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Research Article

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Impaired Vestibular Function and Low Bone Mineral Density: Data from the Baltimore Longitudinal Study of Aging

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ABSTRACT

Animal studies have demonstrated that experimentally induced vestibular ablation leads to a decrease in bone mineral density, through mechanisms mediated by the sympathetic nervous system. Loss of bone mineral density is a common and potentially morbid condition that occurs with aging, and we sought to investigate whether vestibular loss is associated with low bone mineral density in older adults. We evaluated this question in a cross-sectional analysis of data from the Baltimore Longitudinal Study of Aging (BLSA), a large, prospective cohort study managed by the National Institute on Aging ($N = 389$). Vestibular function was assessed with cervical vestibular evoked myogenic potentials (cVEMPs), a measure of saccular function. Bone mineral density was assessed using dual-energy X-ray absorptiometry (DEXA). In two-way *t* test analysis, we observed that individuals with reduced vestibular physiologic function had significantly lower bone mineral density. In adjusted multivariate linear regression analyses, we observed that older individuals with reduced vestibular physiologic function had significantly lower bone mineral density, specifically in weight-bearing hip and lower extremity bones. These results suggest that the vestibular system may contribute to bone homeostasis in older adults, notably of the weight-bearing hip bones at greatest risk of osteoporotic fracture. Further longitudinal analysis of vestibular function and bone mineral density in humans is needed to characterize this relationship and investigate the potential confounding effect of physical activity.

Keywords: vestibular, bone mineral density, aging, osteoporosis

INTRODUCTION

Bone mineralization assessed by bone mineral density (BMD) declines with aging in all humans, although more rapidly in postmenopausal women than in men of the same age. An estimated 30 % of women over the age of 50 have osteopenia or osteoporosis. Low BMD is a risk factor for highly morbid outcomes including fall-related and spontaneous fractures (Greenspan 1994; Marshall et al. 1996). Female sex, menopause, low vitamin D and calcium levels, smoking and limited physical activity/weight-bearing exercise are known risk factors for accelerated decline of BMD, although they explain only a portion of the variability of BMD and rates of BMD decline across individuals (Kroger et al. 1994).

Recent studies in animals have found that experimentally induced loss of vestibular function leads to decreases in bone mineral density, possibly through effects mediated by the sympathetic nervous system (Levasseur et al. 2004; Denise et al. 2009; Vignaux et al. 2014; Vignaux et al. 2015). Although these

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studies reported no difference in physical activity between control and vestibular-deafferented mice, physical activity level may play an important role as a mediator and/or confounder of the association between vestibular function and BMD. A recent qualitative study found patients with vestibular impairments report decreased physical activity (Harun et al. 2016), while another study found decreased gait speed in older adults which may in part be due to changes in saccular function (Layman et al. 2015). The vestibular system is an evolutionarily ancient sensor of gravitational force, and it has been hypothesized that vestibular input is essential for the development of appropriate bone architecture in the direction of gravity (Vignaux et al. 2013; Vignaux et al. 2015). In addition, there is evidence that spinal scoliosis and other disorders of postural alignment are often accompanied by impaired vestibular function in both animals and humans (Lambert et al. 2013). A recent epidemiologic study from the National Health and Nutrition Examination Survey observed an association between lower bone mineral density and poorer performance on the modified Romberg test, a postural metric that estimates vestibular function (Mendy et al. 2014). Given that vestibular function and bone mineral density both decline with age (Peterka et al. 1990; Welgampola and Colebatch 2001; Baloh et al. 2001; Agrawal et al. 2009), we sought to evaluate whether a relationship exists between vestibular loss and reduced bone mineral density that occurs with age.

In this study, we used data from the Baltimore Longitudinal Study of Aging (BLSA) to explore the association between vestibular function and bone mineral density in older adults. Our analysis consists of a cross-sectional cohort of healthy older adults in which rigorous physiologic tests of vestibular function and bone mineral density are conducted. We hypothesized that older individuals with reduced vestibular function have lower bone mineral density relative to older individuals with preserved levels of vestibular function. This study provides insight into potential pathophysiological mechanisms by which loss of bone mineral density occurs with aging.

METHODS

BLSA Sample

The BLSA is a prospective cohort study of volunteers aged 21–103 in the National Institute on Aging Clinical Research Unit at Harbor Hospital in Baltimore, MD. Volunteer participants from the community are enrolled in the study if they pass a health and functional screening. Following enrollment in the study, participants return to the BLSA for extensive testing every 1–4 years, depending on age. Further details on the BLSA have been published previously (Shock et al. 1984). This study evaluated a cross-sectional sample of BLSA participants who underwent vestibular testing and dual-energy X-ray absorptiometry (DEXA) testing. Vestibular function tests were added to the BLSA in February 2013, and the present analysis includes visits through December 2014. In our sample, 17 participants had two visits to the BLSA; we analyzed data only from the more recent visit. All participants provided written informed consent, and the BLSA study protocol was approved by the NIEHS Institutional Review Board (North Carolina).

BLSA Vestibular Function Tests. Quantitative vestibular physiologic tests were added to the BLSA test battery in February 2013. We specifically considered the function of the saccule, the vestibular end-organ responsible for measuring gravitational force, given that hypothesized mechanisms for the association between vestibular function and bone mineral density involve the vestibular perception of gravity. The cervical vestibular-evoked myogenic potential (cVEMP) test measures saccular function, and testing methods have been published in detail previously and are discussed briefly here (Nguyen et al. 2010; Li et al. 2014). Participants sat on a chair inclined at 30° from the horizontal. Trained examiners placed recording electromyographic electrodes on the sternocleidomastoid muscles and at the sternoclavicular junction bilaterally, and a ground electrode was placed on the manubrium sterni. Sound stimuli consisted of 500 Hz, 125-dB SPL tone bursts delivered monaurally via headphones. The presence or absence of cVEMP responses was recorded for each ear, as indicative of normal or impaired saccular function, respectively. Since vestibular testing started in February 2013, 389 individuals have undergone cVEMP and bone mineral density testing. Of these, 96 (25 %) had absent cVEMP responses bilaterally, indicating globally reduced saccular function.

BLSA Bone Mineral Density Measurement and Osteoporosis Ascertainment. Bone mineral density was measured by trained examiners. Measurements (in g/cm^2) of the femoral neck, femoral trochanter (which articulates with the hip), femoral shaft, hip, legs, arms, ribs, spine, trunk, head, and total body were made by dual-energy X-ray absorptiometry using the Lunar Prodigy Scanner. Right and left bone mineral density were averaged when measurements were available bilaterally, consistent with prior reports from the BLSA (Canepa et al. 2014). Osteopenia was defined as a DEXA T-score less than −1.0 in the femoral neck, trochanter, shaft, or hip. Similarly, osteoporosis was defined as a DEXA T-score less than −2.5 in the femoral neck, trochanter, shaft, or hip. Participants were also asked by trained interviewers in the medical history questionnaire if a physician has ever diagnosed them with osteoporosis.

BLSA Sociodemographic and Health-Related Covariates. Demographic information, smoking history, and physical activity level were collected from extensive participant interviews. Participants were grouped into three race categories: white, black, or other. History of smoking was ascertained by asking participants "Have you smoked at least 100 cigarettes over your entire life," "Have you smoked at least 50 cigars over your entire life," and "Have you smoked at least 3 packages of pipe tobacco over your entire life"; an affirmative answer to any of these questions constituted a positive smoking history. One participant had missing smoking data. Subjective physical activity was ascertained by a series of questions asking if individuals had done different activities in the previous 2 weeks. Individuals with a positive response to questions about weight training or vigorous physical activity in the previous 2 weeks were considered subjectively physically active. Four participants had missing subjective physical activity data.

Given the potential intermediary link of autonomic function and BMD we sought proxy variables to account for autonomic functional status. The presence or absence of orthostatic hypotension was defined as a decrease of 20 or more mmHg systolic blood pressure or 10 or more mmHg diastolic blood pressure at measurement 3 minutes after postural change from supine to standing (Robertson 2008). Diabetic neuropathy may also serve as a proxy for autonomic function. As a proxy variable for diabetic neuropathy, we used proprioception threshold, measured by proprioceptive threshold testing equipment designed and built for the BLSA. Detailed methods are available elsewhere (Ko et al. 2015). Sixty-six individuals did not complete proprioception testing (due to time constraints, equipment malfunction, tester availability, or participant refusal). Audiometry was performed by trained examiners in a sound-proof booth using headphones. Pure tone averages (PTAs) were calculated based on the mean of the audiometric thresholds at 500, 1000, 2000, and 4000 Hz in the better hearing ear. Sixty-two participants had missing audiometric data due to cerumen impaction. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Statistical Analysis

Student's t -test was used to analyze the association between vestibular function and bone mineral density. To further characterize the relationship and attempt to account for potential confounders, multivariate linear regression models were utilized. Multivariable linear regression models provide β coefficients, which are measures of association between the independent variable (e.g., vestibular function) and the dependent variable (e.g., femoral neck BMD). The basic model for linear regression is $Y_i = \beta_0 + \beta_1 x_{i1} + \ldots \beta_n x_{in} + \varepsilon_i$, where Y_i is the dependent variable, β_0 is the intercept, x_{in} are the dependent variables, β_n are the parameters to be estimated, and ε_i represents an error term. A β coefficient greater than 0 indicates that increases in independent variable x are associated with increases in dependent variable Y. If the 95 % confidence interval (CI) for the β coefficient crosses 0, this indicates that the β coefficient is not statistically significantly different from 0 at a p value of 0.05. We used two different multivariable linear regression models to explore the contribution of potential confounding variables. Model 1 was adjusted for age, gender, and race, while model 2 was adjusted for age, gender, race, body mass index (BMI), smoking history, and subjective physical activity, as these additional variables have been shown to impact bone mineral density. We additionally added proxy variables for autonomic nervous system function (orthostatic hypotension and proprioception threshold) to model 2 to determine if these variables are significant mediators of the relationship between vestibular function and BMD. We then performed a separate analysis adding PTA to model 2. Multivariable logistic regression analysis using model 1 and model 2 was performed to analyze the association between DEXA-defined and physician-reported osteopenia or osteoporosis. Logistic regression yields an odds ratio (OR); an OR >1 indicates an increased odds of the outcome. Whereas an OR <1 indicates a decreased odd of the outcome, ORs with 95 % confidence intervals crossing one are not statistically significant at a p value of 0.05. All analyses were performed using STATA version 13 (College Station, TX, USA).

RESULTS

Characteristics of BLSA Sample

Demographic characteristics of the 389 individuals with vestibular function data in the Baltimore Longitudinal Study of Aging are shown in Table 1. Mean (SD) age was 71.5 years (13.3), and 56 % of participants were female. Caucasian individuals comprised 65 % of the sample, African Americans 27 %, and other races 8 %. Mean (SD) BMI was 27.0 kg/m^2 (4.7). A positive smoking history was reported by 40 % of individuals. Sixty-one percent reported engaging in subjective physical activity. Vestibular dysfunction defined as bilaterally absent cVEMP responses was present in 25 % of participants. Twenty-two percent of participants reported having been diagnosed with osteoporosis by a physician.

TABLE 1

Demographic characteristics and vestibular function at the Baltimore Longitudinal Study of Aging 2013–2015

Age (mean years)	*71.5 (SD 13.3)*
Sex	
Male	44 %
Female	56 %
Race	
White	65 %
African American	27 %
Other	8 %
Smoking history	
Yes	40 %
No	60 %
Physical activity	
Yes	61 %
No	39 %
Vestibular saccular function	
Normal	75 %
Absent	25 %
Physician diagnosed osteoporosis	22 %
Osteopenia (*T* less than −1.0)	33 %
Osteoporosis (*T* less than or equal to −2.5)	2 %

Smoking history—100 or more lifetime cigarettes. Physical activity—weight training or vigorous exercise in the past 2 weeks. Vestibular saccular function measured by cervical vestibular evoked myogenic potentials, abnormal defined as bilateral absence. $n = 389$

Two-Way Analyses

Results of two-way Student's t - tests of bone mineral density and vestibular function are shown in Table 2. Bone mineral density was significantly lower in individuals with impaired vestibular saccular function in all areas measured, with the exception of the spine and head.

Regression Analyses

Multivariate linear regression analyses was used to assess the differences in bone mineral density between individuals with impaired vestibular saccular function and those with retained vestibular function after adjusting for potential confounders. Model 1, adjusted for age, sex, and race, demonstrated significantly lower BMD in individuals with vestibular loss at the femoral trochanter, femoral shaft, and hip. The association between vestibular loss and femoral neck BMD was not statistically significant. See Table 3 for a complete list of β coefficients, 95 % confidence intervals, and p values. Vestibular loss was not associated with changes in BMD in the legs, arms, ribs, spine, trunk, head, or overall bone mineral density. Model 2, adjusted for age, sex, race, BMI, smoking history, and subjective physical activity, similarly demonstrated that individuals with vestibular loss had significantly lower BMD at the femoral trochanter, shaft, and hip, without significant associations at the femoral neck. Vestibular loss was not significantly associated with bone mineral density in other bone segments of the body (Table 3). In supplementary analyses, orthostatic intolerance and proprioception were added as proxy variables for autonomic function; the relationship between vestibular function and BMD was not substantially altered (data not shown). PTA hearing thresholds were added to the model 2 regression, which resulted in neither vestibular function nor PTA being significantly associated with BMD. Notably, there was collinearity between PTA and other variables in the model, including cVEMP (data not shown).

TABLE 2

Bone mineral density and vestibular saccular function in unadjusted analysis, Baltimore Longitudinal Study of Aging 2013–2015

	Vestibular saccular function		
	Preserved	*Absent*	*p**
Hip and lower extremity bone mineral density (g/cm^2)			
Femoral Neck	0.911	0.841	0.0001
Trochanter	0.831	0.766	0.0008
Shaft	1.160	1.068	0.0002
Hip	0.989	0.911	0.0001
Legs	1.269	1.191	0.0004
Head, trunk, and upper extremity bone mineral density (g/cm^2)			
Arms	0.883	0.826	0.0006
Ribs	0.676	0.645	0.0080
Spine	1.129	1.091	0.1250
Trunk	0.944	0.908	0.0151
Head	2.161	2.122	0.2782
Total	1.178	1.128	0.0014

Vestibular saccular function measured by cervical vestibular evoked myogenic potentials, abnormal defined as bilateral absence. Bone mineral density assessed by DEXA

*Student's t test, $N = 389$

There was no significant association between vestibular function and self-reported doctor diagnosed osteoporosis in this cohort in model 1 (OR 1.07, 95 % CI 0.60–1.91, $p = 0.820$, $n = 389$) or model 2 (OR 1.05, 95 % CI 0.58–1.90, $p = 0.874$, $n = 385$). Similarly, DEXA-defined osteopenia was not associated with vestibular function in model 1 (OR 0.99, 95 % CI 0.57–1.73, $p = 0.977$, $n = 389$) or model 2 (OR 0.94, 95 % CI 0.54–1.66, $p = 0.841$, $n = 385$). DEXA-defined osteoporosis was also not associated with vestibular function in model 1 (OR 3.07, 95 % CI 0.43–21.66, $p = 0.261$, $n = 389$) or model 2 (OR 3.58, 95 % CI 0.48–26.72, $p = 0.214$, $n = 385$).

DISCUSSION

In this analysis, we observed that older individuals with vestibular loss had significantly lower bone mineral density relative to older adults with preserved levels of vestibular function. These results are consistent with an emerging body of animal literature demonstrating that experimentally induced lesions of vestibular system cause a subsequent loss of bone mineral density (Denise et al. 2009; Vignaux et al. 2013; Vignaux et al. 2014).

Some lines of evidence suggest that vestibular contributions to the sympathetic nervous system explain the association between poor vestibular function and impaired bone metabolism leading to bone loss. The vestibular system sends projections to autonomic nervous system centers including brainstem medullary and pontine nuclei (Balaban 1999; Luxon and Pagarkar 2013; Holstein et al. 2014). Moreover, the effect of vestibular ablation on bone mineral density seen in rats was abrogated by the concurrent administration of a sympathetic antagonist and in beta receptor knockout mice (Denise et al. 2009; Vignaux et al. 2013; Vignaux et al. 2014; Vignaux et al. 2015). Interestingly, the changes in bone mineral density following vestibular lesion in rodents were limited to the weight-bearing lower extremity bones (Levasseur et al. 2004; Denise et al. 2009; Vignaux et al. 2013; Vignaux et al. 2014). To characterize the impact of the autonomic nervous system on the relationship between vestibular function and BMD using our data, we included orthostatic hypotension and proprioception as proxy variables for autonomic function. Notably, the inclusion of both variables did not substantially alter the relationship between vestibular function and BMD in our models (data not shown). However, orthostatic hypotension and ankle proprioception are both incomplete proxy measures of autonomic function and further study is required to better characterize the relationship between vestibular function, autonomic function, and BMD. The co-occurrence of vestibular and hearing abnormalities has been previously identified (Rosengren and Colebatch 2006; Zuniga et al. 2012). Our study aim was to evaluate the association between cVEMP and BMD, and while we added hearing to our regression model in a supplementary analysis, sample

TABLE 3
Multiple linear regression of bone mineral density and vestibular function: Baltimore Longitudinal Study of Aging 2013–2015

	Model 1 (n = 389)			*Model 2 (n = 385)*		
	cVEMP absent			*cVEMP absent*		
	β	*(95 % CI)*	*p*	*β*	*(95 % CI)*	*p*
Hip and lower extremity bone mineral density						
Femoral neck	−0.031	(−0.065 to 0.002)	0.067	−0.027	(−0.061 to 0.005)	0.092
Trochanter	*−0.038*	*(−0.074 to −0.003)*	*0.033*	*−0.034*	*(−0.067 to −0.0004)*	*0.047*
Shaft	*−0.048*	*(−0.094 to −0.002)*	*0.042*	*−0.044*	*(−0.088 to −0.001)*	*0.046*
Hip	*−0.041*	*(−0.079 to −0.004)*	*0.032*	*−0.037*	*(−0.072 to −0.002)*	*0.041*
Legs	−0.026	(−0.059 to 0.007)	0.129	−0.021	(−0.053 to 0.010)	0.187
Head, trunk, and upper extremity bone mineral density						
Arms	−0.015	(−0.039 to 0.010)	0.241	−0.012	(−0.034 to 0.010)	0.278
Ribs	−0.0048	(−0.024 to 0.014)	0.617	−0.0028	(−0.019 to 0.014)	0.733
Spine	−0.0069	(−0.049 to 0.036)	0.751	−0.001	(−0.039 to 0.037)	0.958
Trunk	−0.0076	(−0.033 to 0.017)	0.550	−0.0032	(−0.025 to 0.018)	0.765
Head	0.0067	(−0.063 to 0.076)	0.850	0.0064	(−0.063 to 0.075)	0.857
Total	−0.013	(−0.039 to 0.013)	0.313	−0.010	(−0.034 to 0.014)	0.410

Model 1 adjusted for age, sex, and race. Model 2 adjusted for age, sex, race, body mass index, smoking, and subjective physical activity. Vestibular saccular function measured by cervical vestibular evoked myogenic potentials, abnormal defined as bilateral absence. β coefficient <0 indicates that absent cVEMP is associated with lower bone mineral density

CI confidence interval

Crossing 0 indicates $p > 0.05$ (italicized for clarity)

size restriction and collinearity of hearing with other variables in the model limited the value of this analysis. Our study is insufficient to disentangle the joint relationship between vestibular loss, hearing loss, and BMD.

Another potential mechanism to explain the link between vestibular loss and reduced bone density is a change in physical activity, given the known impacts of physical activity on bone density (Maïmoun and Sultan 2011; Vignaux et al. 2013; Vignaux et al. 2014). However, the data supporting this mechanism are equivocal. The animal studies described previously found no significant differences in physical activity levels between rats with and without vestibular lesions, although it is conceivable that differences in physical activity could have contributed to the differences in BMD in these animal studies. In humans, vestibular function was found to be associated with gait speed in older adults (Layman et al. 2015), and qualitative studies have suggested individuals with vestibular dysfunction limit their physical activity because of their condition (Harun et al. 2016). A population-based study found an association between self-reported dizziness/imbalance and lower physical activity in older adults, although dizziness/imbalance may reflect other impairments in addition to the vestibular system (Kollén et al. 2016). In the current study, we attempted to account for physical activity as a confounder by including a subjective physical activity variable in model 2. The significant association between vestibular function and BMD did not substantially change with the inclusion of subjective physical activity, but it should be noted that subjective self-reported measures of physical activity have been shown to be inaccurate and may not capture true differences in physical activity (Troiano et al. 2008). The subjective physical activity variable was itself not associated with BMD, providing further evidence that it is a poor measure of true physical activity, given the known association between activity and BMD (Maïmoun and Sultan 2011). Our data, in combination with the previous work in the animal literature, are not sufficient to disentangle the complex relationship between vestibular function, physical activity, and BMD, and future research is needed in this area.

The present study focuses on the function of the saccule, the organ within the vestibular system responsible for detecting gravitational sensory information. Studies of the effects of microgravity environments (e.g., outer space) in which saccular inputs are temporarily altered are consistent with our findings. These studies have shown that astronauts' bone mineral density decreases with increased time spent in microgravity, despite attempts to prevent bone loss with physical activity and resistance training (Cavanagh et al. 2005; LeBlanc et al. 2007). A more recent study examined the BMD of astronauts using a new high resistance exercise regimen while in microgravity, and the addition of a bisphosphonate drug to the high resistance exercise. Although exercise alone did not significantly prevent BMD loss, the combined regimen significantly reduced BMD loss during space flight (Leblanc et al. 2013). This study suggests a complex relationship between physical activity, vestibular impairment, and BMD. Drawing conclusions about the effect of vestibular impairment from the space medicine literature is difficult due to the numerous potential confounders inherent to the complex nature of space flight and microgravity.

Previous human studies of vestibular function and bone mineral density in normal gravity environments are limited. One study analyzed data from 5438 adults in the National Health and Nutrition Examination Survey and found individuals with low BMD were more likely to fail the modified eyes closed Romberg on foam, a balance test considered to be an indicator of vestibular function because it alters proprioceptive sensory information and eliminates visual cues (Mendy et al. 2014). Mendy et al. hypothesized that the low bone mineral density altered temporal bone anatomy and caused impaired vestibular function, although their data found an association between vestibular function and total BMD, but not head BMD (Mendy et al. 2014). Another study, examining postural metrics and BMD in 220 postmenopausal women, found no association between postural balance and BMD, although the postural balance testing was done with eyes open and would therefore not be a meaningful assessment of vestibular function (Cangussu et al. 2012). Prior studies link several molecules, including fetuin A and osteopontin, to sympathetic regulation of BMD (Nagao et al. 2011; Fodor et al. 2013). One study found these molecules could influence calcite crystal deposition and nucleation in vitro (Hong et al. 2015), while another study found no otoconial deficits or impairments in balance in osteopontin knockout mice (Zhao et al. 2008). It is possible that upstream sympathetic disturbances could impact both BMD and otoconia via fetuin A, ostopontin, and other similar molecules, which would be consistent with Mendy's hypothesis that changes in BMD influenced vestibular function. However, based on the experimental animal studies demonstrating a decreased lower extremity BMD following vestibular loss, the osteopontin knockout mouse study demonstrating no changes in otoconia or balance phenotype, and the present study, which demonstrated lower BMD in the femur and hip among older adults with vestibular impairment, we believe the vestibular dysfunction contributes to decreased BMD and not the converse, although future longitudinal studies are needed to better understand the relationship between vestibular impairment, the sympathetic nervous system, osteopontin, and BMD in older adults.

In our study, we did not find a significant relationship between vestibular function and physician diagnosed or DEXA defined osteopenia or osteoporosis. This suggests that the association between vestibular function and BMD may be subtle and not sufficient to cause clinically significant osteoporosis. There is also a bias introduced by the study population—BLSA participants are healthier and more health-conscious than the general population.

Our study has several important limitations. Our ability to make causal inferences is limited by the cross-sectional nature of the BLSA data. We employed adjusted linear regressions using several models, although acknowledge the possibility of residual and unmeasured confounding. Moreover, a limitation of the BLSA data is that participants are healthier than the general population, which limits the external validity of the findings.

Our study provides support for a relationship between vestibular loss and reduced bone mineral density in older adults. Specifically, vestibular loss is associated with bone mineral density in the weight-bearing hip and lower extremity bones. Lower bone mineral density is associated with poor outcomes in older individuals, including hip fractures and death (Greenspan 1994; Marshall et al. 1996). Further extended longitudinal studies are needed to clarify whether these associations are causal, the role of sympathetic activity and/or physical activity mediating the association, and to determine whether treating vestibular loss through vestibular therapy may forestall changes in bone mineral density and the associated sequelae in older individuals.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors declare that they have no conflict of interest.

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REFERENCES

Agrawal Y, Carey JP, Della-Santina CC, Schubert MC, Minor LB (2009) Disorders of balance and vestibular function in US adults: data from the National Health and nutrition examination survey, 2001-2004. Arch Intern Med 169:938–944. doi:10.1001/archinternmed.2009.66

Balaban CD (1999) Vestibular autonomic regulation (including motion sickness and the mechanism of vomiting). Curr Opin Neurol 12:29–33

Baloh RW, Enrietto J, Jacobson KM, Lin A (2001) Age-related changes in vestibular function: a longitudinal study. Ann N Y Acad Sci 942:210–219

Canepa M, Ameri P, AlGhatrif M, et al. (2014) Role of bone mineral density in the inverse relationship between body size and aortic calcification: results from the Baltimore longitudinal study of aging. Atherosclerosis 235:169–175. doi:10.1016/j.atherosclerosis.2014.04.018

Cangussu LM, Nahas-Neto J, Petri-Nahas EA, Rodrigues-Barral ABC, de Buttros DA, Uemura G (2012) Evaluation of postural balance in postmenopausal women and its relationship with bone mineral density–a cross sectional study. BMC Musculoskelet Disord 13:2. doi:10.1186/1471-2474-13-2.

Cavanagh PR, Licata AA, Rice AJ (2005) Exercise and pharmacological countermeasures for bone loss during long duration space flight. Gravitational Sp Res 18

Denise P, Besnard S, Vignaux G, et al. (2009) Sympathetic B antagonist prevents bone mineral density decrease induced by labyrinthectomy. Aviakosm Ekolog Med 43:36–38

Fodor D, Bondor C, Albu A, Simon S, Craciun A, Muntean L (2013) The value of osteopontin in the assessment of bone mineral density status in postmenopausal women. J Investig Med 61:15–21. doi:10.2310/JIM.0b013e3182761264

Greenspan SL (1994) Fall severity and bone mineral density as risk factors for hip fracture in ambulatory elderly. JAMA 271:128. doi:10.1001/jama.1994.03510260060029

Harun A, Li C, Bridges JFP, Agrawal Y (2016) Understanding the experience of age-related vestibular loss in older individuals: a qualitative study. Patient. doi:10.1007/s40271-015-0156-6

Holstein GR, Friedrich VL, Martinelli GP (2014) Projection neurons of the vestibulo-sympathetic reflex pathway. J Comp Neurol 522:2053–2074. doi:10.1002/cne.23517

Hong M, Moreland KT, Chen J, Teng HH, Thalmann R, De Yoreo JJ (2015) Effect of otoconial proteins fetuin A, osteopontin, and otoconin 90 on the nucleation and growth of calcite. Cryst Growth Des 15:129–136. doi:10.1021/cg501001r

Ko S-U, Simonsick E, Deshpande N, Ferrucci L (2015) Sex-specific age associations of ankle proprioception test performance in older adults: results from the Baltimore longitudinal study of aging. Age Ageing: afv005–. doi: 10.1093/ageing/afv005

Kollén L, Hörder H, Möller C, Frändin K (2016) Physical functioning in older persons with dizziness: a population-based study. Aging Clin Exp Res. doi:10.1007/s40520-016-0567-9

Kroger H, Tuppurainen M, Honkanen R, Alhava E, Saarikoski S (1994) Bone mineral density and risk factors for osteoporosis? A population-based study of 1600 perimenopausal women. Calcif Tissue Int 55:1–7. doi:10.1007/BF00310160

Lambert FM, Malinvaud D, Gratacap M, Straka H, Vidal P-P (2013) Restricted neural plasticity in vestibulospinal pathways after unilateral labyrinthectomy as the origin for scoliotic deformations. J Neurosci 33:6845–6856. doi:10.1523/JNEUROSCI.4842-12.2013

Layman AJ, Li C, Simonsick E, Ferrucci L, Carey JP, Agrawal Y (2015) Association between saccular function and gait speed: data from the Baltimore longitudinal study of aging. Otol Neurotol. doi:10.1097/MAO.0000000000000544.

Leblanc A, Matsumoto T, Jones J, et al. (2013) Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight. Osteoporos Int 24:2105–2114. doi:10.1007/s00198-012-2243-z

LeBlanc AD, Spector ER, Evans HJ, Sibonga JD (2007) Skeletal responses to space flight and the bed rest analog: a review. J Musculoskelet Nueronal Interact 7:33–47

Levasseur R, Sabatier JP, Etard O, Denise P, Reber A (2004) Labyrinthectomy decreases bone mineral density in the femoral metaphysis in rats. J Vestib Res 14:361–365

Li C, Zuniga MG, Nguyen KD, Carey JP, Agrawal Y (2014) How to interpret latencies of cervical and ocular vestibular-evoked myogenic potentials: our experience in fifty-three participants. Clin Otolaryngol. doi:10.1111/coa.12277

Luxon L, Pagarkar W (2013) Autonomic failure: a textbook of clinical disorders of the autonomic nervous system. Oxford University Press, Oxford

Maïmoun L, Sultan C (2011) Effects of physical activity on bone remodeling. Metabolism 60:373–388. doi:10.1016/j.metabol.2010.03.001

Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312:1254–1259. doi:10.1136/bmj.312.7041.1254

Mendy A, Vieira ER, Albatineh AN, Nnadi AK, Lowry D, Gasana J (2014) Low bone mineral density is associated with balance and hearing impairments. Ann Epidemiol 24:58–62. doi:10.1016/j.annepidem.2013.10.012

Nagao M, Feinstein TN, Ezura Y, et al. (2011) Sympathetic control of bone mass regulated by osteopontin. Proc Natl Acad Sci U S A 108:17767–17772. doi:10.1073/pnas.1109402108

Nguyen KD, Welgampola MS, Carey JP (2010) Test-retest reliability and age-related characteristics of the ocular and cervical vestibular evoked myogenic potential tests. Otol Neurotol 31:793–802. doi:10.1097/MAO.0b013e3181e3d60e

Peterka RJ, Black FO, Schoenhoff MB (1990) Age-related changes in human vestibulo-ocular and optokinetic reflexes: pseudorandom rotation tests. J Vestib Res 1:61–71

Robertson D (2008) The pathophysiology and diagnosis of orthostatic hypotension. Clin Auton Res 18(Suppl 1):2–7. doi:10.1007/s10286-007-1004-0

Rosengren SM, Colebatch JG (2006) Vestibular evoked potentials (VsEPs) in patients with severe to profound bilateral hearing loss. Clin Neurophysiol 117:1145–1153. doi:10.1016/j.clinph.2005.12.026

Shock NW, Greulich RC, Costa PT, Jr., Andres R, Lakatta EG, Arenberg D, Tobin JD (1984) Normal human aging: the Baltimore longitudinal study of aging. NIH Publication, Washington, D.C.

Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M (2008) Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 40:181–188. doi:10.1249/mss.0b013e31815a51b3

Vignaux G, Besnard S, Denise P, Elefteriou F (2015) The vestibular system: a newly identified regulator of bone homeostasis acting through the sympathetic nervous system. Curr Osteoporos Rep. doi:10.1007/s11914-015-0271-2

Vignaux G, Besnard S, Ndong J, Philoxène B, Denise P, Elefteriou F (2013) Bone remodeling is regulated by inner ear vestibular signals. J Bone Miner Res 28:2136–2144. doi:10.1002/jbmr.1940

Vignaux G, Ndong J, Perrien D, Elefteriou F (2014) Inner ear vestibular signals regulate bone remodeling via the sympathetic nervous system. J Bone Miner Res. doi:10.1002/jbmr.2426

Welgampola MS, Colebatch JG (2001) Vestibulocollic reflexes: normal values and the effect of age. Clin Neurophysiol 112:1971–1979. doi:10.1016/S1388-2457(01)00645-9

Zhao X, Jones SM, Thoreson WB, Lundberg YW (2008) Osteopontin is not critical for otoconia formation or balance function. J Assoc Res Otolaryngol 9:191–201. doi:10.1007/s10162-008-0117-z

Zuniga MG, Dinkes RE, Davalos-Bichara M, et al. (2012) Association between hearing loss and saccular dysfunction in older individuals. Otol Neurotol 33:1586–1592. doi:10.1097/MAO.0b013e31826bedbc