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RESEARCH ARTICLE

Tracking Early Atherosclerosis by Audiometry; A Review of Studies in a High Risk Population

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ABSTRACT

Objectives: Increasing levels of atherosclerosis correlate with increasing degrees of hearing loss. We hypothesized that arterial inflammation observed on FDG-PET/CT scans correlates with audiogram test results and that Major Adverse Cardiovascular Events occur in subjects with severe hearing loss (>40 dB).

Methods: A FDG-PET/CT imaging prospective study was performed in an NIH trial including 115 rheumatoid arthritis subjects over age 50 without a history of cardiovascular disease, and 22 subjects were selected for concurrent audiograms. All were evaluated by 18-fluorodeoxyglucose positron emission tomography computed tomography scans and audiogram tests, at baseline and 6 months. In our institution, 320 similar RA subjects were identified over age 50 with no prior cardiovascular disease and chart review completed for 10 years to evaluate MACE occurrence. Audiograms were available for the 320 retrospective patients.

Results: In the imaging study, at baseline there was a strong correlation between arterial inflammation on FDG-PET/CT and hearing test results ($p<0.002$). Hearing loss over 30 decibels was strongly associated with high levels of inflammation on FDG-PET/CT imaging. In the larger 320 retrospective group, there were 11 MACE (3.4%) in the 10 years period which occurred in subjects with even greater hearing loss (average measurement was over 50 dB).

Conclusion: Atherosclerosis was identified through FDG-PET/CT imaging studies and hearing tests. All MACE occurred in patients with significant hearing loss. Testing comprised a unique population with systemic inflammation from RA. If confirmed in larger studies in the general population, audiograms might provide a cost- effective substitute for FDG-PET/CT imaging and provide potentially an improved individual patient cardiovascular risk assessment. Audiograms may infer cardiovascular disease risk similar to cholesterol on an individual basis.

Keywords: Atherosclerosis, MACE, cardiovascular risk factor, FDG-PET/CT imaging, audiogram

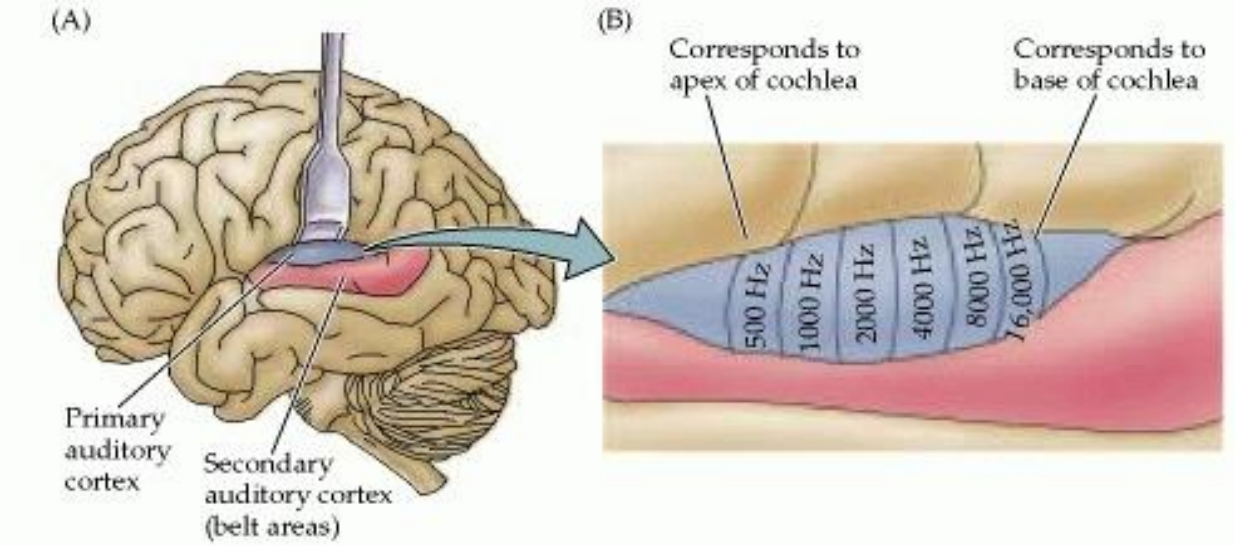
Introduction

This study explores the potential to use audiograms as a tool for monitoring early atherosclerosis in a well known high risk population with inflammatory atherosclerosis, specifically active rheumatoid arthritis (RA)[1]. FDG-PET/CT imaging (PET) is well documented to indicate atherosclerosis vascular inflammation; unfortunately PET remains too expensive to be used widely for cardiovascular disease (CVD) risk assessment. Multiple studies suggest increasing levels of atherosclerosis link to hearing loss.[2,3,4] Hearing loss as a marker of atherosclerosis might prove similar to using cholesterol as a marker. This hypothesis was explored in 2 parts. The first was a prospective assessment over 6 months measuring early atherosclerosis with 18 FDG-PET/CT tomography compared with audiograms (referred to as "Imaging"). The second study tracking atherosclerosis and audiograms in a high risk population collected MACE data retrospectively over a decade for 320 RA patients over age 50 who had no prior cardiovascular disease (referred to as "MACE").

An even earlier study at our institution suggested hearing loss reflected atherosclerosis.[5] This prior study reviewed 87 elderly patients with rheumatoid arthritis (RA), aged 80-101 years old, treated with 20 years of immunosuppression with methotrexate (MTX) and noted only 3 persons with hearing aids, as well as 50% with hearing better than the general public twenty years younger. The preservation of hearing in the elderly RA patients prompted a hypothesis that methotrexate suppressed inflammation in systemic vascular atherosclerosis, and that this mechanism explained preserved hearing. Untreated RA is known to have an increased risk of CVD and hearing losses; we found treated RA had a reduced risk of CVD and less hearing loss. Active RA presents a unique population to study early inflammatory atherosclerosis and CVD over time.[1]

What is measured in the audiogram? The hearing test evaluates the 8th auditory nerve but also auditory processing in the cerebral cortex.[4] The brain identifies sound by frequency, amplitude, and location in space as well as temporal relationships in sound (such as Morse code, multisyllabic speech, and music). The pathophysiology of hearing involves the ganglion cells of the inner ear directly transmitting signals to the superior temporal gyrus, which then identifies the frequency of the incoming sound at the tonotopic map in the primary auditory cortex (Fig 1). The secondary auditory cortex includes the Wernicke's area required to understand words. The final sound processing occurs in the parietal and frontal lobes to understand language, extract the sound from background noise, and assess amplitude needed to appreciate music. Therefore, an audiogram assesses the health of the 8th cranial nerve, the temporal lobe, the parietal lobe and the frontal lobe in processing a sound. An audiogram assesses both peripheral and central processing of sound.

Figure 1: Superior Temporal Gyrus (this anatomy is replicated on the opposite temporal lobe) Afferent nerve fibers from the cochlea arrive in the primary auditory cortex of the temporal lobe. (Adapted with permission from The Auditory Cortex, Neuroscience. 2nd edition. Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Sunderland (MA): Sinauer Associates; 2001.[4] Part of the National Library of Medicine bookshelf.)



With atherosclerotic disease, areas of the cortex have diminished function.[6] From a NIH multi-center prospective RA study of 115 subjects,[7] our single research site conducted a substudy of 22 RA patients with a hearing test at baseline and 6 months in addition to the study proscribed PET testing at baseline and 6 months.[8] The hypothesis was that hearing tests can be utilized as a marker for inflammatory atherosclerosis and work as a surrogate measure for the PET scans. The relationship between CVD and hearing loss is well known, and our current studies confirm that thesis. As discussed later, our data indicate hearing loss can identify early atherosclerosis and that MACE subjects confirm the association between significant hearing loss and end organ events.

Methods

Reviewed here are the methods used in the NIH multicenter prospective trial[7], the methods for the "Imaging" substudy including audiograms[8], and the 10 year observational review for a decade of 320 RA subjects ("MACE").

In a prospective NIH multi-center study, 115 subjects with active RA were randomly assigned to 6 months of immune suppression with "methotrexate-plus." Each subject for 6 months received a stable dose of MTX with either 1) a TNF biologic or 2) oral conventional therapy of sulfasalazine and hydroxychloroquine. (Shown in Table 1). All RA patients achieved equally full suppression of inflammation[9] by PET scans over 6 months on "methotrexate-plus." [7] A substudy of 22 sequential subjects at a single site had hearing tested at baseline and 6 months along with the FDG-PET/CT scans.[8] All imaging substudy subjects were on stable background therapy throughout. Inclusion and exclusion criteria have been published.[7] Key criteria regarding this study of hearing loss in the cohort of 320 RA subjects excluded patients with prior CVD and all were over age 50.

Ethical review committee for the primary study of the full 115 subjects was approved by the MassGeneral Brigham Healthcare Human Subjects Committee, study #NCT 02374021. The subset of 22 subjects given audiograms was issued a waiver by Advarra Institutional Review Board. Audiograms are part of Good Clinical Practice and standard medical practice starting at age 50.[10] The collection of data for MACE events was issued a waiver from Advarra.

Imaging and audiogram data was acquired between May 2019 and September 2021. MACE events were tracked from September 2012 to December 2022.

Audiogram measurement

Pure tone audiometry and word identification scores were conducted in "Imaging" on 22 RA subjects at baseline and 6 months. The testing was conducted using AMBCO 2500 equipment and the modified Hughson-Westlake procedure as specified by the International Organization for Standardization.

The same equipment and technician were used at all time points. Results were recorded for each ear at 250, 500, 1000, 2000, 4000, and 8000 Hertz (Hz). Audiograms were defined as traditional five levels of hearing: level 1) normal at 0-20dB, level 1.5) slight impairment at 30dB, level 2) mild impairment at 31-40dB, level 3) moderate impairment at 40-60dB, level 4) moderately severe impairment at 60-80dB, and level 5) severe impairment above 80dB. Hearing tests record how loud the sound must be for recognition. Hearing at 20 dB is normal, while hearing requiring 40 dB is impaired.

Age, sex, language, socioeconomic status, education, medical history, tobacco use, concomitant medication, and vocation were reviewed on all subjects and all subjects had a complete physical exam and ear examination. No subjects had cerumen impaction, unilateral hearing loss, tinnitus, vertigo, chronic ear infections, history of trauma to the ear, vocational cause for hearing loss, nor any temporal mandibular joint disease.

Hearing impairment was defined as a pure tone audiogram >30dB in either ear. At the 6 month examination, hearing loss was defined as at least 5 dB further loss in both ears, while hearing improvement was an increase of at least 5 dB in both ears.

Imaging measurement

Arterial inflammation was measured using the standardized uptake value (SUV) of 18-fluorodeoxyglucose in the carotid arteries and aorta with tomograms at 5mm intervals and the highest SUV was recorded for each patient. The SUV max was adjusted with target-to-background (TBR) from the lumen of the abdominal aorta. The ascending aorta segment had the highest SUV readings and was chosen as the signal arterial segment for analyses. FDG-PET/CT is a well-established and reproducible method for assessing inflammation often used in multiple studies on cardiovascular inflammation.[11,12,13,14] The FDG-PET/CT scans were conducted using a Siemens machine, evaluated by Dr. Steven Gunberg, analyzing SUV, plaque, and calcium scores (Ca+). Carotid artery ultrasound for intimal medial

thickness (CIMT) and plaque were assessed at baseline and 6 months.

Statistics

Adjustment for multiple confounding factors was not performed due to the small sample size. Confounding factors such as age, gender, hypertension, tobacco use, statin use, and diabetes mellitus were collected and are listed in Table 1 and Table 2.

This was an exploratory evaluation to assess correlation between FDG-PET/CT scans and audiograms. Since the audiogram substudy was offered only in one site, the number of subjects was limited to the 22 subjects at that site. Categorical variables were described as numbers/percentages and continuous variables as mean/standard deviation (sd). To compare continuous variables at baseline and at 6 months, we used paired t-tests and Pearson's correlation coefficient to measure the linear association. A p-value of less than 0.05 was considered statistically significant. The confidence intervals were not adjusted for multiplicity due to the small sample size. The 6 month change in audiometry and FDG-PET/CT were converted to Spearman's rank- order least squares regression model for analysis. In a single subject, the FDG-PET/CT scan at 6 months could not be analyzed for SUV at the ascending aorta, so measurements at 6 months involve only #21 estimates and 95% confidence intervals results. Statistical analyses were conducted using GraphPad Prism, version 9, November 8, 2022.

Results

Baseline characteristics for the "Imaging" study are listed in Table 1. Baseline characteristics included age, gender, body mass index, hypertension, current or history of smoking, statin use, diabetes mellitus, or any use of a corticosteroid, "MTX-Plus" treatment was randomly assigned as Rx #1) MTX+ TNF (n=11) or Rx #2) MTX+ sulfasalazine/hydroxychloroquine (n=11). Both treatment groups had equal immune suppression over the 6 months by PET.[7] From the "Imaging" subgroup, at baseline, 6 subjects showed a mild degree of carotid intimal medial thickness (CIMT) by ultrasound. The average SUV measurement in these 6 subjects at baseline showed SUV inflammation at 3.89 (sd 0.8, 95% CI 3.06,4.73). The average audiogram level in these 6 subjects was impaired at level 1.6 (sd 0.67, 95% CI 0.90,2.3). No subject had CT arterial calcifications (Ca+) at baseline or at 6 months.

Table 1: Baseline characteristics

Age	gender	BMI	HTN	cig	statin	diabetes	BL Audiogram	BL Pet/CT	BL U/S	BL Ca+	Rx#
N=22	22	22	10/22	2/22	8/22	2/22	22	22	21	22	22
Avg 62y	17F/5M	28.1	45%	10%	36%	10%	1.45	3.65			
(sd 8)		(4.4)					(0.54)	(0.74)			
58,65*	-	26.2,30.1	-	-	-	-	1.21,1.67	3.3,3.8	-	-	-
Individual subjects											
50y	M	28.8	yes	yes	no	no	1.1	3.8	normal	0	1
50y	F	27.3	yes	no	no	no	2.0	3.87	normal	0	2
50y	F	26.7	no	no	no	no	1.0	3.14	normal	0	2
50y	F	30.0	no	no	yes	no	1.0	3.43	normal	0	1
53y	F	23.6	no	no	no	no	1.0	3.28	CIMT	0	1
55y	F	26.5	no	no	no	no	1.1	2.95	normal	0	2
55y	F	31.5	no	no	no	no	1.0	2.79	normal	0	1
57y	F	29.1	no	no	no	no	1.0	2.98	normal	0	2
61y	M	38.6	yes	no	no	yes	2.4	4.7	CIMT	0	2
63y	F	27.1	yes	no	no	no	1.2	3.56	normal	0	1
62y	M	24.9	no	no	no	no	1.2	3.08	CIMT	0	2
63y	M	29.8	yes	no	yes	yes	1.5	4.96	normal	0	2
64y	F	35.7	yes	no	yes	no	2.5	4.94	CIMT	0	2
64y	M	33.6	no	no	no	no	1.2	4.07	CIMT	0	1
66y	F	24.3	yes	no	yes	no	1.3	3.29	CIMT	0	1
67y	F	33.6	yes	no	yes	no	1.5	4.53	normal	0	2
68y	F	22.8	no	no	yes	no	1.0	3.4	normal	0	1
70y	F	23.2	yes	no	yes	no	1.2	2.6	normal	0	2
71y	F	24.9	no	no	no	no	2.0	3.56	normal	0	1
72y	F	22.0	no	no	no	no	1.3	2.65	normal	0	1
79y	F	28.1	yes	yes	yes	no	2.8	4.1	na	0	1
79y	F	26.5	no	no	no	no	1.5	4.6	normal	0	2

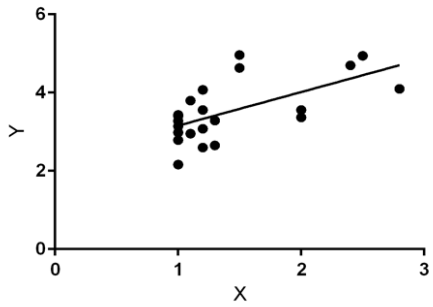
Legend: MTX+ treatment was randomly assigned as 1) MTX+ TNF (n=11) or 2)MTX+ sulfasalazine/hydroxychloroquine (n=11). All subjects showed equal suppression of RA by DAS28-CRP for the 6 month period. At baseline, 6 subjects showed mild carotid intimal medial thickness (CIMT) by ultrasound and no subject had CT arterial calcifications (Ca+). *95% CI.

Table 1 lists characteristics for subjects in the "Imaging" study who were 50% Hispanic and 50% White-non Hispanic. Average age was 61.5 years (sd 8.2, range 49-79) and 77% female. The average body mass index was 27.7 (sd 4.8, 95% CI 26.2,30.1). All subjects were on methotrexate 20 mg/week, folate 1 mg daily, and 81 mg daily aspirin. All subjects took "MTX Plus" randomly assigned to #1 or #2 to suppress inflammation, which proved to have equal suppression.[7] Of the 22 subjects, 2 subjects smoked cigarettes, 2 took oral diabetes medication, 50% took hypertension medication, 36% were on statins, and none took corticosteroid medication.

Baseline Results

The primary outcome of the "Imaging" study was the association of hearing loss assessed by arterial inflammation assessed by PET scans and audiogram (figure 2). At baseline simple linear regression was significant with R square 0.38, p< 0.002. The Pearson coefficient was r= 0.620, p<0.002 also showing significant strength and direction in the relationship between the two measurements.

Figure 2: Simple Linear Regression: Baseline audiogram vs. FDG-PET



R square 0.38, F12, (1,20)
P<0.002
Y= 0.86X + 2.3

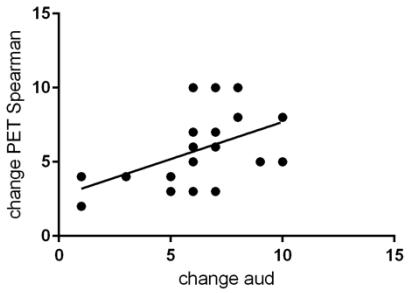
Legend: On the x axis are worsening hearing levels: #1= 0-20 dB, #1.5= 30 dB #2= 31-40 dB, #3= 41-60 dB. On the y axis are shown FDG-PET/CT results as SUV standardized uptake value units in the ascending aorta (chosen as the most affected segment). For every worsening of hearing level, the SUV increased 0.86 (nearly 1 SUV).

At baseline, no subject required a hearing aid. Hearing did decrease with age; with linear regression, r square 0.176, DF 20, p<0.05. At baseline, 73% of subjects had hearing equal to or better than 30dB. The predictive value of a 30dB or worse measure of hearing loss had a 71% concurrent arterial inflammation above 3.5 SUV.

Results after suppression of inflammation for 6 months in the "imaging" study

Vascular inflammation was suppressed by 6 months in the imaging study, documented by improvement in PET measurement. The audiograms also improved. An average of the audiogram measurements for both ears was compared to baseline. Figure 3 demonstrates a strong correlation in the changes at 6 months for hearing (dB) and PET measured as Spearman rank coefficient, r = 0.708, p<0.0003.

Figure 3: Results at 6 months for audiogram dB improvement vs. FDG-PET/CT improvement



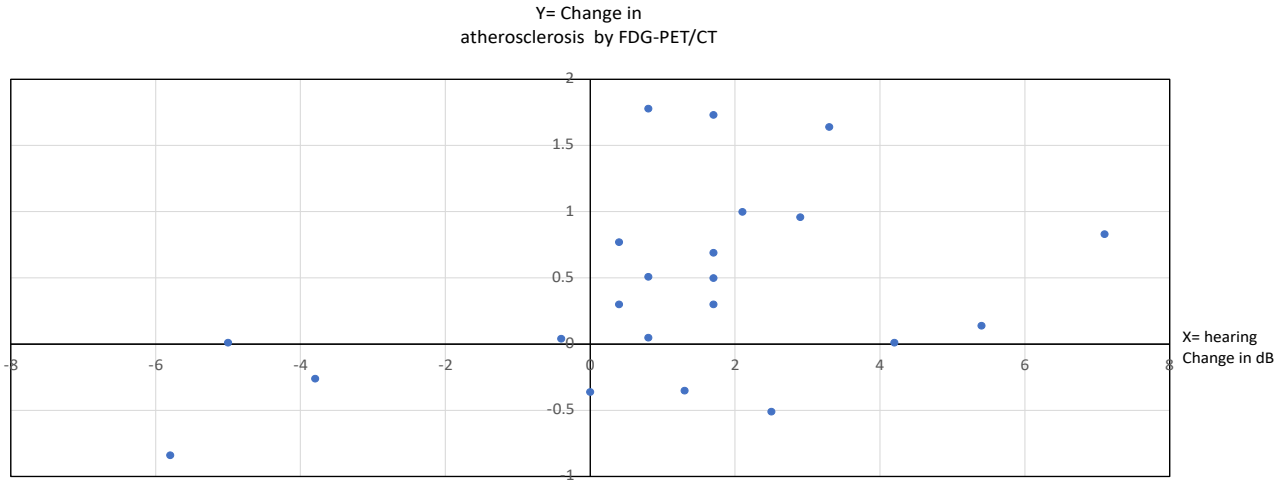
r coefficient= 0.708, n=21,
p<0.0003

Legend: FDG-PET/CT SUV improvement measures were ranked to assess Spearman linear coefficient. The improvement measured as change in audiograms is the average hearing test change at 12 frequencies, in absolute dB for each individual.

With RA treatment in the "Imaging" subgroup, as shown in figure 3, repeat imaging found a high correlation between improvement for both arterial inflammation on imaging and hearing tests ($p<0.0003$).

Changes in each individual in their hearing test and SUV at 6 months are shown in figure 4. On average, there was a significant improvement for hearing ($p<0.0001$) and for FDG-PET/CT measurement ($p<0.0125$). Concordance between imaging and audiogram individual results was over 80%. All but 4 subjects had improvement or sustained hearing on testing over the 6 months with immunosuppression (82% improved). All subjects but 5 experienced reductions in inflammation measured in SUV units between baseline and 6 months (76% improved). Of the 5 subjects without improvement in inflammation by imaging, 3 of them had no improvement in hearing. The average change in SUV improved at the ascending aorta by 10% on average, by -0.378 (sd 0.73, CI -0.71 to -0.05).

Figure 4: Change in hearing and FDG-PET/CT at 6 months



Legend: Y axis indicates changes in atherosclerosis by FDG-PET/CT scan over 6 months vs X axis for changes in hearing in each individual. The average increase in hearing was 7% and SUV improved by 10%.

The majority of the 22 subjects improved by PET and hearing by 6 months. Results show that hearing can improve over time in these subjects with treatment of an underlying inflammatory disease. There were no changes to report for cardiac calcium scores nor changes in CIMT over the 6 months. There were no changes in word identification scores reflective of higher brain processing for any individual over the 6 months.

MACE results

In the "MACE" study of 320 RA subjects retrospectively reviewed over a 10 year period, 55% were Hispanic, 40% White-non Hispanic, 5% Asian, and 18% were male. All were over 50 years of age (average age 63.7, sd 9.1) with no prior CVD. The average BMI was 28.1 (sd 4.4, CI 26.3-30.1). Over 95% of these RA subjects were on methotrexate (a standard in our clinic), and while 30% were taking only MTX, it was used in combination therapy for 35% with tissue necrosis inhibitor (TNF), 28% with Janus kinase inhibitor (JAK), 4% with abatacept, 2% with rituximab, and 1% with an IL6 inhibitor. Over 80% were in good control (Clinical Disease Activity Index, CDAI <10). In this group of 320 older RA subjects, 10% used tobacco products, 60% took medication for hypertension, 38% took statin therapy, 20% were on diabetic medication, and none took chronic corticosteroids nor narcotic medication (oral prednisone and narcotics are not prescribed for RA in our institution). Audiograms showed 60% had normal hearing, and 25% had mild hearing impairment with an average measurement of 25 dB (9.1). In the 320 subjects without a MACE event, average hearing loss was 25 dB, and 60% of RA subjects in this age group had normal hearing.

Table 2 lists the characteristics of the 11 patients with MACE recorded in the 10 year observation period. All had more than 2 cardiovascular known risk factors and 85% were current or recent smokers. Only 10% of the overall group of 320 subjects were smokers. Tobacco use was clearly a major factor for MACE. Over half of these MACE outcomes occurred in men, despite the fact that RA patients are over 80% female. All had hypertension, all had elevated cholesterol, and 20% had diabetes mellitus. None were on MTX

alone for their RA therapy. Most were on a combination of MTX and JAK. All had hearing loss in excess of 40dB (range 40-70) at the time of the MACE event. The average measurement on the audiogram was 51.1 dB (8.4) which was significantly worse than the hearing loss in the 320 cohort as a whole ($p<0.001$.

Table 2 Characteristics of Subjects with MACE

Gender	Age	Hearing dB	Hx RA	MTX + Med	**Smoking**	Statin	HTN	AODM	Outcome
M	76	70	10 yr	IL6	**yes**	yes	yes	no	MI fatal
M	81	45	5 yr	JAK	no	yes	yes	no	CVA
M	69	50	5 yr	JAK	**yes**	yes	yes	yes	MI
M	51	50	10 yr	JAK	**yes**	yes	yes	no	MI
M	67	50	20 yr	JAK	no	yes	yes	no	MI
F	58	45	1 yr	TNF	**yes**	yes	yes	no	MI fatal
F	70	60	15 yr	TNF	**yes**	yes	yes	no	MI fatal
F	82	65	20 yr	JAK	**yes**	yes	yes	no	CVA fatal
F**	62	40	10 yr	JAK	**yes**	yes	yes	no	CABG
F**	57	45	20 yr	JAK	**yes**	yes	yes	no	stent
M**	73	55	15 yr	JAK	**yes**	yes	yes	no	CABG

Legend: Tumor necrosis factor (TNF), Janus kinase inhibitor (JAK), Interleukin-6 inhibitor (IL6)
*** These subjects were proactively referred to cardiology and a definitive procedure completed.

Discussion

The small exploratory "Imaging" study aimed to investigate whether inflammation in rheumatoid arthritis affects both vascular imaging and audiograms. These measurements did have a high correlation. Although the sample size is small, all the results consistently demonstrated a strong association between audiometry and PET imaging, even at the individual level. As shown in figure 4, concordance between imaging and audiogram measurement was over 80%. The aims of the study were to confirm the physiology that atherosclerosis is a key factor in hearing loss, and that hearing loss results might identify specific individuals at risk for cardiovascular disease, similar to the use of cholesterol tests for an individual. The "Imaging" study focused on the early phase of atherosclerosis, which is characterized by inflammation detected on PET imaging. PET has been used extensively to explore early atherosclerosis in heterozygous familial hypercholesterolemia (HeFH)[15], diabetes mellitus[16], and the general population.[17] PET scans provide insights into the pathophysiology of early plaque formation and inflammation.[11] Several studies have utilized PET imaging to observe arterial inflammatory changes over a period of six months or less, including investigations involving statin treatments or diabetes medications.[18,19,20] We propose that audiogram measurement may help track vascular inflammation.

When studying atherosclerosis over a six-month timeframe, it is essential to focus on a high-risk population prone to atherosclerotic disease. Numerous studies have established a correlation between systemic inflammation and atherosclerosis.[21] In the early stages of atherosclerotic lesions, immune cells are present, cytokines contribute to inflammation, and then platelets and macrophages begin arterial plaque formation. Therefore, controlling inflammation can potentially reduce atherosclerotic disease seen in patients with immune disorders.[22,23,24] It is worth noting that individuals with rheumatoid arthritis (RA) experience systemic inflammation, which increases their risk of cardiovascular disease (CVD).[5] Moreover, managing inflammation has been shown to decrease cardiovascular disease risk in the general population.[25] Rheumatoid arthritis is a suitable model to observe changes in inflammatory atherosclerosis within a six-month period.

Audiograms may function as a surrogate marker for systemic early atherosclerosis; hearing tests do not reflect only evaluation of the 8th cranial nerve, but reflect atherosclerotic disease in the temporal, parietal and frontal lobes.[26] Statin use has been shown to reduce the risk of CVD but also to reduce hearing loss by 11% in 70 year-olds from the general population.[27] Among diabetic subjects, statin use reduced hearing loss by 25% presumably by improving cerebral micro-circulation.[28]

Atherosclerosis compromise triggers neuro degeneration and results in hearing loss.[29] Many articles have explored the link between brain volume loss with hearing loss, and the link is consistent with circulatory small vessel damage.[30]

Historical data in previous studies have linked age-related hearing loss to increasing levels of atherosclerotic disease.[3,31,32] Studies have shown that hearing acuity decreases with age and correlates with atherosclerotic small vessel disease.[33] The first prospective study to report an association between measures of subclinical atherosclerosis and hearing loss was performed by the Beaver Dam study, comparing audiometry and ultrasound measurement of carotid intimal medial thickness (CIMT) in 1,984 subjects.[3] Nash also found in the Beaver Dam cohort that vascular disease assessed by examination of retinal vessels correlated with hearing loss.[34] In one cross- sectional study of 5,107 patients, cardiovascular disease was clearly associated with hearing loss.[35] Another cross sectional study in the elderly found that hearing impairment is related to cardiovascular disease with an odds ratio over 3.[2] In rheumatoid arthritis, subclinical atherosclerosis pathology was associated with hearing impairment in a group of 41 patients.[36] Methotrexate in RA improved inflammation and audiograms[1] just as statin use improved hearing acuity[27,28] and lessens inflammation[37] in the general population. These results suggest that audiometry can be used to track improvement and deterioration of both hearing and atherosclerosis. Audiograms might in the future substitute for PET imaging. Audiometry is an objective, reproducible, and inexpensive method of measurement widely available, and not influenced by local language or culture. Unique to the "Imaging"study is the finding that an individual hearing test correlates with that individual's degree of arterial inflammation. In the "MACE" study, a hearing test helped identify individuals at risk for cardiovascular damage.

The present "Imaging" study used the RA model, with audiograms, ultrasound measurement of carotid vasculature, arterial calcium scores, and PET scans at both baseline and at 6 months. The purpose of this subset of 22 subjects was to determine whether audiograms could be used to track early atherosclerosis. Both the audiograms and repeated PET scans demonstrated consistently concurrent results, demonstrating in a short duration study concurrent improvement in both atherosclerosis inflammation and hearing. The CIMT and Ca+ scores did not change presumably because these imaging techniques evaluate later phases of atherogenesis. Development of simple and reproducible measurements of early phase atherosclerosis to track disease can permit proactive actions and prevent MACE outcomes. In the long term observation in "MACE," most events were in men, nearly all were smokers, and all had significant hearing loss on audiograms. Earlier referral to cardiology once the audiogram demonstrates hearing loss over 30dB, may prevent myocardial infarction and stokes. In 3 of the 11 MACE subjects, early referral to cardiology based on their audiogram exams resulted in one elective stent procedure and 2 elective cardiac bypass grafts (CABG). (See Table 2) We hope to build on early referral for RA subjects before MACE in the future by acting on audiogram data.

Risk calculators are the current recommended tools for assessing CVD risk for primary prevention.[38,39,40] Multiple newer calculators include RA in the assessment[41,42] due to the established increased risk of CVD with active immune disease. All of the RA subjects with MACE had more than 2 cardiovascular known risk factors, but not every RA patient with baseline risk can reasonably be sent for PET imaging. The CT calcification scores and U/S measurements also missed the subjects with early inflammatory atherosclerosis. If the audiogram proves consistent with PET in larger studies, audiograms may factor into risk calculators. If a patient has a high cardiovascular risk score, more aggressive treatment for primary prevention could be considered such as adding a statin for lowering LDL below 70 and colchicine to suppress inflammation. Understanding that hearing loss is associated with cardiovascular disease may motivate a patient to follow recommendations regarding diet, exercise, and use of medications like a statin, anti-hypertensives, or colchicine. Hearing loss is a concrete concept that patients understand and thus may help increase compliance.

Limitations of the "Imaging" study are the small sample size. A sample size of 18-25 subjects provides a 90% chance that results are real with a 10% margin of error. The small sample size of 22 subjects precluded assessment of confounding factors for atherosclerosis, such as age, gender, diabetes mellitus, hypertension, and statin use, listed in Table 1. However, much larger cross-sectional studies have repeatedly confirmed the association of hearing loss with atherosclerosis, independent from hypertension, cholesterol, and diabetes.[34,43,44,45,46] While RA can cause hearing impairment independent of atherosclerotic disease (such as involvement of the stapes) these sequelae would not affect a 6 month study. Nearly all

subjects were in clinical control from RA inflammation with MTX or "MTX Plus."[7]

This was not a study comparing choice of RA therapy, but in the MACE group there was an over representation of treatment with JAK inhibitors, which are known to increase risk of CVD in RA patients over 50 years of age.[47,48,49] Realizing that a specific RA patient has hearing loss might therefore deter the use of JAK inhibitor in that patient, but further exploration of the use of audiometry in RA is needed. There is the limitation that all subjects were evaluated at a single center, balanced by the advantage of only one audiology technician and one radiologist, as well as providing a consistent approach to treatment for RA over many years. Methotrexate has been the stalwart choice used by 95% of the clinic RA patients and MTX is known to reduce morality in RA.[50,51] Of note these results in a unique population at high risk for early atherosclerosis may not be generalizable to the overall population. Larger trials are needed to assess if audiometry can provide an appropriate screening test for atherosclerosis in individuals in the general population. In the "Imaging" study, hearing loss greater than 30dB was associated with a PET SUV of 3.5 or greater, which indicates significant arterial inflammation. Such an individual might benefit from measures for primary prevention of CVD and may warrant a referral to a specialist. Since PET imaging has already been proposed as an independent prognostic marker of cardiovascular risk, these preliminary results suggest audiograms might be a cost-effective surrogate for PET scans.[52,53] The potential to evaluate hearing as a marker for atherosclerosis prospectively in large numbers might warrant adding audiograms to ongoing large studies of the general population.[54,55,56] Such large populations would provide proof of concept whether for example adding an audiogram to risk calculators would be significant, useful, and practical.[57]

Conclusion

The "Imaging" study showed a strong correlation between atherosclerosis inflammation and audiograms, at baseline and over time. The "MACE" study showed a strong correlation between hearing deficits and MACE. Hearing loss over 30 dB as a potential marker of atherosclerosis risk may influence choice of RA therapy, and increase patient compliance for preventive therapy of atherosclerosis, such as diet, exercise, statins, and anti-hypertension agents in an individual patient. Further research is needed to validate these findings prospectively in a larger number of patients. For the general population, future research may be useful to determine the significance of adding audiograms to identify specific individuals at risk for cardiovascular disease or to improve cardiovascular risk calculators.

Disclosure

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