EJR European Journal of Rheumatology

DOI:10.5152/eurjrheum.2025.23076

Review Article

Hearing Loss in Connective Tissue Diseases: A Systematic Review

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Abstract

Hearing loss may be found in patients with systemic autoimmune disorders such as connective tissue diseases (CTD). This work aimed to review the literature on ear involvement in CTD. A systematic search of articles published in PubMed/MEDLINE, EMBASE, and SCOPUS from 1966 to June 2023 following PRISM guidelines was done. Seventy-nine papers were selected: 39 on rheumatoid arthritis; 16 on systemic lupus erythematosus; 14 on scleroderma; 6 on Sjogren's syndrome; 1 on mixed connective tissue disease; and 3 that approached more than one CTD. Most of them showed that hearing loss (HL) in connective tissue disease patients was higher than in controls, mainly of the sensorineural type and at high frequencies. Associations with clinical features and autoantibodies profile of underlying conditions varied widely among the results. In conclusion, sensorineural hearing loss is common in individuals with CTD, and it is essential to be aware of this complication in order to establish an effective treatment.

Keywords: Connective tissue disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma sjögren's syndrome, ear abnormalities

Introduction

Connective tissue diseases are chronic autoimmune entities that have a wide range of clinical manifestations. Articular and extra-articular manifestations involving multiple organs and systems such as the lungs, eyes, heart, and peripheral vascular system are common. Among the affected extra-articular structures are the ears, causing hearing difficulties or deafness, tinnitus, and dizziness, among other problems.[1-3] These symptoms impair the patient's quality of life.

The ear may be damaged by the immune system even in cases not linked to rheumatic diseases, as an organ-specific autoimmune disease; in those with already established autoimmunity, the risk is increased. A study by Rossini et al[4] has shown that individuals with autoimmune diseases have a 4.27 times higher risk of sensorineural hearing loss (SNHL) than controls, mainly at high frequencies.

The pathogenesis of hearing loss (HL) associated with autoimmune diseases is not entirely understood. One hypothesis is that the ear's vascular supply may be injured. The inner ear's vascular system is considered vulnerable to blood circulation issues due to its end-arterial nature and the cochlea's high metabolic demands.[5] It can be damaged by immune complex deposition that favors endothelial lesions and thrombus formation.[6] Immune complexes and autoantibodies against inner ear proteins have been detected in RA patients with hearing loss.[7] Moreover, infarctions due to microcirculation thrombosis, histologically proven and associated with antiphospholipid antibodies, have been found in systemic lupus erythematosus (SLE) patients with SNHL.[8] Microangiovasculopathy is also a cardinal feature found in scleroderma (SSc).[9] Furthermore, uncontrolled chronic inflammation in rheumatic diseases may be another factor linked to vascular damage, as it is associated with accelerated atherosclerosis.[10]

The cellular autoimmune lesion is another hypothesis that may explain the hearing loss (HL) association with autoimmune diseases. T cell lymphocytes specifically responsive to human inner ear antigens and increased levels of interferon γ have been detected in individuals with HL.[11]

An additional explanation proposed is the damage to the ossicles in the middle ear that transmit sounds from the air to the cochlea. The incudostapedial and incudomalleolar joints are authentic diarthrodial joints

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Cite this article as: Skare TL, Freire de Carvalho J. Hearing loss in connective tissue diseases: A systematic review. *Eur J Rheumatol.* 2025; 12(1), 0076, doi: 10.5152/eurjrheum.2025.23076.

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Received: September 13, 2023
Accepted: September 13, 2024
Publication Date: March 10, 2025

subjected to rheumatoid damage. Damage to these structures may lead to middle ear stiffness and even ossicular discontinuity, causing conductive deafness.[9,12] Copeman described this possibility in 1963, calling it rheumatoid oto-arthritis.[13]

Finally, neurological deficits may contribute to HL. They may occur due to vasculitis or by compression of cranial nerves by fibrous tissue, as seen in SSc.[9]

Herein, a review of hearing loss in connective tissue diseases aims to summarize the present knowledge on this issue.

Methodology

A systematic search of articles published in PubMed/MEDLINE, EMBASE, and SCOPUS from 1966 to June 2023 was conducted using the following MeSH entry terms: "ear" OR "hearing" and "rheumatic" OR "rheumatoid arthritis" OR "systemic lupus erythematosus" OR "Sjögren's syndrome" OR "myositis" OR "systemic sclerosis" OR "mixed connective tissue disease." The search had no language restriction. The reference lists of the selected articles were analyzed to identify other publications.

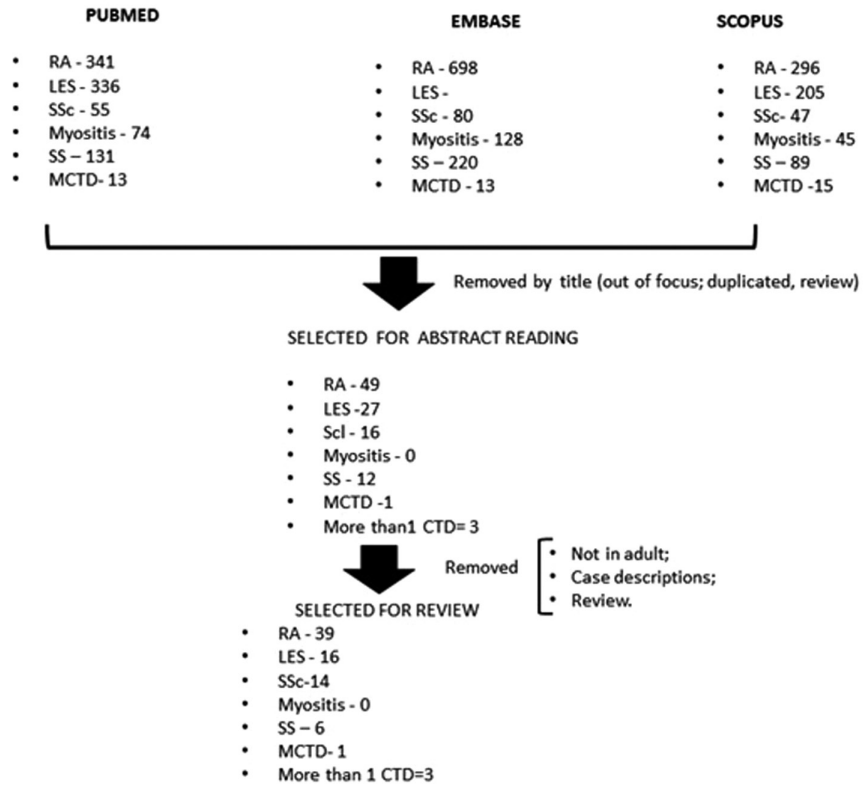
Initially, two authors (xx and yy) performed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by abstracts. The authors followed PRISMA guidelines.[14] A standardized form to extract the information from relevant articles was designed, including authors, year of publication, number of patients studied, demographic data, disease duration, instruments used to evaluate ear involvement, and results.

Results

The flow chart with articles selection is in Figure 1.

Main Points

- Hearing loss may be found in patients with systemic autoimmune disorders.
- 79 articles were selected in rheumatoid arthritis, in systemic lupus erythematosus, in scleroderma, in Sjogren's syndrome, in mixed connective tissue disease.
- Most of them showed that hearing loss (HL) in connective tissue disease patients was higher than in controls, mainly of the sensorineural type and at high frequencies.



RA=rheumatoid arthritis; SLE=systemic lupus erythematosus; SSc= scleroderma; SS= Sjögrens' syndrome; MCTD= mixed connective tissue disease; CTD= connective tissue disease.

Figure 1. Flow chart of articles selected for review.

The results were summarized according to the baseline disease.

Results in Rheumatoid Arthritis (RA)

Table 1 displays the results found in RA. Among the 39 identified articles were 7 cross-sectional studies;[13,15-20] one retrospective;[21] 1 prospective,[22] and 30 case-control.[8,12,23-50]

The prevalence of HL in these patients ranged from none in two studies[17,23] to over 90%.[39,48] Most of the studies showed a prevalence of HL in RA that is greater than in controls, and that was, most of the time, neurosensorial and predominantly in high-frequency sounds simulating presbycusis.[12,15,21,22,24,25,28,35,37,38,47] The subjective HL was less frequent than audiometric findings, ranging from 16%[24] to 29.6%[15] Conductive HL was found to a lesser degree. Lasso de la Vega et al could not find conductive defects in their 53 patients, nor could Rosenberg et al,[23] Trevino-Gonzáles et al,[17] nor Öztür et al[26] Others detected values around 25%[19,27] while Rkain et al[33] detected conductive HL in 63.6% of their sample. Still, this last author studied only 22 patients.

Analysis of the influence of RA characteristics on HL is contradictory. Association with autoantibodies such as anti-cyclic citrullinated protein (CCP) and rheumatoid factor (RF) were positive in four studies[24,38,40,49] and negative in another four.[15,19,40,48] It must be taken into account that the prevalence of these autoantibodies varied widely among the studied samples. Lasso de la Vega et al[35] found a positive association with the presence of anticardiolipin antibodies, and Garcia-Callejo et al[28] detected anti-cochlear antibodies in 12% of their RA sample with HL. Regarding the possible influence of disease activity, the results are also diverse: among the authors who studied this variable, six found a positive association,[24,27,33,37,42,46,47] while four did not.[15,17,31,50]

Two authors studied the association of HL with carotid media-intima thickness (cIMT), and both found it positive.[19,36] Consistently, Huang et al[21] and Almasi et al[50] found HL association with dyslipidemia; the first author, who studied a vast number of patients, also found an association with cardiovascular diseases such as stroke and coronary artery disease.[21]

Goodwill et al[13] examining three sets of ear ossicles could not detect any abnormality; however, when this study was done with more sophisticated resources such as electron

Table 1. Studies on Ear Function in Rheumatoid Arthritis (RA)

Author, Year	Study Design	N	Sex/Age	Disease Duration/Serology	Tests	Results
Goodwill IJ et al, 1972[13]	Cross-sectional	RA = 76	84.2% females; mean age— 52.8 yo	NA	Air and bone conduction; Audiometry	3 patients complained of deafness spontaneously; 4 upon questioning; 16 patients with nodules with sensorineural impairment; One patient with conductive deafness; Hearing loss did not associate with disease duration of activity; 3 post-mortem studies—no evidence of RA in the ossicles
Rosenberg JN et al, 1978[23]	Case control	RA = 38; Controls = 30	NA	From 1 to 33 yo RF+ = 72%	PTA. Otoadmittance meter	None (RA and controls) had a conductive or sensorineural hearing loss by PTA; Abnormal otoadmittance response42% of RA and 7% controls
Poorey VK et al, 2001[24]	Case control	RA = 25 Controls = 16	Sex = NA; Age = 20-60 yo	From 6 months to 20 yo RF+ = 68%	PTA; Tympanometry; Tone decay test (Carhart technique)	64% of RA patients had abnormal audiograms; 16% were symptomatic; 12% had bilateral conductive HL (↑with age); 52% had SNHL; 32% had abnormal tympanogram (↑ RF+ and with disease activity)
Ozcan M et al, 2002[25]	Case control	RA = 37 Controls = 35	81.% females Age—NA	Mean = 8.2 yo RF+ = 75.6%	PTA; Tympanometry	35.1% of RA patients with SNHL; 24.3% of RA patients with conductive loss; 10.8% RA patients with mixed HL; Tympanograms: abnormal in 37.8% of RA patients versus 17.1% of controls; Hearing loss is associated with cumulative damage
Öztürk A et al, 2004[26]	Case control	RA = 74 Controls = 45	94.5% females; Mean = 47.9 yo	Mean = 10.0 yo Serology—NA	Standard and high-frequency audiometric tests; Tympanometry; Acoustic reflex test; Speech test	↑threshold of pure tones in RA; RA with disease duration 1-5 yo—hearing loss exceeds the levels of 20 dB; RA with disease duration of 6-10 yo—hearing loss began at 4.000 Hz; RA with disease duration > 16 yo—high threshold in all frequencies; No conducting type hearing loss

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Table 1. Studies on Ear Function in Rheumatoid Arthritis (RA) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration/Serology	Tests	Results
Salvinelli F et al, 2004[27]	Case control	RAn = 40 Controls-n = 38	75% females Mean = 61 yo	Disease duration—NA Serology—NA	PTA; impedance audiometry	26.3% of RA patients with SNHL; 47.6% of RA patients with mixed hearing loss; 26.1% RA patients with conductive hypoacusis; Tympanometry findings were equal in patients and controls; Hearing impairment is associated with active disease but not age or disease duration
Garcia-Callejo FJG et al, 2007[28]	Case control	RA = 194 Controls = 107	Ratio male/female = 0.38 Mean = 40.3 yo	Disease duration = NA Serology = NA	PTA; anticoclear antibodies (western blot)	42.7% had hearing loss (38.6% neurosensorial) vs 15.9% controls; 12% of RA patients with hypoacusis (vs 0% of controls) had anti-cochlear antibodies; RA group- associated hypoacusis with low HAQ, pain VAS but not disease activity
Murdin L et al, 2008[15]	Cross-sectional	RA = 54	85% females Mean = 41.5 yo	Mean = 8.7 yo RF+ = 76% ANA+ = 31%	PTA; TEOAEs	Symptomatic HL—29.6%; HL predominant sensorineural at low and middle frequency; Conductive hearing loss—1.9% There is no association with disease activity, presence of RF, nodules, bone erosions, or drug use
Dikisci NO et al, 2009[29]	Case control	RA = 20 Controls = 20	65% females Mean = 53.4 yo	NA	PTA. TEOAEs	RA HL: bilateral in 40%; unilateral in 5%; No differences in air conduction, bone-conduction threshold by PTA; No differences in speech discrimination and hearing thresholds in HFA; Elderly patients with longer disease duration, RA nodules, and higher methotrexate cumulative doses, hearing thresholds ↑ and TEOAE ↓
Milisavljevic D et al, 2010[12]	Case control Ear ossicles	RA = 9 pairs Controls = 5 pairs	NA	NA	Scanning electron microscope	RA auditory ossicles had erosions (mainly on the long process of incus); Presence of cartilage destruction and proliferative granular tissue on synovial tissue; ↑in surface lysis of incus and degenerative articular changes correlated with age and duration of RA. Changes in mallei were insignificant

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Table 1. Studies on Ear Function in Rheumatoid Arthritis (RA) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration/Serology	Tests	Results
Baradaranfar MH et al, 2010[30]	Case control	RA = 50 Controls = 50	84% females Mean = 47.5 yo	NA	PTA; Speech discrimination; Tympanometry; Acoustic reflex; Acoustic reflex decay; Tone decay test	Hearing threshold (mainly at high frequencies) ↑than controls; Results of tone decay, reflex decay, and speech discrimination suggested cochlear pathology; Acoustic reflex was absent in the RA group; No influence of disease duration or NSAID use on the hearing threshold
Alonso A et al, 2011[31]	Case controls	RA = 45 Controls = 45	91% females Mean = 44.1 yo	Duration—78% > 2 years Serology—NA	Tonal audiometry (air and bone conduction); Logoaudiometry; Impedanciometry	Air conduction test RA + → 42.2% normal versus 73.3% controls; RA deterioration of high and low-frequency auditive threshold (more than controls); Only 4.4% had an abnormal threshold for phonemic discrimination; 53.2% RA patients had rigidity on the tympanum-ossicular complex versus 39% controls; No differences according to RA activity and disease duration
Milisavljevic D et al, 2014[16]	Cross-sectional	RA treated oral prednisone = 38; RA-treated intratympanic MPN = 11	NA	Duration = NA Serology = NA	PTA	Mild to moderate hearing loss improved: • 60.5% → oral prednisone • 68.6% with intratympanic methylprednisoloneAddition of methotrexate to non-responders → improved 11%
Özkiris M et al, 2014[32]	Case control	RA = 81 Controls = 81	85.1% females Mean = 40.8 yo	Duration—NA Serology—NA	Low and high-frequency audiometry Tympanometry; VNG	Hearing thresholds were higher in RA than in controls at high frequencies; Tympanometric values were similar in the two groups; VNG revealed central abnormalities in 24.6% of RA patients; VNG abnormalities did not associate with age, sex, disease duration, vertigo complaint, treatment drugs, and hearing levels

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Table 1. Studies on Ear Function in Rheumatoid Arthritis (RA) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration/Serology	Tests	Results
Rkain I et al, 2014[33]	Case control	RA = 22; Controls = 17	90.9% females Mean = 44.2 yo	Duration = 41 months Serology—NA	PTA. Tympanometry	CHL—in 63.6% RA versus 11.7% controls; Stapedial reflex absent in 45.4% RA versus 0 controls; SNHL in 18.1% RA versus 0 controls; HL is associated with active disease
Pascual-Ramos V et al, 2014[22]	Prospective	RA = 104	89.4% females Mean = 43.4 yo	Median = 5 yo RF+ = 86.5% Anti CCP+ = 93.3%	Otoscopic evaluation; PTA; Tests were done at 0-6-12 months	At admission, - 24/104 had hearing impairment (sensorineural in 91.7%); 12.5% developed an incidental hearing impairment in the next 1 year; Incidental HL was 90% sensorineural; Incidental HL associated with disease activity
Treviño-Gonzáles et al, 2015[17]	Cross-sectional	RA = 117	100% females; Mean = 47.4 yo.	Duration—NA; RF+ = 78.6%; Anti-CCP+ = 47%	Audiometry high frequency; Tympanometry	Symptomatic hypoacusis in 20.5%; A high prevalence (94%) of sensorineural hypoacusis for high-frequency sounds; None with conduction hypoacusis; • 50 years old—problems with language discrimination-;No association with disease activity; Hearing thresholds using PTA and EHFA were higher in patients than in controls
Heydari N et al, 2015[34]	Case controls	RA = 25 Controls = 20	76% females Mean = 33.3 yo	Duration = NA Serology NA	PTA; Acoustic immittance; cVEMPs; bithermal caloric test (eye movements recorded by videonystagmography)	14 (56%) of RA patients had complained about the vestibular disorder: 14 = vertigo and 8 = dizziness; SNHL in 40% (5 of them with cVEMPs with prolonged latencies) Unilateral weakness in RA patients was higher than control Values of directional preponderance were similar in both groups
Jeong H et al,2016[18]	Cross-sectional; data from KNHANES (2010-2012)	RA = 297 Controls = 14 861	75.4% females Mean = 56.7 yo	Duration = NA Serology = NA	PTA	RA is associated independently with low/mid-frequency hearing impairment; RA did not associate with high-frequency hearing impairment in multivariate analysis

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Table 1. Studies on Ear Function in Rheumatoid Arthritis (RA) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration/Serology	Tests	Results
Lasso de la Vega et al, 2016[35]	Case control	RA = 53 Controls = 71	73.5% females; Mean = 50.5 yo	Duration = NA Serology = NA	PTA + HFA	43% had hearing loss (sensorineural) (-↑ males); No conductive or mixed hearing loss; 69.8% had high-frequency sensory neural loss HL is associated with aCL positivity
Macias-Reyes H et al, 2016[19]	Cross-sectional	RA = 41	95.1% females; Mean = 46 yo	Mean = 7.05 yo RF+ = 48.5% CCP+ = 39%	PTA; Impedance; cIMT	53.6% had bilateral SNHL (58.5% on the left and 63.4% on the right side); 9.7% had conductive impairment; cIMT associated with SNHL No association of SNHL with FR and anti-CCP
Kim GT et al, 2016[36]	Case control	RA = 64 Controls = 70	Sex—NA Age—NA	Duration—NA Serology—NA	PTA; cIMT	Hearing loss in RA → 65.5%; in controls—37.1% Age and cIMT correlated with hearing loss
Uildirim A et al, 2016[37]	Case control	RA = 88 Controls = 50	72.7 yo Mean 46.9 yo	Mean = 58 months Serology—NA	PTA. Tympanometry	Thresholds were higher in the RA group, mainly at high frequency; Higher thresholds in patients with active disease
Lobo FS et al, 2016[38]	Case control	RA = 43 Controls = 23	86.6% females age - ↓ 60 yo	Mean = 10.3 yo RF+ = 55.8% anti CCP = 55.8% anti MCV = 62.7%	PTA; Logoaudiometry; Tympanometry; Stapedial reflex; DPOAEs; Anti-CCP and anti-MCV	46.5% of RA patients had hearing impairment (more sensorineural) vs. 30.4% in controls Speech discrimination was affected only in RA with SNHL; RA patients with HL had longer disease duration, were older, and female, HL associated with anti-CCP and MCV antibodies
Huang CM et al, 2017[21]	Retrospective	RA = 18-267 newly diagnosed patients. Controls = 73 068	78.4% females; Mean = 53.6 yo	Duration = NA Serology = NA	Database analysis using claims data	HL was higher in RA patients (aHR = 1.91) than in controls; Males and older people had the highest risk; NSAID, prednisolone, DMARDs, and anti-TNF use ↓ HL Hypertension, dyslipidemia, stroke, ischemic heart disease, and CKD are associated with HL. RA patients on adalimumab had the lowest HL

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Table 1. Studies on Ear Function in Rheumatoid Arthritis (RA) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration/Serology	Tests	Results
Kiakojuri K et al, 2017[39]	Case control	RA = 60 Controls- = 30	91.6% females, Mean = 47.2 yo	Mean = 12.5 yo Serology = NA	PTA; Tympanometry; Speech audiometry	All RA patients had SNHL; 5% RA with abnormal tympanometry; Speech recognition threshold: RA = control; Speech discrimination: RA worse than controls; HL did not associate with disease duration
Ahmadzadeh A et al, 2017[40]	Case control	RA = 42 Controls = 40	91.6% females; Mean = 53 yo	Mean = 8.6 yo Serology—NA	PTA. Tympanometry. Distortion product; Otoacoustic emissions testing	No differences in the prevalence of sensorineural or conductive HL; Higher bone conduction threshold at some frequencies in the RA group; Association of SNHL with azathioprine, cyclosporine, and etanercept; No association of HL with inflammatory markers or anti-CCP
El-Dessouky TM et al, 2017[41]	Case control	RA = 40 Controls = 20	87.5%—females; Mean age—45.5 yo	duration—NA in the whole sample Anti-CCP+ = 97.5%	PTA; VNG	Mean threshold air conduction at high frequency in RA < controls; Speech reception threshold and discrimination were equal; VGN - central abnormalities in 30%, peripheral abnormalities in 22.5% of RA individuals; VGN abnormalities did not associate with age, sex, disease duration, and vertigo complaints
Zrour S et al, 2018[42]	Case control	RA = 90 controls = 46	NA	NA	ENT examination; Tonal audiometry	ENT involvement in 78% (↑ in RA than controls); Deafness in 42% (27% sensorineural, 13% conductive, and 2% mixed); Association with age at disease onset and disease activity
Nasution MES et al, 2018[43]	Case control	RA = 19 Controls = 19 controls-with other joint diseases	73.7% females; Mean = 32.8 yo	≤5 yo → 78.9% >6 yo → 21.8% serology - NA	PTA; Tympanometry	52.6% of RA patients with SNHL; 15.8% with conduction HL; 10.5% with mixed HL; Degree of hearing loss correlated with disease duration and ESR

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Table 1. Studies on Ear Function in Rheumatoid Arthritis (RA) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration/Serology	Tests	Results
Nasutionan ME et al, 2018[44]	Case control	RA = 21 Controls = 21	76.2% females; Age from >20 to ≤41 yo	≤5 yo → 66.7% 6-10 yo → 33.3% serology: NA	PTA; Tympanometry; Dosage of plasma MMP-3 (ELISA)	76.2% had SNHL; 14.3% had conductive HL; 9.5% had mixed HL; 66.7% HL was mild RA patients had increased As tympanogram. Mean hearing, air conduction, and bone conduction thresholds were ↑ in RA than controls. Mean MMP3 plasma levels were higher in RA patients with HL than in those without it
Gökçe et al, 2019[45]	Case control	RA = 30 Controls = 30	73.3% females mean = 45.9 yo	NA	Pure voice audiometry; Otoacustic emission tests; Tympanometry	Hearing thresholds for air conduction in RA were higher at all frequencies; Bone conduction hearing in the RA group was more affected at 4 kHz; Air-bone conduction differences in RA were greater at 0.5, 1, and 4 kHz Tympanometry and acoustic reflex were equal in both groups
Lee YS et al, 2019[8]	Case control data 2002-2013 from Korean National Insurance Service	RA - n = 7619 Controls - n = 30 476	77.1% females Age = from 20 to more than 85 yo	NA	Recorded audiometric studies	Sudden SNHL in 0.8% versus 0.6% in controls ($P = .02$); SSNHL in the RA group is more common in ages above 50 yo and men
El-Reheem et al, 2020[46]	Case control	RA = 55 Controls = 55	100% females Mean = 42.1 yo	Mean = 88.1 months serology = NA	PTA; Speech audiometry; Immittancemetry	SNHL loss in 29.9%; Conductive HL in 1.8%; Mixed hearing loss in 5.4%; Total HL in 36.5% RA versus 5.4% controls; RA patients with low static compliance; High average acoustic reflex; Disease activity correlated with average acoustic reflex in LE; Disease activity correlated negatively with an air-bone gap in RE and LE
Ismaiel AH et al, 2021[47]	Case control	RA = 25 Controls = 25	92% females Age = 50-60 yo	Mean = 11.2 yo Serology = NA	Brainstem auditory evoked potential	Delayed latencies and alteration of brainstem waves; Parameters of brainstem auditory evoked potentials correlated with disease activity, VAS pain, and functional class

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Table 1. Studies on Ear Function in Rheumatoid Arthritis (RA) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration/Serology	Tests	Results
Gamal NM et al, 2021[48]	Case control	RA = 95 Controls = 100	89.5% - females; Mean = 46.5 yo	Mean = 9.6 yo RF+ = 60% anti CCP+ = 57.8%	PTA + HFA; EHFA	HL by PTA = 68.4% RE; 64.2% in LE; HL by EHFA = 100% RE; 97.8% LE; HL correlated with age, age at disease onset, disease duration, DAS28, and RARBIS; No association with RF or anti-CCP
Elnagdy OH et al, 2022[49]	Cross-sectional	RA = 50	Sex—NA age from 16 to 50 yo	Median = 8 yo RF+ = 46% anti CCP+ = 76%	PTA; EHFA; Tympanometry; Acoustic reflex test.	80% normal hearing by PTA and 22% by EHFA; 46% had absent otoacoustic emission (early cochlear hearing loss); Abnormalities associated with RF+ and CCP+; EHFA, TEOAE, acoustic reflex test associated with CCP+
Sadek HA et al, 2022[20]	Cross-sectional	RA = 16	87.5% females; Mean = 35.7 yo	Mean = 7.7 yo Serology—NA	PTA; VHIT	50% of RA patients with HL; HL did not associate with sex or age but with disease duration and ESR; VHIT is expected in all patients
Almasi S et al, 2023[50]	Case controls	RA = 100 Controls = 30	78% females; Mean = 53.9 yo	Mean = 12.7 yo RF+ = 54%; CCP+ = 80%	PTA; Speech audiometry; Tympanometry; Acoustic reflex; Tone decay test; Clinical profile; DAS-28	Abnormal hearing in 71% of patients (mainly neurosensorial) ; 18% had HL at low frequencies; 19 at mid, and 57% at high frequencies; Higher PTA thresholds for RA than controls; Disease activity did not associate with HL; Patients with HL were older and had more dyslipidemia

aCL, anticardiolipin antibodies; aHR, adjusted hazard ratio; ANA, antinuclear antibody; anti MCV, anti mutated citrullinated vimentin; CCP, cyclic citrullinated peptide; CHL, conductive hearing loss; CKD, chronic kidney disease; CRP, C reactive protein; DAS-28-disease activity score using 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HFA, high frequency audiometry; HL, hearing loss; KNHANES, Korean National Health and Nutrition Examination Survey; LE, left ear; MPN, methyl prednisolone; n, number; NA, not available; NSAID, nonsteroidal anti-inflammatory drugs; PTA, pure tone audiometry; RA, rheumatoid arthritis; RARBIS, Medical Records Based Index of Severity; RE, right ear; RF, rheumatoid factor; SNHL, sensory neural hearing loss; SSNHL, sudden sensorineural hearing loss; TEOAEs, transient evoked oto-acoustic emission; VAS, visual analogic scale; VEMPs, cervical vestibular-evoked myogenic potentials; VGN, video nystagmography; VHIT, video head impulse test.

Table 2. Results on Systemic Lupus Erythematosus (SLE)

Author, Year	Study Design	N	Sex/Age	Disease Duration	Tests	Results
Sperling NM et al, 1998[51]	Cross-sectional	Survey = 84 Audiometry = 10	100% females Mean = 41 yo	NA	Questionnaires; Audiometry	31% with aural symptoms (tinnitus; fluctuating hearing, vertigo balance impairment); Creatinine and C3 levels associated with aural symptoms; Sudden HL in 4%; 7/10 patients with abnormal pure tone thresholds
Sone M et al, 1999[52]	Cross-sectional	Lupus = 7 14 temporal bones	85.7% females range = 14 to 76 yo	From 3 months to 26 yo	Hematoxylin and eosin stain; Bone treatment with rabbit anti-human polyvalent immunoglobulins	Loss of spiral ganglion cells; Hair cell loss; Atrophy of stria vascularis; 1 patient with fibrous and bone tissue formation through cochlea and observation of vasculitis; 1 patient with cochlear hydrops No deposition of immunoglobulins in the inner ear in 13 patients
Kastanioudakis M et al, 2002[53]	Case control	Lupus = 38 Controls = 50	100% females Mean = 47.8 yo	Mean = 11.7 yo	PTA; Impedance; Speech audiometry; Clinical, auto-antibody, and treatment profiles	22.5% had HL (n = 8 with sensorineural; n = 1 with conductive) No influence of age or disease duration, No influence of clinical and auto-antibodies profiles or treatment
Jiménez-Alonson J et al, 2002[54]	Case control	Lupus = 91 Controls = 87	95.6% females Mean = 40.6 yo	Mean = 96.2 months	Audiometry SLEDAI; Immunologic profile	15.4% had SNHL (vs. 2.3% controls); No influence of treatment, disease duration, or disease activity; No effect of autoantibodies profile; 1 patient had sudden SNHL
Roverano S et al, 2006[55]	Case control	Lupus = 30 Controls = 25	100% females mean = 35 yo	Mean = 48 months	Audiometric test; Tympanometry	66% sensorineural loss (vs. 16% controls); 3.3% conductive (vs. 12% in controls) - all asymptomatic; No association of HL with AAF or antimalarial use; No association with disease activity
Gomides APM et al, 2007[56]	Case control	Lupus = 45 Controls = 45	100% females Mean = 30.9 yo	Mean = 57 months	Clinical profile; Autoantibodies profile; SLEDAI; Tone audiometry; Impedance	Symptoms (vertigo, hypoacusis, ear fullness, tinnitus): 55% of one or more symptoms versus 11.1% of controls; 15.6% had HL (vs. 2.2% controls); 6.7% had impedance alterations (vs. 4.4% controls); No association with clinical parameters, SLEDAI, and disease duration
Karabulut H et al, 2009[57]	Case control	Lupus- = 26 Controls = 30	88.4% females Mean = 36.3 yo	NA	PTA; Distortion product and transient evoked otoacoustic emissions; Clinical profile; SLEDAI	Higher thresholds in SLE than controls (more at low frequency); Distortion product OAE signal response was different at 750 HZ; No association of distortion product OAE or transient evoked OAE with clinical parameters

(Continued)

Table 2. Results on Systemic Lupus Erythematosus (SLE) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration	Tests	Results
Maciaszczyk K et al, 2011[58]	Case control	Lupus = 35 Controls = 30	94.2% females Mean = 47.8 yo	until 5 yo → n = 7 6-10 yo → n = 8 > 10 yo → n = 10	PTA; Acoustic immittance; ABR audiometry	71.4% had vertigo, 40% tinnitus; 17.1% hearing loss, 14.3% balance disturbance; SNHL in 28.6% (mainly bilateral and affecting high frequencies); Longer ABR latency averages; HL did not associate with disease severity.; HL did not associate with autoantibodies; HL is associated with disease duration
Lin et al, 2013[59]	Case control Data-Taiwan National Health Insurance Research Database.	Lupus = 7168 Controls = 35 840	88.4% females Mean = 35.7 yo	NA	Analysis of claims	Sudden sensory HL was 2.22—fold higher in the SLE group; 6.5 versus 2.9 /10 000 persons-year; Age was an independent risk factor; In the SLE group - females had a 2.1—fold higher risk. No association with comorbidities (stroke, CAD, chronic renal disease, and DM)
Batuecas- Caletrio A et al, 2013[60]	Cross-sectional	Lupus = 89 interviewed Lúpus = 21—examined	87% females mean age females = 49 yo mean age males = 53 yo	NA	PTA; Tympanometry	56% had recurrent headaches (29% of them with migraine); 9% had peripheral vertigo; 12% subjective HL; 19% hearing loss by audiograms; SHNL is associated with vertigo but not headache; 6/21 had low complement (5/6 with SNHL); No vestibular deficits; 1 woman with canal paresis
Abbasi M et al, 2013[61]	Case control	Lupus = 45 Controls = 45	Female/male ratio = 13.9 Mean = 34.9 yo	Mean = 4.4 yo	Audioscopy. PTA. SDS. Tympanometry. Clinical profile and SLEDAI	Complaints: 11% hearing loss; 8.9% otorrhea; 6.7% tinnitus; 26.4% with sensorineural hearing loss (vs. 8.9% in controls); No relation between HL and disease activity; No relation with treatment (antimalarials, glucocorticoid, and methotrexate); 8.9% with abnormal SDS (vs. 0% in controls); No association of hearing threshold with disease duration
Ferrari AL et al, 2014[62]	Cross-sectional	Lupus = 89	100% females Mean = 38.9 yo	Mean = 10.2 yo	Audiometry; Clinical profile; Cardiovascular risk factors	16% had asymptomatic SNHL; LDL associated with SNHL

(Continued)

Table 2. Results on Systemic Lupus Erythematosus (SLE) (RA) (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration	Tests	Results
Abir N et al, 2014[63]	Case control	Lupus = 20 Controls = 20	Females—100% Mean = 24.6 yo	Mean = 47.8 months	PTA; Acoustic immittance; speech audiometry; clinical and auto-antibodies profiles	Tinnitus in 20%; vertigo in 5% PTA is abnormal in 65% versus 0% of controls Acoustic immittance and speech audiometry- normal Lupus nephritis associated with lower hearing levels Azathioprine and antimalarials are associated with lower hearing levels No influence of aCl and LA auto-antibodies
Karyia S et al, 2015[64]	Case control	Lupus = 15 samples Controls = 17 samples	87.5% females Mean = 40.3 yo	Mean = 11.8 yo	Histopathology of the temporal bone (Peripheral vestibular system)	Type I hair cells in the saccular macula, utricular macula, and semicircular canals were lower in SLE; The mean density of vestibular hair cells did not correlate with the patient's age at death or the duration of SLE
Kariya S et al, 2016[65]	Case control	lupus = 15 samples Controls = 17 samples	87.5% females Mean = 40.3 yo	Mean = 11.8 yo	Histopathology of the temporal bone (Cochlea)	Smaller stria vascularis area in SLE; The lower number of inner hair cells (but not statistically); Loss of outer hair cells was higher than in controls; The tendency of correlation between loss of cochlear cells and SLE duration
Lasso de la Vega et al, 2016[66]	Case control	Lúpus = 55 Controls = 71	85.4% females Mean = 41.5 yo	NA	PTA; EHFA; autoantibodies profile	30.9% of SLE had HL by PTA (sensorineural); No cases of conductive HL; HL associated with age at diagnosis; 70% SLE with HL by HFA; Disease activity, cryoglobulins associated with high-frequency HL No association with sex or age
Polanski JF et al, 2020[67]	Case control	Lúpus = 43 Controls = 41	97.6% females Mean = 40.8 yo	Mean = 10.0 yo	PTA; WRS; Tympanometry	Tympanometry was normal in all participants; 23.2% SLE group had a sensorineural loss; No correlation with disease duration; No association with clinical profile or autoantibodies; Antimalarials did not associate with HL
Tharwat S et al, 2021[68,69]	Case control	lupus = 48 Controls = 12	Females = 83.3% Mean = 39.5 yo	Median = 7 yo	PTA; Audiological history	Hearing impairment in 24% of SLE versus 4,2% controls; 35.4% had vertigo; 32.4% had tinnitus; More hearing impairment in those using antimalarials
Chen H et al, 2022[70]	Case control	lupus = 91 (hospitalized) Controls = 30	90.1% females Mean = 37.3 yo	Mean = 6.2 yo	PTA; EHFA	27.4% with hearing loss (vs. 3.3% controls), mainly sensorineural; Association of hearing loss with SDI and sSS

ABR, auditory brainstem response; aCl, anticardiolipin; CAD, coronary artery disease; DM, diabetes mellitus; DPOAE, distortion product otoacoustic emission; EHFA, high frequency audiometry; HL, hearing loss; LA, lupus anticoagulant (antibody); n, number; NA, not available; PTA, pure tone audiometry; SDI, Systemic Lupus International Collaborating Clinics Damage Index; SHNL, sensorineural hearing loss; SLEDAI, SLE diseaase activity index; sSS, secondary Sjogren's syndrome; WRS, word recognition score; (speech discrimination test).

Table 3. Results on Systemic Sclerosis (SSc)

	Study Design	N	Sex/Age	Disease Duration	Tests	Results
Tosti et al, 1984[71]	Cross-sectional	SSc = 22	100% females Mean = 63 yo	NA	Audiological evaluation.	59% (13/22) had audiological impairment: mild in 10/22 patients and important in 3/22; SNHL did not associate with age or drug consumption.
Kastanioudakis I et al, 2001[72]	Case control	SSc = 34 Controls = 45	97% females mean age = 50 yo	Mean = 8.6 yo	PTA; Impedance; Speech audiometry.	20% had SNHL; No association of hearing loss with age, clinical and autoantibody profiles, and treatment; Speech audiometry- compatible with cochlear disease; No differences in mean static compliance; 10% with patulous eustachian tubes.
Amor-Dorado JC et al, 2008[73]	Case control	lSSc = 35 (CENPB+) controls = 59	94% females mean age = 64.5 yo	Mean = 19.3 yo	PTA; SRT and SDT; Impedance; Oculographic test; Vestibular function tests.	30% with subjective vestibular symptoms (vs. 0% in controls); 54% with subjective hearing loss (vs. 0% in controls); 77% with abnormal audiograms - (vs. 26% controls); 88.8% abnormal audiograms with SNHL; 20% abnormal tympanogram (vs. 0% in controls); 37% with absent stapedius reflex (vs. 0% in controls); None (patients and controls) with alterations in reflex decay; None (patients and controls) with abnormal SDT; No differences (patients vs controls) in oculographic; Increased the frequency of OCR, head shaking nystagmus, positional nystagmus, and abnormal caloric tests in patients; No association of abnormal vestibular tests with clinical and epidemiological profiles; Hypoacusis associated with age and presence of digital ulcers.
Bassyouni H et al, 2010[74]	Case control	SSc = 30 Controls = 29	100% females Median = 49 yo	Median = 7 yo	CDP; Capillaroscopy; Clinical profile.	33% had vestibular dysfunction ($P = .01$with controls); Vestibular dysfunction associated with capillaroscopy; No association with age, disease duration, clinical profile, and autoantibodies; No association with the disease subset.
Maciaszczyk K et al, 2011[75]	Case control	SSc = 20 Controls = 26	95% females Most of the patients aged 40-50 yo	Mean = 6.6 yo	PTA; Speech audiometry Impedance; ABR.	Symptoms: 60% had vertigo; 50% tinnitus; 40% hyperacusis; 40% HL; 30% had ear fullness; 40% had SNHL; Air conduction hearing thresholds were poorer in SSc ABR was similar between groups; No differences in speech discrimination; No association of HL with Raynaud's phenomenon, neither with disease duration nor the SSc subgroup.

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Table 3. Results on Systemic Sclerosis (SSc) (*Continued*)

	Study Design	N	Sex/Age	Disease Duration	Tests	Results
Monteiro TA et al, 2011[76]	Case control	dSSc = 26 Controls = 52	83% females mean age = 47.0 yo	Mean = 9.8 yo	PTA; Speech audiometry; Impedance.	25% subjective HL; 21% aural fullness; 21% tinnitus; 21% dizziness; 46% had HL by audiogram (vs. 19% controls); all SNHL 54% with cochlear involvement; No association of HL with disease duration or organ involvement; Age was associated with HL.
Lanciano E et al, 2013[77]	Cross-sectional	SSc-n = 19	94.6% females; age = 15 to 77 yo	mean = 10 yo	Audiological and Vestibular exam.	53% had HL (47% was SNHL).
El-Wakd MM et al, 2015[78]	Case control	SSc = 30 Controls = 30	86.7% females mean age = 40.1 yo	mean = 5.9 yo	PTA; VEMP; Speech audiometry; Acoustic immittance tests; mRss; Clinical profile.	36.6% with hearing loss by PTA (vs. 0 in controls); 16.6% with subjective hearing loss; 60% vertigo; 20% tinnitus; 80% abnormal VEMP (suggesting retro labyrinthine lesion); HL associated with age, disease duration, presence of digital pitting, and ulcers; VEMP did not associate with clinical findings.
Gheita TA et al, 2016[79]	Case control	SSc = 35 Controls = 35	100% females Mean = 40.3 yo	Median = 7.3 yo	PTA; Speech audiometry; Impedance; ABR; mRss and clinical profile; Medsger severity index.	77.1% mild bilateral SNHL (mostly high frequencies); Hearing thresholds, pure tone average, and speech threshold higher than controls; Patients with HL- more acro-osteolysis, telangiectasia, arthralgia, and peripheral neuritis.
Shenavandeh S et al, 2018[80]	Case control	SSc = 54 Controls = 60	94.4% femalesmean = 43.9 yo	Mean = 8.6 yo	PTA; Speech audiometry; Speech reception threshold, Clinical profile; Capillaroscopy.	18.5% had subjective HL (vs. 10% controls); 66.7% had objective HL (vs. 28.3% controls); SNHL, abnormal PTA, and abnormal speech reception threshold are more frequent in SSc. HL- showed no association with capillaroscopy, disease duration, skin score, interstitial lung disease, digital ulcers, and gastrointestinal involvement.

(Continued)

Table 3. Results on Systemic Sclerosis (SSc) (*Continued*)

	Study Design	N	Sex/Age	Disease Duration	Tests	Results
Silva M et al, 2018[81]	Prospective	SSc = 50 SSc = 12 at the second evaluation	82% females mean age = 49.2 yo		Clinical survey; PTA; Impedance.	40% subjective hearing loss; 42% with difficulties in speech discrimination at baseline; 70% with vertigo at baseline; 64% with tinnitus at baseline; 46% with hearing loss at audiometry (mostly sensorineural at high frequency); Worsening of hearing threshold (up to 10 dB) in 66.6% in 3 years; No changes in the impedance findings.
Turan K et al, 2021[82]	Case control	SSc-n = 47 (55.2% lSSc; 44.7% dSSc) controls-= 44	85.1% females mean age = 49.8 yo	7 yo	Clinical profile; Capillaroscopy; Medsger severity index; Valentini activity index; PTA; Speech audiometry; Tympanometry; Otoacustic emission tests.	23.4% had subjective HL; 27.7% had vertigo; 36.2% had tinnitus; 19.1% had ear fullness; 23.4% had SNHL (38.1% dSSc and 11.5% lSSc); SNHL associated with disease duration, age, DLCO; Amputation and immunosuppression use were more frequent in those with HL; Medsger and Valentini's index correlated with PTA.
Mazeda C et al, 2022[83]	Case control	SSc = 24 Controls = 20	73.6% females mean = 58.4 yo	Mean = 50.3 months	Complete ENT exam; PTA; Speech audiometry; Impedance; SSc clinical profile; EQ - 5D; Capillaroscopy.	38% had tinnitus and vertigo; 13% had a subjective hearing loss; 45.8% abnormal tympanometry; SNHL in SSc vs. controls → $P = .03$; Abnormal speech reception threshold in SSc versus controls → $P = .04$; No association with capillaroscopy or organ involvement; HL is associated with a history of digital ulcers.
Amor Dorado JC et al, 2023[84]	Case control	SSc + RP = 37 pRP = 20 Controls - 57	100% females SSc-mean = 34.5 yo pRP- mean = 26.1	SSc-mean = 116.6 months; pRP-mean = 73 months	PTA; Speech reception threshold; SDT; Immittance study; Vestibular functional tests; Balance studies; MRI if persistent nystagmus.	Comparison- pRP versus controls—no ≠ in auditory and vestibular symptoms or hearing thresholds. 0% SNHL in pRP; 10.8% of SSc with subjective HL and SNHL by audiogram; No SSc conductive HLwith SSc with 11.8% vertigo; 14.7% dizziness (both higher than controls); SSc significantly differed in vHIT gain, caloric test, CTSIB, and CDP.

CDP, Computerized Dynamic Posturography; CENP-B, antibody against major centromere protein B; CPD, computerized dynamic platform posturography; CTSIB, clinical sensory integration and balance testing; DLCO, Diffusing capacity for carbon monoxide; dSSc, difuse scleroderma; EQ-5D, European Quality of Life- 5 Dimensions; HL, hearing loss; lSSc, limited scleroderma; mRss, modified Rodnan skin score; MRI, magnetic resonance; OCR, oculocephalic response (OCR); pRP, primary Raynaud Phenomenon; PTA, pure tABR, auditory brainstem response; one audiometry; RP, Raynaud Phenomenon; SDT, speech discrimination test; SDT, free field audiometric speech discrimination test; SRT, speech reception threshold; SNHL, sensorineural hearing loss; SSc, scleroderma; VEMP, vestibular evoked myogenic potentials; vHIT, Audiometric and vestibular testing.

Table 4. Results in Sjögren's Syndrome

Author, Year	Study Design	N	Sex/Age	Disease Duration	Tests	Results
Tumiati B et al, 1997[85]	Case control	pSS = 30 Controls = 40	100% females mean age = 52 yo	Range = 2 to 10 yo	Otologic examination; PTA Fowler balance test; Short increment sensitivity index Rosemberg threshold tone decay test Auto-antibodies profile	46% had SNHL → clinically significant in 5 patients versus 2.5% controls) Only one patient with conductive HL. 2 patients with severe HL and retro cochlear disease had normal BSER and cerebral RMN Middle ear pressure is normal in all patients; No association of HL with the Raynaud phenomenon or with vasculitis; No association of HL with ANA and complement levels (C3 and C4) 64% of patients with HL had antiphospholipid antibodies vs. 18% of controls) Anti-Ro was present in all patients with SNHL (and in 90% of the whole sample)
Ziavra N et al, 2000[86]	Case control	SS = 40 Controls = 40	100% females mean = 56.8 yo	Mean = 8,3 yo	PTA; Impedance; Speech audiometry; Autoantibodies profile	22.5% SNHL (vs. 0% controls); all cases of cochlear damage; SNHL correlated with disease duration; No correlation with age; No association with systemic manifestations or autoantibodies.
Boki KA et al, 2001[87]	Case control	SS = 48 Controls = 48	Sex—NA Mean = 53.2 yo	Mean = 7.0 yo	Clinical and auto-antibodies profiles; Impedance audiometry; PTA; BSER; ENG (in 10 patients with dizziness).	The statistical difference only at 4000 and 8000 Hz; No clinical or laboratory variable predicted HL; Raynaud phenomenon and lung involvement showed a trend to associate with HL; 7 SS patients and 5 controls with abnormal BSER; 4/10 abnormal ENG vs 4/9 controls;
Montoya-Arnada I et al, 2010[88]	Cross-sectional	SS = 29 86% → sSS with RA 3.4% → sSS with SSc	Sex =- NA Mean = 41 yo	Mean = 5 yo	Audiometry Logoaudiometry Tympanogram	66.6% with HL; 13.7% had tinnitus; 3.4% hyperacusia; Logoaudiometry → 53.4% normal speech discrimination.
Calzada AP et al, 2012[89]	Cross-sectional	SS = 4 n = 8 temporal bones	Female - 55 yo sSS → JIA female—65 yo sSS → SLE female - 63 yo sSS → RA female - 66 yo pSS	NA	Hematoxylin eosin stain PAS stain Immunohistochemistry (igG1)	3 patients with severe loss of stria vascularis cells; 1 patient with degeneration of the organ of Corti; 2 patients with shrinkage of spiral ganglia neurons; 2 patients with thickening of the basal membrane of stria vascularis; 2 patients had IgG deposition in the basal membrane of stria vascularis; Patient with pSS → almost normal cochlea and no IgG deposition.

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Table 4. Results in Sjögren's Syndrome (*Continued*)

Author, Year	Study Design	N	Sex/Age	Disease Duration	Tests	Results
Treviño-González JL et al, 2017[90]	Case control	SS = 63 Controls = 188	95.2% females Mean = 49.5 yo	NA	Extended high-frequency audiometry; Tympanometry; ESSPRI scale	46% with subjective HL; 26% with vertigo; 39% with tinnitus; 95.2% with SNHL (in very high frequencies); 3 patients with abnormal tympanogram; No association of HL with disease activity.
Thanooja CV et al, 2018[91]	Cross-sectional	SS = 37	97.2% females mean = 45.8 yo	Median = 24 months	ENT examination; PTA; Impedance audiometry; Anti RO/SS-A; anti LA/SS-B Antiphospholipid antibodies Complement: C3 and C4	78.3% with objective HL (most SNHL); 17.2% with subjective HL; 18.9% absent acoustic reflex; No association with age; No association with sicca symptoms, clinical and immunological profile
Gündüz B et al, 2019[92]	Case control	pSS=36 (ESSDAI < 14) controls = 36	100% females mean = 51.4 yo	Mean = 31.0 months	PTA; Tympanometry; Acoustic reflex; DPOAE Suppression of DPOAE.	Differences in the hearing threshold between SS and controls at all frequencies; Speech audiometry correlated with hearing threshold for all subjects At tympanometry-static compliance of the SS group was lower than controls; The acoustic reflex threshold was higher than controls; DPOAE responses were similar to both groups No differences in the suppression of DPOAEs. No differences in hearing performance in SS with and without antimalarials.
Seeliger T et al, 2020[93]	Cross-sectional	SS = 30 (with polyneuropathy)	57% females mean = 59 yo.	NA	PTA Freiburg speech comprehension audiometry TEOAE BEER	80% with abnormal tests; 33% had HL by PTA (severe in 10%); 23.3% abnormal TEOAE; 6.6% discrimination loss; 46.6% had retro cochlear auditory dysfunction.
Ulusoy B et al, 2022[94]	Case control	SS = 35 Controls = 35	100% females mean = 50.5 yo	NA	PTA Tympanometry Nystagmus examination, Romberg test Dix Hallpike test Dysdiadokinesia /dysmetria tests cervical and ocular vestibular-evoked myogenic potentials tests; and video head impulse tests.	14.3% SNHL in SS (vs. 0% controls) Mean hearing threshold normal in both groups; No symptoms (dizziness, vertigo, diplopia, oscillopsia) in both groups Vestibular pathology indicators- all negative; No difference in the ocular vestibular-evoked myogenic potential tests. N1 latency for the ocular vestibular-evoked myogenic potentials test was ↑ in the SS group

BSER, brainstem evoked response; DPOAE, distortion product otoacoustic emissions; ENG, electronystagmographic; ESSDAI, Eular Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; HL, hearing loss; JIA, juvenile rheumatoid arthritis; n, number; NA, not available; pSS, primary Sjogren's syndrome; PTA, pure tone audiometry; RA, rheumatoid arthritis; SS, Sjogren's syndrome; sSS, secondary Sjogren's syndrome; SLE, systemic lupus erythematosus; SNHL, sensorineural hearing loss; TEOAE, transient evoked otoacoustic emissions.

Table 5. Studies on More Than One Connective Tissue Disease

	Study Design	n	Female Sex	Age	Disease Duration	Tests	Results
Doig JA et al, 1971[95]	Case control	pSS = 22 RA = 21 sSS+RA = 31	NA	NA	NA	ENT examination Audiometry	9/31 (29%) sSS + RA had conduction deafness (6 grade 3 and 3 grade 2 deafness) 15/21 (71.4%) RA patients (9 with grade 3 and 6 with grade 2 deafness) 4/22 (18.1%)—pSS with deafness (all conduction; 1 with sensorineural superimposed)
Galarza Delgado et al, 2018[96]	Case control	pSS = 60 RA = 117 Controls = 251	100% female	RA-mean = 47.5 yo pSS-mean = 49.5 yo	NA	PTA Tympanometry	SNHL at 500-3000 Hz - 36.8% RA and 60% pSS versus 10% controls SNHL at 10.000-16.000 Hz- 94.9% RA and 100% pSS versus 66.1% controls SNHL in RA - 4.7 X↑ and pSS - 4.9X↑ than controls. Hearing threshold in RA and pSS ↑ than controls HL prevalence in RA versus pSS → significant at 500-3000 Hz and worse in pSS
Tsirves GK et al, 2019[97]	Case control	RA = 60 SLE = 41 SS = 24 SSc = 8 Controls = 133	RA = 81.6 % SLE = 82.9% SS = 100% SSc = 75%	RA females = 64.6 yo SLE females = 49.0 yo SS females = 62.1 yo SSc females = 70.8 yo	RA = 13.5 yo SLE = 15.3 yo SS = 13.6 yo SSc = 13.3 yo	PTA Impedance audiometry Clinical and autoantibody profile Disease activity indexes Autoantibodies profile IgG anti-COCH	SNHL—RA = 66.6%; SLE = 31.7%; SS = 54.1%; SSc = 75%; AHLV in all groups ↑controls; RA AHLV correlated with DAS-28 SLE AHLV did not associate with SLEDAI No associations of HL with sex, disease duration in any group No associations with RF, complement, ANA, aCl, anti-Ro, anti-La, or anti-CCP in any group No differences in treatment in any group. 2 patients with anti-COCH - 1 with RA and 1 with SS.

aCl, anticardiolipin antibody; ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; COCH, cochlin; DAS-28, disease activity score using 28 joints (for rheumatoid arthritis); pSS, primary Sjögren's syndrome; PTA, pure tone audiometry; RA, rheumatoid arthritis; RF, rheumatoid factor; SS, Sjögren's syndrome, SSc, scleroderma; sSS, secondary Sjögren's syndrome; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index.

Table 6. Study on Mixed Connective Tissue Disease

Author/Year	Study Design	n	Female Sex/Age	Disease Duration	Tests	Results
Hajas A et al, 2009	Case control	MCTD = 71 Controls = 51	97.1% females Mean = 57.1 yo	Mean = 14.5 yo	Clinical and serological profile PTA; Speech audiometry; Autoantibodies profile; Determination of serum cytokines; Flow cytometry.	46.4% have SNHL; 30.3% subjective HL; No influence of age, disease duration, and treatments; SNHL associated with Raynaud and secondary APS; SNHL associated with anti-U1RNP, AECA, and aCl IgG; Serum IFN-γ, TNF-α and IL-10 → higher in MCTD with HL than without; Serum IL-4 does not associate with HL; Treg cells (CD4+CD25 ^{high} FoxP3+) were lower in MCTD with HL than in MCTD without HL.

ACl, anticardiolipin; AECA, anti endothelial antibodies; APS, antiphospholipid antibodies syndrome; HL, hearing loss; IFN, interferon; IL, interleukin; MCTD, mixed connective tissue disease; PTA, pure tone audiometry; SNHL, sensorineural hearing loss; TNF, tumor necrosis factor; T reg, regulatory T cell.

microscope scanning, Milisavljevic et al[12] found erosions and cartilage destruction. Moreover, plasma levels of matrix metalloproteinase-3 (MMP-3) in RA patients with HL were more elevated than in those without HL,[44] showing that this enzyme may be implicated in the pathophysiology of these findings.

Milisavljevic et al[16] studied the role of prednisone treatment in patients with HL. They found that both oral and intratympanic administrations had a positive effect, with results slightly better in the intratympanic administration. The addition of methotrexate in refractory patients offered little help. Huang et al[21] observed that patients using adalimumab had the lowest rate of HL, but, contradicting this fact, Ahmadzadeh et al[40] found that HL was significantly more prevalent in patients who used azathioprine, cyclosporine, and etanercept.

Results in Systemic Lupus Erythematosus (SLE)

Table 2 shows the main findings in SLE. Sixteen case-control[53-61,63-70] and 4 cross-sectional[51,52,60,62] studies are summarized in this table.

Hearing loss in SLE patients was higher than in the general population; the prevalence ranged from 16%[52] to 70%,[66] with most studies finding results around 20 to 30%. Sensorineural type predominated. There was no association of HL with disease activity in three studies,[54-56] but it was positive in two.[56,66] Moreover, no link could be established with clinical or autoantibody profile[53-58,63,67] except by the study of Lasso de la Vega et al, which found an association of HL with cryoglobulins.[66]

Karyia et al[64,64] found that type I hair cells from the saccular macula, in the utricular macula, and semicircular canals, as well as in the cochlea, were lower in SLE than in controls. Sone et al could not detect the deposition of immunoglobulins in the inner ear tissues but verified vasculitis in one patient.[52]

An interesting finding was the association of HL with HDL cholesterol in the work by Ferrari et al,[62] suggesting that atherosclerosis may be one of the causal elements of this process. Nevertheless, an extensive survey by Lin et al[59] could not associate sudden hearing loss (SSHL) with coronary artery disease or stroke.

Regarding antimalarial use, two studies found a positive association of HL with the use of this drug,[63,68] but others did not.[55,57,67]

Results in Scleroderma (SSc)

About 14 papers on hearing loss in systemic sclerosis have been identified: 11 case-controls,[72-80,82-84] 1 prospective,[81] and 2 cross-sectionals.[71,77] The main results are in Table 3. The prevalence of objective HL found ranged from 20%[72] to 88.8%,[73] and it was mainly sensorineural; but, again, like in the other connective tissue diseases, the prevalence of subjective HL was much lower. Age predisposed to HL in three studies[73,76,78] but not in another two.[71,72] Also, no differences could be found according to disease subset (limited or generalized).[74,75]

Regarding the association of HL with known SSc organ manifestations, some authors did not find an association of HL with the SSc clinical profile.[74,76,80] Still, Amor-Dorado et al,[73] Mazeda et al,[83] El Wakd et al[78] and Turan et al[82] associated HL with the occurrence of digital ulcers, digital pitting, or amputations, suggesting a possible association with peripheral arterial insufficiency. Three authors studied the possible association of periungual capillaroscopy (a reflection of microcirculation in SSc) with HL, and none of them found a relationship.[80,82,83]

An interesting work by Amor Dorado et al compared SSc patients with Raynaud phenomenon with those with primary Raynaud and found that patients with the primary form of Raynaud had hearing tests similar to those of controls, but not those with Raynaud phenomenon secondary to SSc.[84] Maciaszczyk et al,[75] studying the association of HL with SSc clinical findings, could not link it with the Raynaud phenomenon.

Results on Sjogren's Syndrome

The results of Sjögren's syndrome search are displayed in Table 4. Ten studies were identified: six case controls[85-87,90,92,94] and 4 cross-sectionals.[88,89,91,93] The prevalence of objective HL went from 14.3%[94] to 95.2%,[90] mostly SNHL.

Clinical manifestations could not be linked to HL[86,87,91] or disease activity.[90] Moreover, the autoantibodies profile was not associated with HL, although Tumiati et al[85] described that 64% of their patients with HL had anticardiolipin

antibodies; Thanooja et al[91] could not prove this association. Age did not influence the prevalence of HL in SS patients.[86,91]

Results on Studies of More Than One Connective Tissue Disease Simultaneously and in Mixed Connective Tissue Disease

Finally, three case-control studies (in which more than one connective tissue disease was considered simultaneously) and one in MCTD were found. Their results are in Table 5. Doig et al[95] studied the prevalence of deafness in primary SS, RA, and RA with secondary SS and found it worst in RA patients. Galarza-Delgado et al[96] found that patients with primary SS performed worse than those with RA. Tsirves et al[97] did not compare the different types of CTD but studied the presence of anti-cochin antibodies in blood samples and found a very low prevalence (2/133 or 1.5%).

The only study in MCTD (Table 6) showed an association of HL with Raynaud's phenomenon, secondary antiphospholipid syndrome, presence of anti-endothelial antibodies, anti-U1RNP, and anticardiolipin IgG antibodies. Additionally, this study showed a decrease in T reg cells and overexpression of interferon γ and tumor necrosis factor (TNF)-α in those with SNHL, suggesting their participation in the pathogenesis of the process.[98]

Discussion

This revision shows that HL is a feature of connective tissue diseases, mainly sensorineural type, appearing in all disorders included in this group. Associate sudden hearing loss may even be the presenting symptom in SLE[99] and scleroderma.[100]

However, in the reviewed studies, the prevalence of HL and its association with the clinical features of underlying disease differs widely among authors. The heterogeneity of studied samples likely causes this. Connective tissue diseases have complex etiopathogenesis with the influence of genetic background and environmental factors that may modulate the clinical profile.[101,102] Moreover, access to a prompt diagnosis and treatment is decisive in the progress and severity of these diseases and may also differ according to the studied geographical region. One example of such heterogeneity noticed in this review is the prevalence of seropositivity in the RA samples. The presence of anti-CCP went from 39% in the study by Macias-Reye et al[19] to 93.3% in the study by Pascual-Ramos et al[22] Similarly, RF positivity ranged from 46% in the study by Elnagdy et al[49] to 86.6% in the study by Pascual-Ramos et al[22] Seropositive and seronegative RA may diverge in the expression of extra-articular manifestations.[103] Systemic lupus erythematosus is also a very heterogeneous disease with clusters of autoantibodies and clinical manifestations that direct the clinical manifestations differently.[104] Scleroderma, in turn, has a subset classification with groups showing a different pattern of clinical findings; this classification was not always considered in the presented studies. So, it is comprehensible that HL's prevalence and clinical associations may vary.

Despite these difficulties, the awareness of HL as part of these diseases' burden isticle important as the treatment may revert or stop the progression. Steroids are the primary drugs used in this context and may be used orally, systemically, or locally (intratympanic).[106,107] The role of immunosuppressors or biologics needs to be better defined and deserves further studies. The work by Hajas et al[98] on mixed connective tissue diseases, showing higher levels of TNF- α and interferon γ in patients with HL compared to those without it, raises the possibility that biological drugs may help. In RA, Ahmadzadeh et al[40] found that the use of etanercept was associated with poor performance, while Huang et al[21] found the lowest prevalence of HL in those using adalimumab. Nevertheless, the use of these drugs cannot be dissociated from their indications, and biological drugs are usually used in more severe diseases, and this may affect the prevalence of HL.

Some limitations are that a relatively low number of rheumatic diseases were studied. In addition, the effects of rheumatic disease treatments, except glucocorticoids in a few disorders, were not observed regarding ear abnormality improvement.

Concluding, this review points to a high prevalence of HL in individuals with connective tissue diseases, and this must be recognized by those managing these diseases to minimize the risk of ear function loss.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.L.S., J.F.C.; Design – T.L.S., J.F.C.; Supervision – J.F.C.; Resource – T.L.S., J.F.C.; Materials – J.F.C.; Data Collection and/or Processing – T.L.S., J.F.C.; Analysis and/or Interpretation – T.L.S., J.F.C.; Literature Search – T.L.S., J.F.C.; Writing – T.L.S., J.F.C.; Critical Reviews – T.L.S., J.F.C.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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