Limited evidence for the effect of sodium fluoride on deterioration of hearing loss in patients with otosclerosis

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Limited Evidence for the Effect of Sodium Fluoride on Deterioration of Hearing Loss in Patients With Otosclerosis: A Systematic Review of the Literature


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Objective: To determine the protective effect of sodium fluoride on the deterioration of hearing loss in adult patients with otosclerosis.

Data Sources: PubMed, Embase, the Cochrane Library, and CINAHL.

Study Selection: A systematic literature search was conducted. Studies reporting original study data on the deterioration of hearing loss in otosclerosis patients treated with sodium fluoride were included.

Data Extraction: Directness of evidence (DoE) and risk of bias (RoB), using the Cochrane Collaboration’s tool for assessing risk of bias, of the selected articles were assessed. Studies with low DoE, high RoB, or both were excluded. Absolute risks, mean deterioration of hearing in decibels, risk differences, and their 95% confidence intervals were extracted from the included studies.

Data Synthesis: Our search yielded 168 original titles, of which, 2 placebo-controlled studies were eligible for data extraction. The results of these 2 studies were conflicting. One of the included studies, with high DoE and moderate RoB, reported an absolute risk reduction for deterioration of hearing loss of 18% [95% CI 17; 19] when treating with sodium fluoride. The other included study, with high DoE and moderate RoB, reported no clinically significant difference in mean deterioration of bone-conduction, air-conduction, or air-bone gap between the sodium fluoride group and the placebo group.

Conclusion: There is weak evidence from one study with significant limitations that deterioration of hearing loss in otosclerosis patients receiving sodium fluoride treatment is less than in patients treated with a placebo. Key Words: Hearing loss—Otosclerosis—Otospongiosis—Pure-tone audiogram—Sodium fluoride—Treatment.


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TABLE 1. Search for studies on the effect of sodium fluoride on deterioration of hearing loss in patients with otosclerosis (performed on 28th of August 2013)

<table>
<thead>
<tr>
<th>Database</th>
<th>Search syntax</th>
<th>Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed, Cochrane Library, CINAHL</td>
<td>(otoscl* OR otospongio*) AND (fluoride OR fluorides OR fluorine OR fluorines OR fluorid OR florin OR floride OR florides OR flavours OR sodiumfluoride OR NaF OR ‘Na Fl’ OR fluor)</td>
<td>Title/Abstract</td>
</tr>
<tr>
<td>Embase</td>
<td>(otoscl<em>ab,ti OR otospongio</em>ab,ti) AND (fluoride:ab,ti OR fluorides:ab,ti OR fluorine:ab,ti OR fluorines:ab,ti OR fluorid:ab,ti OR fluorin:ab,ti OR floride:ab,ti OR florides:ab,ti OR fluorine:ab,ti OR fluorines:ab,ti OR sodiumfluoride:ab,ti OR naf:ab,ti OR ‘na fl’:ab,ti OR fluor:ab,ti)</td>
<td>Title/Abstract</td>
</tr>
</tbody>
</table>

Study Assessment

Remaining records were assessed for their directness of evidence and risk of bias by three of the authors (M. A. H., P. H., and D. L. V. D. V.). Directness of bias concerned the applicability of the study findings for answering the research question. Directness of evidence involved the evaluation of patients, compared treatments and outcomes (see Table 2 for assessment criteria): patients, notably 1) patients diagnosed with otosclerosis (cochlear and/or fenestral), treatment comparison, notably comparison of 2) sodium fluoride treatment to 3) placebo, and outcomes; notably, our 4) outcome of interest was the extent of deterioration of hearing loss measured by difference in pretreatment and posttreatment air- and bone-conduction thresholds and air-bone gap closure on pure-tone audiometry (PTA) at 5) 1-year follow-up. Studies were classified as having a high directness of evidence if they complied with all the 5 criteria, moderate risk of bias if they satisfied at least 3 criteria, and the remainder was classified as low directness of evidence.

FIG. 1. Flowchart for selection of studies investigating the effect of sodium fluoride in patients with otosclerosis.
TABLE 2. Study assessment of studies on the effect of sodium fluoride treatment in patients with otosclerosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size of study (n)</th>
<th>Study design</th>
<th>Directness of evidence</th>
<th>Risk of bias</th>
<th>Blinding of outcome</th>
<th>Missing data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient</td>
<td>Treatment</td>
<td>Comparator</td>
<td>Outcome</td>
</tr>
<tr>
<td>Bretlau et al. (1989) (8)</td>
<td>95</td>
<td>RCT</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>De Oliveira Vicente et al. (2012) (14)</td>
<td>18</td>
<td>RCT</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Ramsay and Linthicum 1994 (12)</td>
<td>146 (ears)</td>
<td>RCS</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>•</td>
</tr>
<tr>
<td>Felix-Trujillo, et al. (2009) (10)</td>
<td>100</td>
<td>PCS</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>•</td>
</tr>
<tr>
<td>Shambaugh and Causse (1974) (13)</td>
<td>1436</td>
<td>RCS</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>•</td>
</tr>
<tr>
<td>Derks et al. (2001) (9)</td>
<td>41</td>
<td>RCS</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>•</td>
</tr>
<tr>
<td>Forquer et al. (1986) (11)</td>
<td>394</td>
<td>RCS</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>•</td>
</tr>
<tr>
<td>Béhéar and Headreville (1977) (15)</td>
<td>40</td>
<td>RCS</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>•</td>
</tr>
<tr>
<td>Debry et al. (1988) (16)</td>
<td>136</td>
<td>RCS</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>•</td>
</tr>
</tbody>
</table>

**Directness of evidence**
- Patient: satisfactory when study population ≥18 years with otosclerosis; Treatment: satisfactory when patients were treated with sodium fluoride and did not undergo stapes surgery during follow-up period; Comparator: satisfactory when a placebo was used in the control group; Outcome: satisfactory when pure-tone audiometry was carried out; Follow-up: satisfactory when follow-up was ≥1 year.

**Risk of bias**
- Randomization: satisfactory when patients were randomly assigned to treatment groups (e.g., a computer generated sequence); Concealed allocation: satisfactory when assignment to treatment groups was concealed (e.g., central allocation); Standardization (treatment): satisfactory when treatment frequency, duration and dosage of sodium fluoride/placebo was standardized; Standardization (outcome): satisfactory when outcome was uniformly assessed using a protocol (with regard to pure-tone frequencies and equipment used); Blinding of outcome: satisfactory when outcome was measured without knowledge of treatment assignment; Missing data: satisfactory when missing data did not exceed 10%.

n indicates number of patients; RCT, randomized controlled trial; RCS, retrospective cohort study; PCS, prospective cohort study; T, treatment; O, outcome; •, satisfactory; o, not satisfactory; ?, unclear.
Assessment of risk of bias involved the evaluation of the extent of selection and information bias. Using the Cochrane Collaboration’s tool for assessing risk of bias, the selected studies were assessed for their risk of bias (4). Assessment of risk of bias involved evaluation of selection bias, notably 1) random and 2) concealed treatment assignment and 3) completeness of reported data; and information bias, notably 4) blinding of treatment and outcome assessment, 5) standardization of treatment, and 6) standardization of outcome assessment. If studies complied with all of these criteria, they were classified as having a low risk of bias. Studies were classified as having a moderate risk of bias if they satisfied at least 3 criteria, and the remainder was classified as high risk of bias. When an item of the study assessment was reported, it was classified as either “satisfactory” or “unsatisfactory.” When an item was not reported, it was rated “unclear.” Initial discrepancies between independent reviewers were resolved by discussion, and reported results are based on full consensus. Studies with either or both low directness of evidence and high risk of bias were excluded from further review.

### Data Extraction

Three authors (M. A. H., P. H., and D. L. V. D. V.) independently extracted descriptive data considering the study population and interventions from the included studies. For the outcomes of interest, the absolute risks and their risk differences with 95% confidence intervals (95% CIs) were extracted or calculated using GraphPad Software, Inc. The primary outcome measure was pure-tone audiometry. Preferably details on deterioration of bone-conduction, deterioration of air-conduction, and deterioration of air-bone gap were extracted. If these outcome measures were not available or could not be calculated, we reported the findings as used in the article.

### RESULTS

#### Search and Selection

A total of 282 titles were retrieved, of which, 168 were unique studies (see Fig. 1; date of last search was August 28, 2013). Articles published in Russian (5) or Yugoslav (6,7) were excluded. After selection based on title and abstract, and subsequent full-text screening, we included 9 articles (8–16) for further review. Cross-reference checking revealed no additional articles.

#### Study Assessment

All 9 included articles were assessed on directness of evidence and risk of bias, as shown in Table 2. Three studies provided direct evidence (8,12,14), and in 6 studies, the directness was found low or moderate (9–11,13,15,16). Some of the studies included patients that underwent stapes surgery during the observation period (10,11,15,16) or did not use a placebo comparator (9–13,15,16). The risk of bias was moderate in 3 studies (8,10,14) and high in the other 6 (9,11–13,15,16). Adequate randomization and concealed treatment assignment was not achieved in any of the studies (8–16). In most of the included 9 studies, either a large amount of outcome data was missing (8,10,14), or it was unclear whether data were missing (9,11–13,15,16). Standardization of treatment and blinding of outcome was achieved in only 3 studies (8,10,14). Two articles, with high directness of evidence and moderate risk of bias, represented the best available evidence and were included for further review (8,14). Seven studies with either or both low directness of evidence and high risk of bias were excluded from further review (9–13,15,16).

#### Data Extraction

An overview of treatment characteristics of all 9 studies is provided in Table 3. These 9 studies differ greatly in their approach to the dosage and duration of treatment and the use of comedication. Dosage varied from 1.5 to 75 mg/d and treatment duration from 6 to 96 months. Comedication, in the form of calcium with or without vitamin D, was used in 2 studies (8,11). None of these 9 studies provided an explanation for their choice of treatment.

The extracted outcome data of the 2 included, placebo-controlled studies are described in Table 4. Risk differences are positive when results favor sodium fluoride treatment and negative when results favor the placebo group. The 2 selected studies included, in total, 113 patients. Both studies did not differentiate between cochlear and fenestral otosclerosis, although in the study performed by de Oliveira Vicente et al. (14), all patients underwent CT imaging examination. No baseline characteristics were available for the study performed by Bretlau et al. (8). In the study performed by de Oliveira Vicente et al. (14), a
TABLE 4. Results of studies on the effect of sodium fluoride treatment in patients with otosclerosis

<table>
<thead>
<tr>
<th>Study</th>
<th>NaF (n)</th>
<th>Control (n)</th>
<th>Follow-up duration (months)</th>
<th>Outcome measure</th>
<th>NaF</th>
<th>Control</th>
<th>Risk difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bretlau (1989) (8)</td>
<td>43</td>
<td>52</td>
<td>12–24</td>
<td>Deterioration of &gt;10 dB on pure-tone audiometry ( % )</td>
<td>7.0%</td>
<td>25.0%</td>
<td>18.0 [16.8; 19.2]</td>
</tr>
<tr>
<td>De Oliveira Vicente (2012) (14)</td>
<td>9</td>
<td>9</td>
<td>6</td>
<td>Mean deterioration bone-conduction (dB)</td>
<td>0.5 kHz</td>
<td>-0.67</td>
<td>-1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 kHz</td>
<td>-0.66</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 kHz</td>
<td>-0.67</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 kHz</td>
<td>0.67</td>
<td>-4.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean deterioration air-conduction (dB)</td>
<td>0.5 kHz</td>
<td>-1.33</td>
<td>-2.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 kHz</td>
<td>-2.33</td>
<td>-1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 kHz</td>
<td>-2.34</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean air-bone gap (dB)</td>
<td>0.5 kHz</td>
<td>26.00</td>
<td>29.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 kHz</td>
<td>26.67</td>
<td>25.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 kHz</td>
<td>12.33</td>
<td>10.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 kHz</td>
<td>20.00</td>
<td>24.33</td>
</tr>
</tbody>
</table>

When risk difference is positive, this favors treatment with sodium fluoride.
NaF indicates sodium fluoride; n, number of patients; 95% CI, 95% confidence interval;
\( \* \) Three-frequency pure-tone audiometry using 0.5, 1 and 2 kHz.

significant difference in air- and bone-conduction, in favor of the sodium fluoride group, was present at baseline. Differences in pretreatment bone-conduction ranged from 1.33 dB for 500 Hz to 15.67 dB for 4,000 Hz. Differences in pretreatment air-conduction ranged from 6.00 dB for 500 Hz to 15.00 dB for 4,000 Hz. In other words, disease was more severe in the placebo group than in the sodium fluoride group at baseline.

In the study performed by Bretlau et al. (8) \( n = 95 \), an absolute risk reduction for deterioration of hearing loss \( (>10 \text{ dB}) \) of 18% \[95\% \text{ CI, 17; 19}\] was achieved when using sodium fluoride 40 mg/d. Risk differences for mean deterioration of bone-conduction ranged between \(-5 \text{ dB [-5; -5]} \) and 1 dB \[1; 1\] for the frequencies 0.5, 1, 2, and 4 kHz in the study performed by de Oliveira Vicente et al. (14) \( n = 18 \). Risk differences for mean deterioration of air-conduction for the same frequencies ranged between \(-3 \text{ dB [-4; -3]} \) and 1 dB \[1; 1\]. Reported risk differences for mean posttreatment air-bone gap ranged between \(-1 \text{ dB [-1; -1]} \) and 4 dB \[4; 4\].

Data on potential adverse events, such as gastric complaints, allergic dermatitis, arthritic symptoms, hair loss, and motting of tooth enamel, were not systematically collected. De Oliveira Vicente did mention that two of their patients (22%) treated with sodium fluoride had mild epigastric complaints (14).

DISCUSSION

This review of the literature provides limited evidence for the effectiveness of sodium fluoride in patients with otosclerosis. Two placebo-controlled studies that carry moderate risk of bias were identified (8,14). The results of these 2 studies are conflicting. One of the included studies reported an absolute risk reduction for deterioration of hearing loss of 18% \[95\% \text{ CI, 17; 19}\] when treating with sodium fluoride (8). The other included study reported differences in mean deterioration of bone-conduction, air-conduction, or air-bone gap between the sodium fluoride group and the placebo group that were too small to be clinically meaningful (14).

When interpreting our results, there are some considerations one needs to take into account. First, the designs of the included studies differ in their approach to the dosage and duration of treatment, the use of comedication, the choice of outcome measure and pure-tone audiometric frequencies, and follow-up duration. Otosclerosis is a slowly progressive disease, and therefore, long-term follow-up is needed to reliably estimate treatment effects. High pure-tone audiometric frequencies were not evaluated in 1 study (8), and follow-up did not reach 1 year in the other (14). No consensus exists, regarding optimal dosage of sodium fluoride and studies comparing effectiveness of different dosages, have not been published. In 1 study, vitamin D and calcium were coprescribed in both groups (8), without providing an explanation for doing so. Possibly, calcium carbonate was added to the treatment regimen, because it reduces gastric irritation caused by sodium fluoride (17). Second, the best available studies carry moderate risk of bias because of a lack of randomization, treatment allocation, and blinding of observations. Moderate or high risk of bias can lead to overestimation or underestimation of true intervention effects. Third, sample sizes are small: a total of 113 patients were evaluated in the two included studies and confidence intervals...
were unrealistically narrow. Larger, well-designed studies are needed to make accurate statements about the effect of sodium fluoride on the deterioration of hearing.

An ideal study would have adequately randomized and concealed treatment allocation. Both patients and outcome assessors (audiologists) should not be aware of treatment assignment. The outcome should be assessed in a standardized manner. The same equipment and pure-tone frequencies should be used for pure-tone audiometry in all patients, and follow-up duration should be equal in all patients. Not only outcome, also treatment should be standardized. Treatment frequency, duration, and dosage of sodium fluoride treatment should be standardized. Lastly, it is important to note that significant and selective loss to follow-up and/or missing data can result in over- or underestimation of treatment effects.

Sodium fluoride may have a wide applicability: as initial treatment in patients with cochlear otosclerosis, when surgery is contraindicated or for those patients rejecting surgical treatment. Possibly these patients would benefit from treatment with sodium fluoride. Unfortunately, none of the included articles have differentiated between cochlear and fenestral otosclerosis. Therefore it is not possible to make evidence-based statements about the effect of sodium fluoride on cochlear otosclerosis. Furthermore, it may be worth considering fluoride treatment as an early preventive measure in families with otosclerosis. Treatment with sodium fluoride will not prevent the need for surgical intervention, but might slow down the process and postpone surgery.

The included articles provide limited information on adverse events. Six small case series were identified that evaluated adverse events of sodium fluoride treatment in osteoporosis patients. Sodium fluoride dosages varied across these studies from 40 to 80 mg/d. The following adverse events were described in these reports: allergic dermatitis, arthritic symptoms, hair loss, and dental fluorosis (mottling of tooth enamel). The occurrence rate of these complaints varied from 12.5% to 50% (14,15,18–20).

**CONCLUSION AND RECOMMENDATION**

There is weak evidence from one study with significant limitations that deterioration of hearing loss in otosclerosis patients receiving sodium fluoride treatment is less than that in patients treated with a placebo. It remains important to emphasize that with current evidence-based medicine (EBM) insights, this available literature shows evidence of moderate risk of bias, with effects ranging from a clinically relevant absolute risk reduction for further deterioration of hearing loss in favor of sodium fluoride treatment to a negligible effect of sodium fluoride treatment. Still, for patients not eligible for surgery, for example, those with cochlear otosclerosis, sodium fluoride may provide a safe treatment option, but the anticipated effect is limited. Like with all medication, before prescribing sodium fluoride, careful consideration is warranted.

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**REFERENCES**