Otosclerosis
-Basic science and clinical significance-

-IFOS World Course 2019-

Department of Otolaryngology

Keio University
K Ogawa MD, PhD
Otosclerosis is caused by a single or multiple spongifying lesions beginning in the endocochlear layer of the capsular bone. Characteristic pathological finding is otospongiosis in which bone formation and bone resorption are both present. Incomplete autosomal dominant transmission with low penetrance (40%).
Clinical otosclerosis and histological otosclerosis

- **Clinical otosclerosis**
  “Otosclerosis diagnosed clinically and audiologically”

- **Incidence**
  - Caucasian: 0.3% of population
  - Japanese: less than 1/5~10 of Caucasian

- **Histological otosclerosis**
  “Otosclerosis diagnosed by autopsy”

- **Incidence**
  - Caucasian: 8.3%
  - Black: 1.0%
  - Japanese: 1.3%
# Etiology

## (1) genetics

- The incidence differs among races suggesting that the genetic factor may involved in the etiology (Incomplete autosomal dominant transmission).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Report</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTSC1</td>
<td>Tomek et al. 1998</td>
<td>15p25-q26</td>
<td>unknown</td>
</tr>
<tr>
<td>OTSC2</td>
<td>Van Den Bogaert et al. 2001</td>
<td>7q34-q36</td>
<td>unknown</td>
</tr>
<tr>
<td>OTSC3</td>
<td>Chen et al. 2007</td>
<td>6p22.3-p21.2</td>
<td>unknown</td>
</tr>
<tr>
<td>OTSC4</td>
<td>Brownstein et al. 2006</td>
<td>16q21-q23.2</td>
<td>unknown</td>
</tr>
<tr>
<td>OTSC5</td>
<td>Van Den Bogaert et al. 2001</td>
<td>3q22-q24</td>
<td>unknown</td>
</tr>
<tr>
<td>OTSC6</td>
<td>N/A</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>OTSC7</td>
<td>Thys et al. 2007</td>
<td>6q13-q16.1</td>
<td>unknown</td>
</tr>
<tr>
<td>CD46</td>
<td>Karosi et al. 2008</td>
<td>1q32</td>
<td>CD46/measles virus receptor</td>
</tr>
<tr>
<td>TGF-beta1</td>
<td>Thys et al. 2007</td>
<td>19q13.2: 19q13.1</td>
<td>TGF-beta1</td>
</tr>
<tr>
<td>COL1A1</td>
<td>McKenna et al. 1998</td>
<td>17q21.33</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>BMP2</td>
<td>Schrauwen et al. 2008</td>
<td>20p12</td>
<td>Bone morphogenetic protein</td>
</tr>
<tr>
<td>BMP4</td>
<td>Schrauwen et al. 2008</td>
<td>14q22-q23</td>
<td>Bone morphogenetic protein</td>
</tr>
</tbody>
</table>
Etiology

(2) latent measles infection

- 1981 Paget’s disease = paramyxovirus infection
- 1986 McKenna: measles nucleocapsid
- 1989 Arnold: paramyxovirus IgG in footplate
  - measles, rubella, mumps (?)
- 1994 Niedermyer: measles virus RNA
- 1996 Arnold: measles in perilymph
- 2000 Niedermyer: 83% (+)
- 2000 Grayeli: no evidence of measles virus infection (n=35)
- 2004 Karosi: footplate 20/34 (+)
- 2007 Karosi: measles virus receptor (CD46)
- 2011 Komune: no evidence of measles virus infection in Japanese otosclerosis
Pathophysiology of otosclerosis

Genetics: COL1A1, BMP2,4 polymorphism, OTSC1~8 gene, alternative splicing of CD46

Measles virus

Otosclerosis
Otospongiosis

Inflammation
- TNFα
- TGFβ1
- IL-1, IL-6
- OPG
- RANK, RANKL

Autoimmune

Horminич
- Estrogen
- Progesteron
Animal model of otosclerosis

- Morphological changes in the ossicles and changes in hearing in \textit{opg} knock out mouse
- \textit{opg} KO (\textit{----}), hetero (\textit{+/-}), wild (\textit{+/+}) mice
  6,10,15 week-old \(\varphi\)

1) Morphology of the ossicles
   A) macroscopic, B) microscopic (paraffin embedded sections)
2) TRAP activity (tartrate-resistant acid phosphate) which suggests osteoclast activity.
3) \(\mu\)CT analysis (10 week-old \(\varphi\))
   malleal and tibial cortical thickening
4) Acoustic brain stem response (ABR)
   2, 4, 12, 20 kHz
Bone remodeling

Bone resorption

normal

Bone formation

osteoclast

osteoblast

Bone resorption

osteoporosis

Bone resorption

osteopetrosis

Bone resorption

osteoporotic

When bone resorption is up-regulated, the bone will become osteoporotic.
Mechanism of bone resorption

**Normal**

- **Osteoclast**
  - **RANKL**: Receptor Activator NFkB Ligand
  - **RANK**: Receptor Activator NFkB
  - **OPG**: Osteoprotegerin

**Activated osteoclast**

**Inactivated osteoclast**

**Bone resorption**

**Osteoporosis/otosclerosis**

- **Osteoclast**
  - **RANKL**: Receptor Activator NFkB Ligand
  - **RANK**: Receptor Activator NFkB
  - **OPG**: Osteoprotegerin

**Activated osteoclast**

**Bone resorption↑**
Ossicles and osteoclasts

Red staining suggests the higher activity of osteoclast. From these results of TRAP staining, we can clearly observe the higher activity of osteoclast in the opg KO mouse.
The number of osteoclasts increased 6~7 times higher in opg KO mice than in the controls.
in *Opg* KO mice, no ligament exists and the junction is replaced with bone tissue which fuses the stapes and the otic capsule.

These changes are similar to the changes in otosclerosis.
Hearing threshold increased as age.

These data suggest that osteoporotic changes result in progressive hearing loss, which is similar to hearing loss in otosclerosis.
Sodium risedronate can prevent hearing loss

Bisphosphonate (sodium risedronate): anti-osteoporosis medicine
- Bind to bone mineral surface and uptake into osteoclasts
- Inhibit farnesyl disphophate synthase, a key enzyme of the mevalonate pathway
Sodium risedronate prevents the morphological changes in ossicles

Risedronate treatment prevented bone erosion of malleus, incus and stapes, and the stapedial-cochlear junction
Can risedronate prevent progressive hearing loss?

Subjects: Woman (Otosclerosis + Osteoporosis)

- Risedronate 35mg/wk 10 ears
- SERM 60mg/day 10 ears

Follow-up (3yrs) Audiogram, TG Bone density

Selective estrogen receptor modulators

Compared to the historical control
Bone remodeling

Bone resorption  normal  Bone formation

osteoclast  osteoblast

Bone resorption  osteoporosis  Bone resorption

Bone resorption  osteopetrosis  Bone formation

When bone formation is up-regulated, the bone will become osteopetrotic.
Osteopetrotic ossicles show aberrant thickening
Summary

- *opg* KO mouse shows progressive hearing loss caused by ossicular abnormality such as stapedial fixation.
- OPG may be a key factor of the etiology not only of Paget disease, but also of osteoporosis and otosclerosis.
- OPG is a protective factor against hearing loss caused by bone resorption.
- Risedronate may prevent progressive hearing loss.
- OPG is found in the parilymph (Zehnder 2005).
- Further study will be needed to figure out the role of OPG in the cochlea.
Clinical study
“How to treat otosclerosis?”

454 cases (600 ears) who underwent stapedectomy using an apatite ceramic implant (Apaceram-C) under microscope (+11 ears by TEES)

(1) diagnosis
   audiogram and tympanogram
   progression of hearing loss
   prevention of hearing loss

(2) treatment
   surgical results (hearing, tinnitus, ear fullness)
   long-term prognosis
Subjects

600 surgically proven otosclerosis ears who underwent stapedectomy using an apatite ceramic implant.

- **age**
  - 10~77 (43±13) year-old

- **sex**
  - male: 146 (33%)
  - female: 308 (67%)

- **laterality**
  - unilateral: 98 (22%)
  - bilateral: 356 (78%)

(1) audiogram and tympanogram
(2) progression of hearing loss
Audiogram and tympanogram

Carhart notch
32.0 ± 12.3dB
(postop 27.3 ± 12.6dB)

5dB elevated at 1 and 4kHz
228 ears (38%)

Stiffness curve
10.1 ± 14.3dB

Tympanogram (As: sc<0.4ml)
Progression of hearing loss

Ears whose hearing loss could be observed more than 3 years.

**Rate (dB/year)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate (dB/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (&lt;40dB)</td>
<td>3.1 ± 2.2</td>
</tr>
<tr>
<td>Moderate (&lt;60dB)</td>
<td>1.7 ± 1.7</td>
</tr>
<tr>
<td>Severe (&gt;60dB)</td>
<td>1.7 ± 1.4</td>
</tr>
<tr>
<td>Total</td>
<td>2.3 ± 2.0</td>
</tr>
</tbody>
</table>
Surgical methods using Apa-C

Problems in Teflon-wire pistons

- bio-compatibility
- MRI compatibility (3.0T and 4.7T)
- slippage
- necrosis of incudal long process
- perilymphatic fistula

bio-compatible apatite ceramic
Intraoperative measurement

f2×1 [mm]

Piezoelectric sensor

5×5×40 [mm]

Piezoelectric actuator

Piezo driver

Power source

Control box

A/D converter

D/A converter

ossicular mobility tester
Stapedial fixation

Compliance (Mobility)

\[ \text{Compliance} = \frac{\text{Displacement} [\mu m]}{\text{Load} [N]} \]

Graph showing the relationship between load and displacement for normal and fixed ears.
SFS vs TS、PS

- Stapedotomy (SFS): 466 ears (78%)
- Partial Stapedotomy (PS): 134 ears (22%)
- Total Stapedectomy (TS):
Pre-and post-operative hearing (m±SD)

air-conduction

bone-conduction
Hearing gain in each frequency

Frequency

Gain (dB)

125 250 500 1k 2k 4k 8k

SFS

TS or PS
Criteria for surgical results
(the Japan Otological Society in 2000)

1) Post-operative AB-Gap < 15dB
   94.7% (568/600)

2) Hearing gain > 15 dB
   90.0% (540/600)

3) Post-operative hearing level < 30dB
   56.3% (338/600)

If cases who are fit to one of these criteria are successful, the successful rate is 98%.
Long-term prognosis of postoperative hearing

- 1 year: 30.0±8.1 dB
- 5 year: 28.4±8.7 dB
# Postoperative symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus (402 ears)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disappeared</td>
<td>205</td>
<td>51.0%</td>
</tr>
<tr>
<td>Improved</td>
<td>128</td>
<td>31.8%</td>
</tr>
<tr>
<td>Unchanged</td>
<td>40</td>
<td>10.0%</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>16</td>
<td>7.2%</td>
</tr>
<tr>
<td>Ear Fullness (194 ears)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disappeared</td>
<td>120</td>
<td>61.9%</td>
</tr>
<tr>
<td>Improved</td>
<td>35</td>
<td>18.0%</td>
</tr>
<tr>
<td>Unchanged</td>
<td>21</td>
<td>10.8%</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>4</td>
<td>2.1%</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
<td>7.2%</td>
</tr>
</tbody>
</table>
Conclusion

1. We investigated the surgical results of stapedectomy using an apatite ceramic implant (Apa-C) in 600 otosclerosis under the microscope.

2. Small fenestration stapedectomy was performed in 466 ears (78%), and total or partial stapedectomy in 134 ears (22%).

3. Success rate was 98% in 600 ears, 98% in SFS and 97% in TS or PS.

4. Improved hearing was maintained in the long-term postoperative observation, except 3 ear with cochlear otosclerosis.

5. Tinnitus was improved in 83% of the ears, ear fullness was 80%.