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RESEARCH ARTICLE

RELATIONSHIP BETWEEN DISEASE ACTIVITY AND HEARING IMPAIRMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

Salwa Mahmoud, Aliaa El-Hady, Soad Said El Molla and Mai M. Kamel

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Abstract

Objectives:To compare hearing thresholds between control subjects and rheumatoid arthritis (RA) patients, and between active and remission status.

Materials and Methods: Thirty**(30)** Rheumatoid patients (RA group) and Twenty **(20)** healthy subjects (control group) were included in the study. Both groups were subjected to audiological testing: Pure tone audiometry, extended high frequency audiometry and auditory brain stem response (ABR). In RA group, the disease activity was assessed using DAS28-CRP.

Results: The air conduction pure-tone hearing thresholds were significantly higher at frequencies: 2000, 4000, 8000 Hz in the RA than control group. The extended high frequency audiometry hearing thresholds were significantly higher in Rheumatoid patients at 12000 and 16000 Hz. ABR showed a significant difference between the RA and control group regarding the absolute wave Vlatency only ($P<0.05$).The thresholds of pure tone audiometry and extended high frequency audiometry were higher in active patients than patients with remission, with significant difference at 12000 and 16000 Hz. A significant difference was observed between the active patients and patients with remission for the absolute wave Vlatency only. There was a significant positive correlation between the hearing threshold, ABR wave V latencyand the activity of the RA patients ($P<0.05$).

Conclusion: RA patients are at risk of hearing impairement, especially those with active disease.

Introduction:-

Rheumatoid arthritis (RA) is an inflammatory disorder. It is chronic and affects almost 1% of the world's population. It is characterized by synovial membranes inflammation of diarthrodial joints. This leads to progressive articular and periarticular tissues destruction [1,2].

Extra-articular involvement is a Rheumatoid arthritis characteristic. Several organs and systems could be impacted too, such as auditory system alteration, but with a different damage mechanism affecting the inner ear and resulting in sensory-neural hearing loss (SNHL) [3].

The most common type of hearing impairment in RA patients is sensory-neural hearing loss (SNHL) involving the

Corresponding Author:- Salwa Mahmoud

cochlear mechanism. Conductive and mixed hearing loss (HL) are reportedamong people at a lower frequency [4].

Known causes of hearing loss related to RA are vasculitis as part of mononeuritis multiplex, immune-complex mediated antibodies causing destruction of cochlear hair cell, ototoxicity caused by medications and disease activity[5].

A little number of studies assessed the clinical or serological disease activity and HL correlation. Several parameters, like the erythrocyte sedimentation rate (ESR) [6], bone erosions, rheumatoid factor (RF), the disease activity score-28 joints (DAS28), C-reactive protein (CRP), rheumatoid nodules, and anti-nuclear antibodies [7] were utilized to evaluate the disease activity.

Aims of the work:
1- To compare hearing thresholds between rheumatoid patients and control group.
2- To compare hearing thresholds between active and remission group.

Materials & Method:-

This study was conducted in the audiology department, Hearing and Speech Institute on Rheumatoid patients referred from outpatient clinic of Rheumatology department, National Institute of Neuro-Motor System.

This study composed 30 RA patientswith at least one year of disease duration, diagnosed with the American College of Rheumatology(ACR-1987) [8], and 20 rheumatic-free that have no otological or audiological history. We excluded patients that have other rheumatic disease, middle ear effusion, head trauma, occupational noise exposure, perforated tympanic membrane, congenital HL, Meniere's syndrome, chronic neurological disease, or ototoxic drug.

All participants provided consent. The ethical committee of GOTHI approved this study.

All RA patients had a full medical history and locomotor system evaluation. The disease activity was assessed using the DAS28-CRP, a valid tool for this purpose [9]. It depends on 28 swollen and tender joints and the CRP. The scoring ranges from 0 to 9.4. Remission, mild, moderate, and high disease activity meets the scores <2.6, 2.6 to <3.2, >3.2 to ≤5.1, >5.1 to <9.4 respectively. We used the study RA patients' score to categorize the participants into two groups, remission (DAS28-CRP<2.6) and active groups (DAS28-CRP>2.6).

Audiological examinations done for both patient and control groups were as following:
(i)Tympanometry and acoustic reflexes: probe tone (226 Hz) low frequency with pressure ranged from -400 to 200 dapa. Acoustic reflex threshold (ART) at 500 Hz, 1kHz, 2kHz and 4kHz was detectedfor both ipsilateral and contralateral ears.
(ii) Pure tone audiometry (PTA)was used for performing conventional audiometry (250 Hz -8000 Hz) using TDH39 headphones and extended high frequency audiometry(EHPTA) (12,000Hz - 16,000 Hz) using super aural headphones and bone conduction thresholds at 0.5,1,2,4 KHz Bone vibrator, and bone vibrator B71.
Hearing thresholds morethan 25 dB hearing level at one or more test frequencies was considered abnormal.We classify the hearing impairment on basis of tone audiometry according to World Health Organization as: Mild, Moderate, moderately severe, Severe and Profound hearing loss (HL): 26 to 40 dB, 41 to 55 dB, 56 to 70 dB, 71 to 90 dB and > 90 dB respectively.
(iii) Auditory Brain-stem response (ABR): ABRusing click stimuli withsetting ranged 100 Hz to 3,000 Hz and filtered clicks at a rate of 21.1 /sec. Every response was an average of 1,024 presentations. For both ears monaural recordings were performed at 90 dB nHL. The absolute wave I, III & V latencies and interpeak latencies (IPL) of wave I-III, III-V and I-V were detected.The stimulus was presented twice for checking reproducibility of the waveform. ABR findings with IPL delay of waves I to III, III to V>2.4 msecand wave I-V>4.4 msecwere reported as abnormal.

Equipment:
1-Immittancemeter InteracousticsAZ26.
2- Audiometer Interacoustic AC40
2-Evoked potential system Interacoustics EP25.

Statsiticalanalysis:
The data were entered using SPSS statistical program version 12 and graphs were assessed using Microsoft excel program. Quantitative variables were described by mean and standard deviation,while qualitative variables were described by number and percentages. Comparisons between two groups were tested using two tailed student's T test. Correlationwas done to test for linear relations between variables using pearson correlation test. P-values at <0.05 were reported as statistically significant.

Results:-

Our study was carried out on 30 adults with rheumatoid disease all were females (60 ears), their age ranged from 27 years old to 52 years old (mean± SD 41±10.9) years, and 20 normal female adults (40 ears) with age ranged from 20 years old to 50 years old (mean± SD 40±9.8). The disease mean duration was: 8 ± 4.1 years. Both study and control groups were sex and age matched.

The RA patient's disease activity was measured using DAS28-CRP. The results were, Remission in nine (30%) patients with a mean 2.3±0.1, mild activity in twelve (40%) patients with a mean 3±0.1 and moderate activity in nine (30%) patients with a mean 4.8±0.3 [Table 1].

Table 1:- The disease activity of Rheumatoid arthritis patients.

RA Patients N (%)	DAS28-CRP Score	Mean	SD
9 (30%)	Remission	2.3	0.1
12(40%)	Mild activity	3.0	0.1
9 (30%)	Moderate activity	4.8	0.3

Audiological assessment:
-Tympanogram was type A for both rheumatoid cases and control cases. **Stapedial Reflex Test**: In the RA group, Ipsilateral acoustic reflexes were absent in 3(10%) and present in 27(90%) RA patients. Contralateral acoustic reflexes were absent in 5(16.6%) and present in 25(83.3%) RA patients. For the control group, ipsilateral and contralateral reflexes were absent in 3(15%) and present in 17(85%) subjects.

The air conduction (AC) pure-tone hearing thresholds were significantly higher at frequencies: 2000, 4000, 8000 Hz in Rheumatoid group in relation to the control for both ears (P<0.05). The thresholds at 250, 500, 1000 Hz tended to be higher RA group, the differences were not significant (P>0.05) [Table 2, Fig 1]. The extended high frequency audiometry hearing thresholds at frequencies 12000 and 16000 Hz were significantly higher in Rheumatoid group than control group (P<0.05) [Table 3, Fig 1].

Table 2:- Comparison of thresholds of air conduction pure tone audiometry between RA and control groups.

Frequency Hz	RA group		Control group		
	Mean	SD	Mean	SD	P
250	24.3	0.1	19.3	3.1	0.06
500	24.1	0.2	19.4	3.2	0.06
1000	22.1	2.5	20.9	3.5	0.06
2000	26.2	4.0	19.2	4.0	0.04
4000	28.8	0.1	19.8	4.1	0.013
8000	27.7	3.4	21.0	3.7	0.03

P <0.05 Significant

Table 3:- Comparison of thresholds of air conduction of extended high frequency audiometry between RA and control groups.

Frequency Hz	RA group		Control group		
	Mean	SD	Mean	SD	P
12000	57.3	3.1	39	(1.5)	0.04
16000	58.8	3.2	47.8	(2.8)	0.04

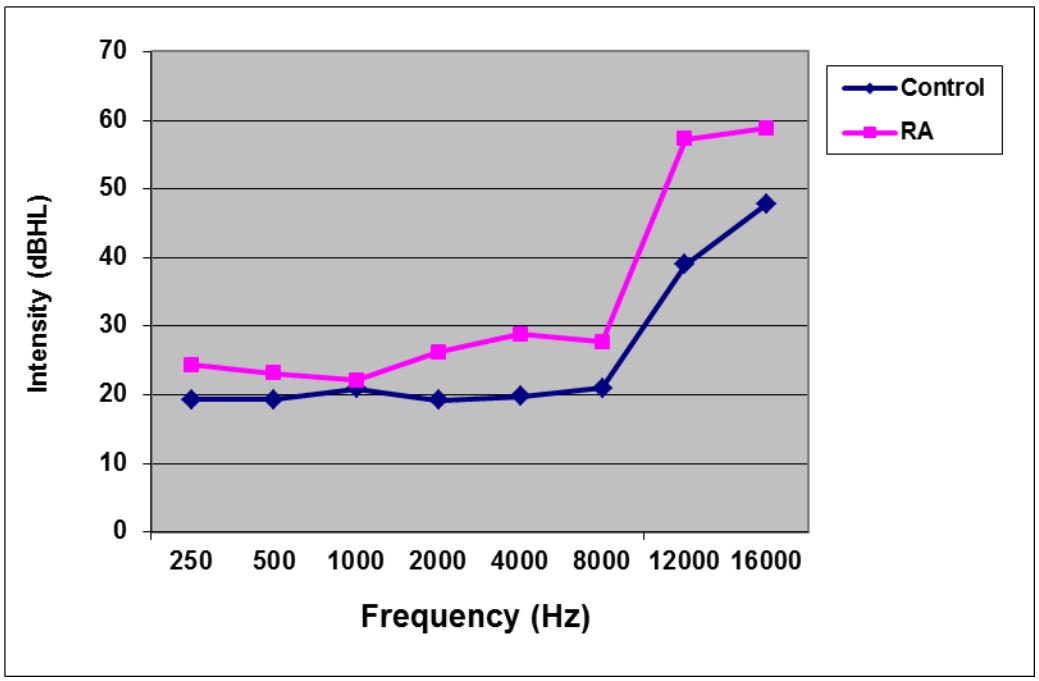

Figure 1:- The thresholds of hearing of pure tone and extended high frequency audiometry in RA and control groups.

Auditory Brainstemresponses(ABR) were recorded for RA and control groups and revealed a statistically significant difference for the absolute wave Vlatencyonly($P<0.05$), with no significant difference at absolute waves I, III latencies($P>0.05$). As regard interpeak latencies, there were only a higher interpeak latencies of I-V, and III-V with no statistically significant difference between both groups ($P<0.05$) [Table 4].

Table 4:- Comparison of Auditory Brainstem Response testing between RA and control groups.

Parameter (Latency)	RA group		Control group		
	Mean	SD	Mean	SD	P
Wave I	1.4	0.4	1.4	0.2	0.51
Wave III	3.47	0.5	3.4	0.5	0.49
Wave V	5.95	0.4	5.5	0.3	0.04
Wave I-III	2.1	0.2	2	0.2	0.6
Wave III-V	2.48	0.1	2.1	0.2	0.06
Wave I-V	4.55	0.5	3.7	0.8	0.06

Regarding the RA patients' hearing thresholds and the disease activity relation, we found that the pure tone audiometry thresholds and extended high frequency audiometry were higher in patients with disease activity compared to patients in remission with significant difference at 12000 and 16000Hz with ($P<0.05$) [Table 5].

Table 5:- Comparison of thresholds of pure tone audiometry and extended high frequency audiometry between active and remission groups.

Frequency Hz	Active group		Remission group		
	Mean	SD	Mean	SD	P
250	24.3	0.1	23.3	3.1	0.07
500	23.1	0.2	22.4	3.2	0.06
1000	22.1	2.5	21.9	3.5	0.08
2000	26.2	4.0	25.8	4.0	0.07
4000	28.8	0.1	27.8	(4.1)	0.07
8000	27.7	3.4	25.0	(3.7)	0.06

12000	57.3	3.1	45.8	(4.1)	0.01
16000	48.8	3.1	40.0	(3.7)	0.04

A statistically significant difference was noticed between the active and remission patients for the absolute wave V latency only (P>0.05), with no significant difference at absolute waves I, III latencies. Regarding interpeak latencies, there was only a higher interpeak I-V, III-V latencies with no statistically significant difference (P>0.05) [Table 6].

Table 6:- Comparison of ABR waves between active and remission groups.

Parameter	Active group		Remission group		
	Mean	SD	Mean	SD	P
Wave I	1.4	0.4	1.3	0.8	0.51
Wave III	3.5	0.5	3.4	0.6	0.49
Wave V	6.0	0.4	5.8	0.4	0.04
Wave I-III	2.1	0.2	2.1	0.2	0.6
Wave III-V	2.5	0.1	2.4	0.2	0.06
Wave I-V	4.6	0.5	4.4	0.8	0.06

A significant positive correlation between the hearing threshold, ABR wave V latency and the RA patients' activity (P < 0.05) was found [Fig 2, 3].

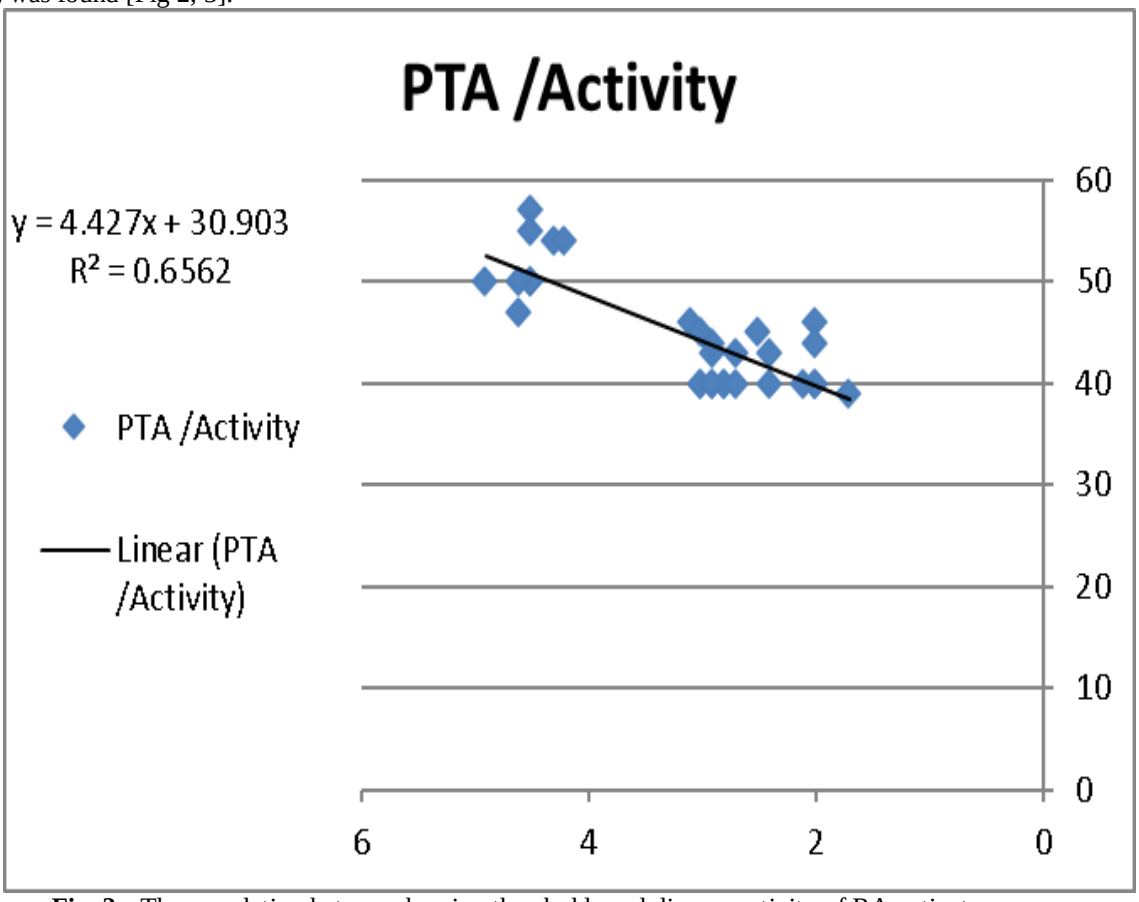

Fig. 2:- The correlation between hearing thresholds and disease activity of RA patients.

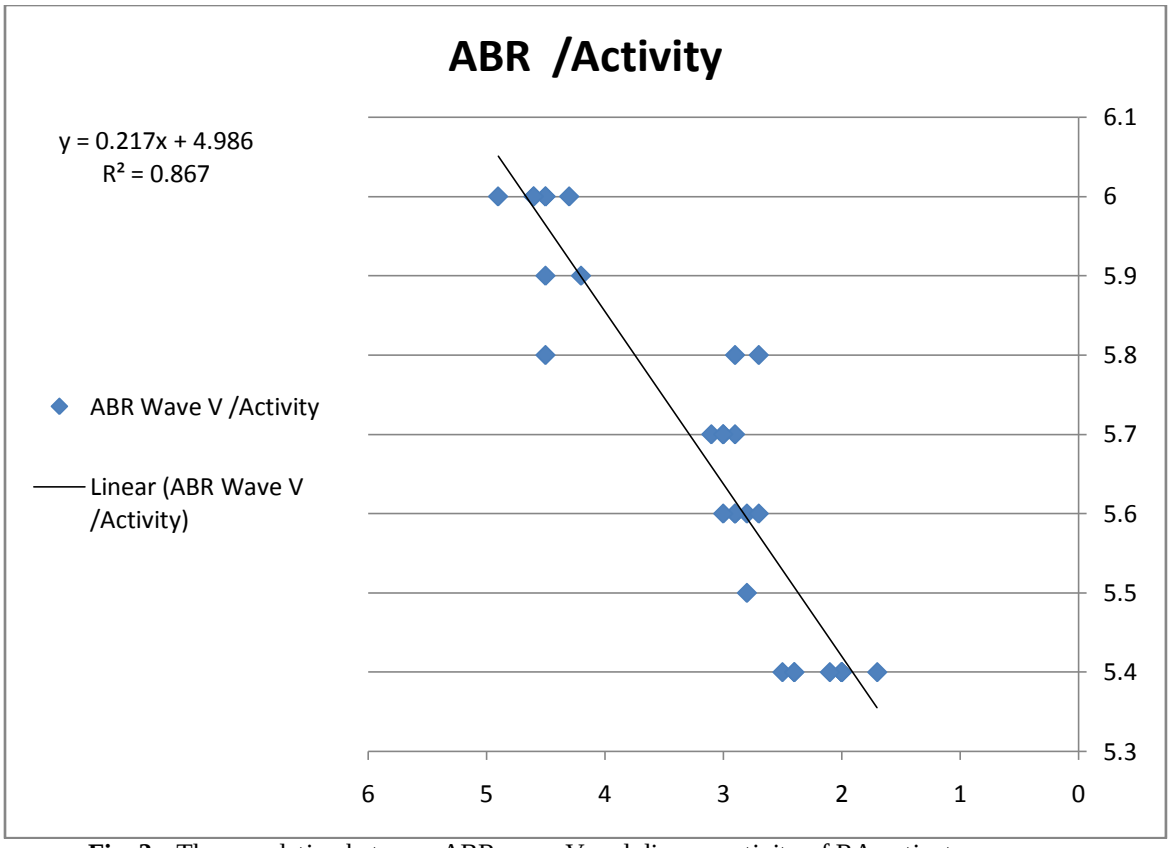

Fig. 3:- The correlation between ABR wave V and disease activity of RA patients.

RA is a chronic inflammatory joint disease that is often associated with a number of peripheral inflammatory symptoms [10]. Extra-articular involvement is a RA characteristic. Several organs and systems could be impacted too [7], like auditory system alteration, but with a different damage mechanism [3,6].

The hearing impairementprobability is higher in RA patients than the healthy (42% vs. 15.9%) [11]. SNHI is the most common hearing damage noticed in RA patients. It happens according to the disease activity, age and extra-articular involvement like vasculitis [12].

RA can produce an autoimmune response to the sensitive cells of the inner ear; the inflammatory cells can enter the cochlea via the spiral modiolar vein leading to SNHL, which is a common auditory disorders' mix caused by dysfunction of the inner ear, auditory nerve, or the auditoryprocessing pathway in the CNS [13].

This study aims comparing the hearing thresholds among control and RA patients, and among RA active and remission groups.

In our work we found that, the AC pure-tone hearing thresholds were significantly higher at frequencies: 2000 , 4000 ,8000 Hz in the RA group in relation to the control group.We also found a significantly higher thresholds in Rheumatoid patients than control group at 12000 and 16000 Hz .

Concerning the damaged frequency, our findings were comparable with previous researches indicating the damage induced in high frequencies in RA patients [1, 7, 11, 14, 15, 16].The authors concluded that the cause could be cochlear hair cells' inflammatory destruction or inner ear with immune complex deposition as a result of autoimmune processes [6]. Ozkiris et al. [17] interpreted hearing loss at high frequencies as an evidence of cochlear involvement as a result of RA's systemic vascular component.

Raut et al. [18] reported a higher hearing loss probability in 500, 1000, and 2000Hz frequencies. Murdin et al. [6] reported a hearing loss probability at low and medium frequencies (from 250 to 4000Hz). Our findings were

different from these studies. Murdin et al. [6] stated that the damage could be due to the RA and endolymphatic hydrops (caused by immune-complex deposits) correlation, which affects the low frequencies and then the high frequencies.

While some studies [19,20] found statistically significant variationsin all frequencies tested between the hearing thresholds of the control population and RA patients, others did not find any significant difference between both groups [21 ,22]. This could be related to variation in sample size.

Regarding Auditory Brainstem responses, we found a statistically significant difference between the RA and control group for the absolute wave Vlatency only. As regard interpeak latencies, there was only a higher interpeak latencies of I-V, and III-V with no statistically significant difference.Another research was done, where a highly statistically significant difference was observed between the RA and control group for the absolute wave I, III and V latency, they also noticed delay in interpeak latency of wave I-III & III-V, though a statistically significant difference was not obtained between the two groups [23]. Takatsu et al. [11] stated no abnormality in auditory brainstem responses in his research**.**

As regard the relation between hearing thresholds and the RA patients' disease activity, we found that the pure tone audiometry thresholds and extended high frequency audiometry were higher in active patients than those with remission with a statistically significant difference at 12000& 16000 Hz.

Lasso de la Vega and colleagues discovered a 33.6-fold increased hearing impairment risk while extended high frequency audiometry was used compared to pure tone audiometry in a case control study[20]. Early stage ofhearing impairment could be detected by theextended high frequencyaudiometry, which tests very high frequencies(>8000 Hz).

Although Yildirim et al. [24] detected hearing impairment at high frequency (4000 Hz) in active RA patients by comparing the audiometric findings of 62 patients with active disease to 26 individuals in remission using the (DAS28CRP) test. However, Salvinelli et al. [25] studied 20 active RA patients, 18 inactive, and 38 healthy controls. He stated that RA patients had higher auditory thresholds than controls but did not demonstrate a statistically significant difference in hearing thresholds between active and inactive patients.

In the RA group, a statistically significant difference was observed between the active patients and those with remission for the absolute wave V latency only, with no significant difference at waves I, III absolute latencies. As regard interpeak latencies, there were only a higher interpeak I-V, and III-V latencies with no statistically significant difference.

The hearing threshold, ABR wave V latency and the RA patients' disease activity had a positive correlation, which indicates that with increased activity of the disease, the hearing is more affected.

The Rheumatic disease activity in RA patients and hearing impairment correlation was obtained, which was similar to other authors [11, 14, 20, 26]. Magaro et al. stated that the hearing loss in RA was correlated with active disease and the rheumatoid factor [14]. Takatsu et al. [11] demonstrated an association between SNHI and ESR, plasma interleukin-6, and plasma matrix metalloproteinase-3, indicating that systemic inflammatory processes may initiate HI and contribute to oxidative damage in inner ear cells.

Other studiesstated no disease activity and HI correlation, while Ozcan et al.[7] used ESR levels and rheumatoid nodules as a disease activity criteria. Murdin et al.[6]found no correlation neither by using the DAS28 score nor any of its individual components. Yildrim et al. 2016 [24] thought that these contradictory results arise from the different methods used in measuring disease activity and reported that DAS28-CRP is a more accurate disease activity measure.

Conclusion:-

The study findings revealed that RA patients are at higher HI risk than the control. The risk increases with the disease activity, especially at high frequencies. Accordingly, the physicians should perform yearly audiological tests and take precautions to avoid the adverse effect of RA on hearing levels.

Limitation:
Small sample size and the absence of high disease activity patients. Thus, further studies with a larger sample size are recommended.

References:-

1- Elwany S, elGarf A, Kamel T. Hearing and middle ear function in rheumatoid arthritis. J Rheumatol (1986) ; 13(5):878–881.
2-Kasper DL, Brounwald E, Fauci AS, Hauser SL, Longo DL, et al. Harrison's Principles of Internal Medicine. (16th ed), McGraw-Hill, New York, USA (2005); pp. 1968-1977.
3-Emamifar A, Bjoerndal K, Hansen IM. Is hearing impairmentassociated with rheumatoid arthritis? a review. Open Rheumatol J 2016;10:26–32.
4-Voulgari PV, Papazisi D, Bai M, Zagorianakou P, Assimakopoulos D, et al. Laryngeal involvement in rheumatoid arthritis. Rheumatol Int 2005 ; 25(5): 321-325.
5-Stevens G, Flaxman S, Brunskill E, MascarenhasM,Mathers CD, Finucane M. Global and regional hearingimpairment prevalence: an analysis of 42 studies in29 countries. Eur J Public Health2013 ; 23:146-52.
6-Murdin L, Patel S, Walmsley J, Yeoh LH. Hearing difficulties are common in patients with rheumatoid arthritis. Clin Rheumatol 2008 ; 27(5):637–640.
7- Ozcan M, Karakuş FM, Gunduz OH, Tuncel U, Sahin H. Hearing loss and middle ear involvement in rheumatoid arthritis. Rheumatol Int 2002;
22(1):16‑19.
8. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31:315-24.
9. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty‑eight‑joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; 38:44–48
10. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010; 376:1094–108.
11. Takatsu M, Higaki M, Kinoshita H, et al. Ear involvement in patients with rheumatoid arthritis. OtolNeurotol2005; 26:755–61.
12. García Callejo FJ, ConillTobías N, Muñoz Fernández N, de Paula Vernetta C, Alonso Castañeira I, Marco Algarra J. Hearing impairment in patients with rheumatoid arthritis. Acta OtorrinolaringolEsp 2007; 58:232-8.
13. Hurley RM, Sells JP. Autoimmune inner ear disease. Am J Audiol 1997; 6:22‑30.
14 Magaro M, Zoli A, Altomonte L et al. "Sensorineural hearing loss in rheumatoid arthritis," Clinical and Experimental Rheumatology 1990; 8(5) : 487–490.
15. Gussen R "Atypical ossicle joint lesions in rheumatoid arthritis with sicca syndrome (Sjogren syndrome). Archives of Otolaryngology 1977; 103(5): 284–286.
16. Baradaranfar MH and Doosti A, "A Survey of relationship between rheumatoid arthritis and hearing disorders". Acta Medica Iranica 2010; 48 (6): 371–373.
17. Ozkiris M, Kapusuz Z, Gunaydin I, Kubilay U, Pirti I, Saydam L. Does rheumatoid arthritis have an effect on audiovestibular tests?. Eur Arch Otorhinolaryngol 2014;271(6):1383–1387
18. Raut VV, Cullen J, Cathers G. Hearing loss in rheumatoid arthritis. J Otolaryngol 2001; 30:289‑294.
19. Oztürk A, Yalçin S, Kaygusuz I, Sahin S, Gök U, et al. High-frequency hearing loss and middle ear involvement in rheumatoid arthritis. American Journal of Otolaryngology 2004; 25(6): 411-417.
20. Lasso de la Vega M, Villarreal IM, Lopez‑Moya J, Garcia‑Berrocal JR. Examination of hearing in a rheumatoid arthritis population: role of
extended‑high‑frequency audiometry in the diagnosis of subclinical involvement. Scientifica 2016; 2016: 571383.
21. Lobo FS, Dossi MO, Batista L, Shinzato MM. Hearing impairment in patients with rheumatoid arthritis: association with anticitrullinated protein antibodies. Clin. Rheumatol 2016; 35: 2327-2332.
22. Rahne T, Clauß F, Plontke SK, KeyßerG.Prevalence of hearing impairment in patients with rheumatoid arthritis, granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), or systemic lupus erythematosus.Clin. Rheumatol 2017; 36:1501-1510.
23. Munjal S, Sud P, Gudwani S, Sharma A, Sharma A, Panda N. Peripheral and Central auditory manifestation of rheumatoid arthritis. Glob J Otolaryngol 2017; 3(1):1–7.
24. Yildirim A, Surucu G, Dogan S, Karabiber M. Relationship between disease activity and hearing impairment in patients with rheumatoid arthritis compared with controls. Clin Rheumatol 2016; 35:309-314

25. Salvinelli F, Cancilleri F, Casale M, Luccarelli V, DI peco V, D'ascanio L. Hearing thresholds in patients affected by rheumatoid arthritis. Clin Otolaryngol 2004; 29:75–79
26. Dikici O, Muluk NB, Tosun AK, and Unlusoy I. "Subjective audiological tests and transient evoked otoacoustic emissions in patients with rheumatoid arthritis: analysis of the factors affecting hearing levels," European Archives of Oto-Rhino- Laryngology 2009; 266(11) : 1719–1726.