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Inflammation as a mediator of the association between osteoporosis and hearing loss in older subjects: a population-based study

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Abstract. – OBJECTIVE: Due to the aging of populations, the prevalence of hearing loss and osteoporosis is increasing. Previous studies have found an association between these conditions. Nevertheless, the pathophysiologic pathway of such an association has not yet been established. The present study aimed at evaluating the association, if any, of hearing loss with osteoporosis in an older unselected population, and whether this association varied according to inflammatory status.

PATIENTS AND METHODS: We assessed the association of osteoporosis with a self-reported hearing loss in all 310 subjects aged 75+ living in Tuscania (Italy), without exclusion criteria. Bone density was assessed by calcaneal quantitative ultrasound; osteoporosis was defined as a T-score ≤ -2.5 Standard Deviation.

RESULTS: Hearing loss was associated with osteoporosis (OR = 1.84, 95% CI = 1.03-3.28; *p* = 0.40) in multivariable logistic regression analysis, after adjusting for potential confounders.

Analysis of the interaction term indicated that this association varied according to the erythrocyte sedimentation rate, ERS (*p* = 0.030), and high-sensitivity C reactive protein, hs-CRP (*p* = 0.017) but not sex (*p* = 0.832). Of notice, this association was significant only for higher levels of inflammatory parameters (OR = 2.82; 95% CI = 1.15-6.90; *p* = 0.023 for the higher ERS tertile; and OR = 3.81; 95% CI = 1.36-10.63; *p* = 0.011 for the higher hs-CRP tertile *vs.* lower tertiles).

CONCLUSIONS: Hearing loss is associated with osteoporosis in community dwelling elderly. Such an association seems to depend upon higher inflammation levels.

Key Words:
Hearing loss, Osteoporosis, Inflammation, Elderly, Epidemiology.

Introduction

Osteoporosis is a systemic disease which impairs functional ability, quality of life, and even the survival of older populations[1]. Hearing loss (HL) is as well a prevalent chronic, disabling condition affecting elderly people[2]. Several studies have reported an association between HL and osteoporosis[3-8]. Interestingly, some proinflammatory conditions have been associated with both osteoporosis and HL[9]. The aim of this study was to investigate the association between HL and osteoporosis in an unselected community dwelling older population, and whether this association might be mediated by inflammation.

Patients and Methods

Patients

The study involved all the subjects, without exclusion criteria, aged 75 or older who were living in Tuscania (Italy) on January 1st, 2004[10].

These participants had been enrolled in a national study on the genetic determinants of health status in six towns. Among 387 participants enrolled, we excluded 77 subjects with missing data for the study variables. None of the participants were on hormonal treatment during the survey. Six participants (1 men and 5 women) were treated with bisphosphonates; of these, two also received vitamin D.

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for expe-

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riments involving humans. The Institutional Review Board approved the protocol of the present study, and all patients provided written informed consent.

Measurement of Bone Mineral Density and Presence Of Osteoporosis

As the study enrolled the whole older population of the site, including homebound subjects, a portable instrument was used to assess bone density (Achilles Express, GE Medical Systems, Madison, WI, USA). This validated instrument measures bone density and structure using ultrasound densitometry. The T-score was automatically calculated according to current World Health Organization (WHO) recommendations[11]. According to the WHO guidelines, osteoporosis was diagnosed by a T-score value of -2.5 or lower. Intra-observer and interobserver correlation coefficients were 0.73 and 0.68, respectively.

Hearing Loss

HL was recorded during the study interview as a self-reported symptom using a questionnaire[12]. For the present analysis, HL was treated as a dichotomous variable according to the question: "Do you have any trouble in hearing?". Any presence of trouble, as well as deafness, was classified as HL.

Inflammatory Parameters

Blood samples were obtained after an overnight fast. The processed specimens were aliquoted into cryovials, frozen at -70°C and shipped to the Department of Experimental Pathology, University of Bologna, Italy. Levels of hs-CRP levels were determined using a high sensitivity enzyme-linked immunosorbent assay (ELISA) and colorimetric competitive immunoassay. The hs-CRP intra-assay coefficient of variation was 5.0%. Erythrocyte sedimentation rate (ESR) was immediately measured using a standard Westergren tube. The rate (in millimeters per hour) at the first hour was recorded.

Covariates

Education was expressed as years of school attendance. Smoking was considered as total lifetime pack years for current, as well as former smokers. Current alcohol consumption was considered for at least two drinks per week.

Nutritional parameters were assessed using a validated questionnaire, already adopted in large Italian populations[13].

Diagnoses were coded according to the International Classification of Diseases, ninth edition, Clinical Modification codes[14]. Drugs were coded according to the Anatomical Therapeutic and Chemical codes[15]. Physical activity was measured using the Physical Activity Scale for the Elderly questionnaire[16]. Cognitive performance was assessed using the Hodkinson Abbreviated Mental Test[17].

Functional ability was estimated using the Katz' activities of daily living (ADLs)[18]; Disability in the ADLs was defined as need of assistance for performing two or more ADLs[19].

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS for Mac version 20.0, 2011, SPSS Inc., Chicago, IL, USA). Differences were considered significant at the $p<0.05$ level. Data of continuous variables are presented as mean values ± standard deviation (SD) or medians and inter-quartile ranges when appropriate. Analysis of variance (ANOVA) for normally distributed variables was performed according to the presence of osteoporosis; otherwise, the nonparametric Mann-Whitney U test was adopted. The two-tailed Fisher exact test was used for dichotomous variables.

Multivariable logistic regression analysis was used to assess the association of osteoporosis, with age, sex, HL, and all those variables, which differed significantly ($p<0.050$) in univariate analysis. Abnormally distributed variables were analyzed after log transformation. Also, in logistic regression analysis, the interaction terms "HL*sex", "HL*hs-CRP" and "HL*ESR" were assessed.

Eventually, the logistic regression model was analyzed for increasing ERS and hs-CRP tertiles.

Results

Osteoporosis was found in 136 (44%) of 310 participants, while HL was reported by 143 (46%).

Participants with HL had lower ultrasound bone mineral density parameters as compared with others (T-score -2.6 (-3.4 – -1.3) *vs.* -1.7 (-2.9 – -0.78); p =.002; Stiffness Index 66 (55 – 82) *vs.* 75 (62 – 87); p=0.004). The prevalence of HL increased with decreasing tertiles of all bone mineral density parameters (Figure 1).

The main characteristics of participants according to osteoporosis is depicted in Table I.

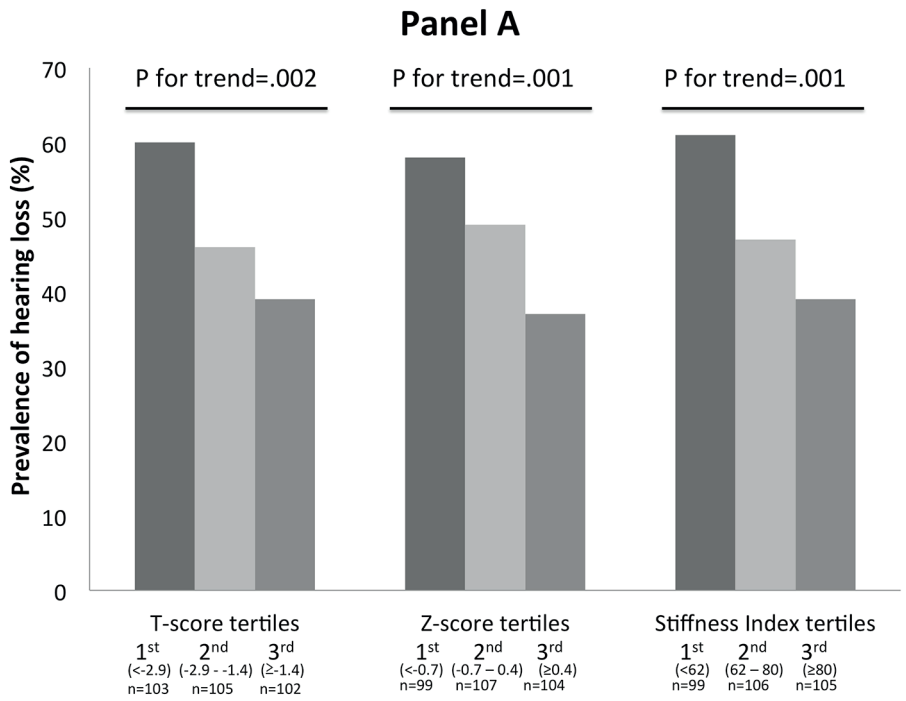

Figure 1. Prevalence of hearing loss according to tertiles of bone mineral density parameters.

Multivariable Analyses

In logistic regression, HL was associated with osteoporosis in the unadjusted model (OR=2.17; 95% CI=1.37-3.44; *p*=0.001), and after adjusting of age and sex (OR=2.02; 95% CI=1.20-3.41; *p*=0.008). The same association was found in the multivariable model (OR=1.84; 95% CI=1.03-3.28; *p*=0.040, Table II), adjusting for those variables which showed significant differences in univariate analyses (Table I). Analysis of the interaction term indicated that the association between HL and osteoporosis did not vary according to gender (*p*=0.832). However, the association varied according to ESR levels (*p*=0.030), and hs-CRP levels (*p*=0.017). Thus, the fully adjusted model was analyzed considering ESR, and hs-CRP tertiles, but not stratified by sex. When the same fully adjusted model was analyzed across increasing ESR tertiles, the association of HL with osteoporosis remained significant only in the higher ESR tertile (OR=2.82; 95% CI=1.15-6.90; *p*=0.023); no association was found in the medium (OR=2.13; 95% CI=0.73-6.19; *p*=0.165) nor in the lower ESR tertile (OR=1.17; 95% CI=0.48-2.94; *p*=0.733). Likewise, the association of HL with osteoporosis was significant only in the higher hs-CRP tertile (OR=3.81; 95% CI=1.36-10.63; *p*=0.011), while no significant association was found in the medium (OR=2.08; 95% CI=0.78-5.54; *p*=0.142), nor in the lower hs-CRP tertile (OR=0.86; 95% CI=0.36-2.06; *p*=0.728).

Discussion

Results of the present study indicate that HL is independently associated with increased probability of osteoporosis. This association might be mediated by subclinical inflammation.

Osteoporosis affects the whole skeletal system, including the temporal bone and the middle ear ossicles. Systemic bone reabsorption might be associated with involvement of the endosteal layer of the otic capsule[3], and demineralization of the cochlear capsule has been associated with HL[5]. Second, osteoporosis has been associated with low serum 25(OH)D levels[19], which has been linked with HL[3]. Third, dysfunction of ionic metabolism in patients with osteoporosis might be involved[3]. Fourth, osteoporosis might be involved in the mineral bone loss of the middle ear bones. Also, endothelial dysfunction might be associated with both osteoporosis and HL[4].

Eventually, inflammation might be involved both in the development of osteoporosis, and in

Table I. Characteristics of 310 participants aged 65, according to the diagnosis of osteoporosis.

	Participants with osteoporosis (n =136)	Participants without osteoporosis (n =174)	p
Demographics and lifestyle habits			
Age (years)	81 (5)	78 (5)	<0.0001
Gender (female)	109 (80)	80 (46)	<0.0001
Education (years)	4 (2-5)	5 (3-5)	0.145
Smoking[a]	881 (848-912)	538 (317-892)	0.410
Current alcohol consumption	81 (60)	128 (74)	0.013
Dairy products consumption[b]	14 (6)	13 (6)	0.433
Protein consumption[b]	8 (3)	10 (3)	0.005
Comorbid conditions			
Chronic pulmonary disease	36 (27)	37 (21)	0.283
Diabetes mellitus	23 (17)	39 (23)	0.254
Inflammatory bowel diseases	2 (1)	6 (3)	0.473
Heart failure	27 (20)	29 (17)	0.461
Renal disease	9 (7)	4 (3)	0.085
Stroke or Transient Ischemic Attack	24 (18)	18 (11)	0.067
Malignancy	11 (8)	16 (9)	0.840
Dysthyroidism	5 (4)	3 (2)	0.304
Systemic inflammatory diseases	8 (7)	9 (6)	0.999
Parkinson's disease	7 (5)	2 (1)	0.046
Hearing loss	77 (58)	66 (39)	0.001
Charlson comorbidity score index	2 (0-3)	1 (0-2)	0.045
Medications			
Neuroleptics	3 (2)	5 (3)	0.998
SSRI[c]	31 (23)	27 (15)	0.109
ARBs[d]	9 (7)	15 (9)	0.669
ACE-inhibitors	31 (23)	33 (19)	0.480
NSAIDS[e]	13 (10)	8 (5)	0.110
Loop diuretics	31 (23)	27 (16)	0.109
Antiepileptics	3 (2)	5 (3)	0.999
Allopurinol	3 (2)	6 (3)	0.736
Corticosteroids	7 (5)	5 (3)	0.378
Statins	14 (10)	17 (10)	0.999
Biohumoral parameters			
Serum creatinine (μmol/L)	88.40 (26.52)	88.40 (17.68)	0.206
Total proteins (g/L)	75 (7)	76 (5)	0.252
Serum calcium (mmol/L)	2.35 (0.13)	2.33 (0.13)	0.483
Hemoglobin (g/dL)	13.5 (3.5)	14.3 (1.5)	<0.0001
Total cholesterol (mmol/L)	5.46 (1.17)	5.57 (1.01)	0.484
Erythrocyte sedimentation rate (mm/h)	16 (10-30)	12 (6-20)	0.004
High-sensitivity C Reactive Protein (nmol/L)	3.05 (1.62-6.76)	2.86 (1.24-5.71)	0.029
Physical and cognitive performance			
Body Mass Index (kg/m^2)	27.4 (5.1)	28.6 (4.2)	0.023
Functional disability[f]	33 (25)	12 (7)	<0.0001
Hodkinson Abbreviated Mental Test	8 (6-9)	9 (7-10)	<0.0001
Physical Activity Scale for the Elderly	136 (57)	163 (59)	<0.0001

[a]Total lifetime pack years. [b]Servings per week. [c]Selective Serotonin Reuptake Inhibitor. [d]Angiotensin II Receptor Blockers. [e]Non steroidal antiflammatory drugs. [f]Defined as an Katz Activities of Daily Living <5.

the loss of auditory function. In keeping with this hypothesis, in our population, the association was significant only among participants with higher inflammation levels. Several proinflammatory cytokines promote bone loss by favoring osteoclast production, and inhibiting osteoblast differentiation[20]. Of notice, the main regulator of osteoclast differentiation is the receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL), which belongs to the tumor necrosis factor (TNF) family[20]. On the other hand, TNF-α affects microvascular tone and reduces cochlear blood flow[2]. Accordingly, increased RANKL expression has been observed in patients with

Table II. Association (Odds Ratios, OR, and 95 confidence intervals, CI) of osteoporosis with the variables of interest according to logistic regression analysis. All the covariates were entered simultaneously into the regression model.

	OR	95 CI	p
Age (each year)	1.08	1.01-1.15	0.023
Sex (female)	4.54	2.23-9.21	<0.0001
Current alcohol consumption	1.09	0.75-1.59	0.649
Protein consumption	0.98	0.90-1.06	0.613
Parkinson's disease	0.36	0.06-2.09	0.256
Charlson comorbidity score index	0.99	0.81-1.20	0.924
Hemoglobin (g/dL)	0.77	0.61-0.96	0.021
Body Mass Index	0.92	0.87-0.99	0.017
Functional disability[a]	2.26	0.79-6.50	0.129
Hodkinson Abbreviated Mental Test	1.06	0.89-1.25	0.516
Physical Activity Scale for the Elderly	0.93	0.87-0.98	0.013
Erythrocyte Sedimentation Rate (mm/h)	0.99	0.97-1.02	0.725
High-sensitivity C Reactive Protein (mg/dL)	1.02	0.91-1.14	0.736
Hearing loss	1.84	1.03-3.28	0.040

[a]Defined as an Katz Activities of Daily Living <5.

bone disorders, as well as in subjects with clinical atherosclerotic disease[20]. Reduced availability of osteoprotegerin, which acts as a decoy receptor for RANKL, has been associated with the development of osteoporosis, atherosclerosis and vascular calcification[20]. In addition, there is increasing evidence that the loss of cochlear cells is exacerbated by inflammation[21]. The direct action of infiltrating immune cell types and their cytokines, as well as reactive oxygen species (ROS) and cytokines generated by resident cochlear cells, lead to irreparable damage of hair cells and neurons[22].

In addition, in older subjects, increased markers of inflammation are associated with elevated hearing thresholds. In a cohort of elderly subjects, those with chronic inflammation had a nearly two-fold probability of developing hearing impairment over a 10 year period as compared with those with normal CRP levels[2].

The present work has been conducted in a whole, unselected Italian population of community-dwelling elderly, with comprehensive information regarding risk factors, comorbid conditions, medications and objective parameters. Nevertheless, due to its cross-sectional design, this study does not allow to ascertain any cause-effect relationships. Another limitation is the lack of measurement of serum parathormone and vitamin D levels. Also, bone mineral density was assessed by ultrasound bone densitometry, instead of Dual X-ray Absorptiometry (DXA). However, the latter technique would be hard to perform at a population level, particularly in homebound subjects. Nevertheless, a strong predictive association has been found between hip bone mineral density measured by DXA and quantitative ultrasound of calcaneus. Also, ultrasound-derived indices of BMD have been found to predict the risk of non-spinal fractures[23].

Eventually, HL was self-assessed, rather than objectively measured. Nevertheless, it has been proven that older subjects tend to underestimate their hearing impairment. This represents a conservative bias, which further supports our finding of an association between HL and osteoporosis.

Conclusions

HL is independently associated with osteoporosis in community dwelling elderly. Such an association seems to be limited to subjects with higher inflammation levels. Research is needed to verify this association in larger populations. Also, it should be assessed whether anti-inflammatory treatment, which has been proven effective against HL in Crohn's disease, might as well be useful in osteoporotic elderly with initial HL.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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