats med god upplösning. CBCT har betydligt lägre stråldos än den idag använda metoden vilket är väsentligt enligt ICRP (International Commission on Radiation Protection) med strävan att använda så låg dos som möjligt i enlighet med ALARA principen (As low as reasonable achievabel).

Behandlingen som erbjuds idag är kirurgisk, där man ”kopplar förbi” den fastvuxna stigbygeln (stapedektomi alternativt stapedotomi), och/eller teknisk med hörapparatrehabilitering. Kirurgi leder i de flesta fall till gott hörselresultat men vad som händer på längre sikt är mera osäkert.

Det övergripande syftet med avhandlingen var att utvärdera otoskleros i ett brett långtidsperspektiv, medicinskt, tekniskt, hälsorelaterad och ur självupplevd hörselfunktions synpunkt.

METODIK

I studien ingår personer som opererades för otoskleros 1977-79 på Sahlgrenska Universitets sjukhus, födda 1930 eller senare (n=65). Hörselprov

utförda före och efter operationen samt operationsberättelser analyserades. En uppföljning utfördes 28-30 år senare med hörselprov (ton-, tal- och impedans audiometri) och öronundersökning. Vid uppföljningen gjordes också en strukturerad intervju inkluderande hälsostatus, utbildningsgrad, tinnitus mm. Samtliga personer besvarade frågeformulär avseende hälso-relaterad livskvalitet (HRQL) (SF-36v2) och hörsel-relaterad funktionsnedsättning (Speech Spatial and Quality; SSQ). De som använde hörapparater svarade på frågeformulär avseende hörapparatanvändning och nytta (International Outcome Inventory of Hearing Aid; IOI-HA). De med bäst (n=10) och de med sämst (n=10) inneröras hörsel (mätt som benledningströskel) genomgick flerskikts- och kon- datortomografi (MSCT, CBCT) med efterföljande analys av anatomi och otosklerosförändringar i mellan och inneröron.

RESULTAT

Tjugoåtta-trettio år efter operation var hörseln jämförbar med hörseln före operationen. Sextiosex procent hade en måttlig till svår hörselnedsättning i det opererade örat. Hörselförsämringen var ffa orsakad av en försämrad sensorineural funktion. Hörselnedsättningens grad var både tidigt och sent i sjukdomsförloppet signifikant sämre jämfört med en ålders och könsmatchad referenspopulation. Ingen signifikant skillnad fanns mellan opererade och icke opererade otosklerosöron avseende hörsel efter ca 30 år (luftledning). Vid uppföljningen hade 95% av studiepopulationen hörselnedsättning av en sådan grad att de skulle ha nytta av hörapparat, trots detta hade endast 54% erhållit hörapparatrehabilitering (26% ett örat och 28% båda öronen). De med hörapparat var i hög grad nöjda och använde sina hörapparater, 94% varje dag och 54% hela dagarna. Hörselrelaterade besvär var framträdande ffa i komplexa lyssningssituationer och vid lokalisation av ljud. Trots hörselsvårigheter hade personerna en hälsorelaterad livskvalitet jämförbar med en ålders- och köns-korrigerad kontrollpopulation. Anatomiska strukturer och otosklerosförändringar visualiserades lika bra med MSCT och CBCT.

KONKLUSIONER

Otoskleros är att betrakta som inte bara en mellan- utan också och en inneröresjukdom med progredierande förlopp, där i stort sett alla opererade otosklerospatienter på lång sikt kommer att behöva hörselrehabilitering. Trots detta hade endast drygt hälften erhållit hörselrehabilitering med hörapparater.

Otoskleros gruppen upplevde hörselrelaterad funktionsnedsättning men den generella livskvaliteten var jämförbar mellan personer med otoskleros och referenspopulationen. CBCT är en teknik som med fördel kan användas vid radiologisk undersökning av otosklerospatienter.

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