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Otolith Deterioration: Factors Affecting Microvascular and Structural Integrity

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Background and Purpose Otoliths degenerate with aging, but the underlying factors are not well understood. We aimed to identify risk factors associated with otolith function in patients with dizziness and vertigo.

Methods This cross-sectional study analyzed 624 patients with benign paroxysmal positional vertigo, benign recurrent vertigo, or persistent postural-perceptual dizziness who presented at a tertiary referral center between March 2017 and July 2021. Otolith function was assessed using summated amplitudes of cervical and ocular vestibular evoked myogenic potentials (SA-cVEMPs and SA-oVEMPs). The relationships between otolith function and potential risk factors were analyzed using two types of generalized linear model: a zero-adjusted gamma model for SA-cVEMPs and a standard gamma model for SA-oVEMPs.

Results In the multivariable model, SA-cVEMP was negatively associated with age (β=-0.012, effect=-1.23%), female sex (β=-0.110, effect=-10.42%), and free thyroxine (β=-0.298, effect=-25.74%), and positively associated with high-density lipoprotein cholesterol (β=0.005, effect=0.46%). SA-oVEMP was negatively associated with age (β=-0.008, effect=-0.84%) and positively associated with female sex (β=0.141, effect=15.19%).

Conclusions The findings of this study suggest that various systemic factors beyond age and sex are related to otolith function via effects on the microvasculature and structural constituents. These findings provide new insights into potential mechanisms of otolith degeneration and highlight the impact of systemic factors on otolith function.

Keywords vestibular system; otolithic membrane; metabolism; aging; vestibular evoked myogenic potentials.

INTRODUCTION

The saccule and utricle are the two otolith organs that sense gravitoinertial acceleration on the head via relative displacements of their gel and otoconial layers.[1,2] Simplified geometric characteristics suggest that the saccule primarily detects gravitational acceleration when the head is upright and tilted in the pitch axis, whereas the utricle does so when the head is tilted along the roll and pitch axes.[1,2] The saccule is specialized in sensing inertial acceleration along the naso-occipital and rostrocaudal axes of the head, while the utricle is specialized along its interaural and naso-occipital axes.[1,2] The saccule and utricle and their related central pathways can be clinically evaluated in various ways, including by measuring cervical and ocular vestibular evoked myogenic potentials (VEMPs),[3] subjective visual verticals,[4] and off-vertical or off-axis rotations.[5] Among these methods, VEMPs enable quantitative assessments of unilateral otolith function and have been increasingly applied in evaluations of various vestibular disorders, although there is still inadequate evidence (Level U) supporting their utility in assessing saccular and utricular functions.[6] Ab-

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normal VEMPs have been reported in various vestibular disorders, including benign paroxysmal positional vertigo (BPPV),[7] Ménière's disease,[8] vestibular neuritis,[9] and vestibular schwannoma.[10] In some patients with recurrent vertigo, isolated VEMP abnormalities are associated with a higher risk of evolution to Ménière's disease.[11] Furthermore, VEMP abnormalities are the most common laboratory findings in patients with persistent postural-perceptual dizziness (PPPD), who commonly report a false sensation of linear motion such as swaying, tilting, floating, or rocking.[12]

It is noteworthy that otoliths undergo age-related degenerative changes, which manifest as a decreased amplitude of VEMPs and a shift in their tuning frequency.[3] In general, the degenerative changes in every organ (including otoliths) are affected by acquired systemic conditions.[13] Experimental studies involving rats have found that estrogen deficiency induces degenerative changes of otoconia characterized by an irregular surface, giant and fused otoconia, tiny crystals, and weakened anchoring.[14] Transient ischemia leads to similar degenerative changes of the otoconia in rats.[15] Some studies have histologically revealed the loss of otolith hair cells in patients with diabetic microangiopathy.[16] The findings of several clinical studies have also implied that acquired systemic conditions affect otolith degeneration. VEMP abnormalities in BPPV are believed to indicate otolith macular degeneration.[7] The associations between BPPV and various systemic disorders such as dyslipidemia,[17] hypertension,[17] diabetes mellitus,[17] osteoporosis,[18] low total vitamin D level,[19] and thyroid disease[20] raise the possibility that the effects of these systemic conditions on VEMP abnormalities reflect otolith degeneration. Associations of cervical VEMPs (cVEMPs) with the estimated glomerular filtration rate (eGFR) and free thyroxine have been reported in patients with benign recurrent vertigo, PPPD, and vestibular migraine.[21]

Nevertheless, the conclusions drawn from previous studies remain vulnerable to random variation and bias due to the small numbers of patients involved, which makes it essential to obtain more evidence from both clinical and histopathological investigations. We therefore aimed to determine the impacts of systemic factors associated with otolith function in a large number of patients with dizziness and vertigo, with the expectation that bone metabolic and microvascular factors would show significant associations with such conditions.

METHOD

Study design, standard protocol approval, registration, and patient consent

This retrospective, observational, cross-sectional study analyzed electronic medical records from a single tertiary hospital. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital, which waived the requirement to obtain informed consent from individual participants (B-2201-735-102).

Study population and measurements

We aimed to characterize the relationships between otolith function and systemic conditions. The medical records of patients who visited our institute due to dizziness and vertigo from March 2017 to July 2021 were screened to identify those with an appropriate diagnosis through systematic evaluations including medical interviews, bedside neuro-otological examinations, and comprehensive vestibular and serological evaluations. Vestibular function tests consisted of 3D video-oculography, video head impulse test, cVEMPs, and ocular VEMPs (oVEMPs). Pure-tone audiometry was also performed to aid the diagnosis of acoustic/vestibular schwannoma, Ménière's disease, and sensorineural or conductive hearing loss. Because the simultaneous evaluation of cVEMPs and oVEMPs was not covered by medical insurance until September 2018, only cVEMP measurements were available for patients screened between March 2017 and September 2018. The laboratory assessment included the complete blood cell count, lipid profile, eGFR, serum hemoglobin A1c (HbA1c), inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and procalcitonin, liver function tests including aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, albumin, uric acid, thyroid-stimulating hormone and free thyroxine, parathyroid hormone (PTH), C-terminal telopeptide, osteocalcin, calcium, phosphate, and total vitamin D.

After initially identifying 1,044 potentially eligible patients, we excluded those with disorders that could potentially affect otolith function in order to minimize confounding from disease-related otolith pathology. These exclusions included patients with Ménière's disease (n=182), bilateral vestibulopathy (n=27), brainstem or cerebellar infarction (n=8), acute or chronic unilateral vestibulopathy, labyrinthitis, or vestibular schwannoma (n=94), cerebellar ataxia (n=33), or stroke affecting areas other than the cerebellum or brainstem (n=18). Meanwhile, we included patients with BPPV, benign recurrent vertigo, and PPPD. BPPV is known to be associated with age-related otolith degeneration,[22] while PPPD can develop either primarily or secondarily.[23] Except for patients with BPPV, those with secondary PPPD associated with the aforementioned disorders were excluded. PPPD following BPPV further supports its potential relevance to age-related otolith dysfunction. Benign recurrent vertigo is defined as recurrent episodes of spontaneous vertigo lasting

from minutes to hours without auditory symptoms or central neurological signs,[12,24] although its underlying pathology remains uncertain. We subsequently further excluded 58 patients with incomplete datasets for the above-mentioned serological tests. Therefore, 624 patients with dizziness and vertigo attributed to BPPV (*n*=97), benign recurrent vertigo (*n*=300), or PPPD (*n*=227) were finally included in the analyses (Fig. 1).

Evaluation of cVEMPs and oVEMPs

cVEMPs and oVEMPs were measured using a Nicolet Viking Select unit (Nicolet-Biomedical). For the cVEMP testing, the patient was placed in a supine position with their head rotated contralaterally and lifted approximately 30° to activate the sternocleidomastoid muscles. The stimulus was a short-burst alternating tone (110 dB nHL [normal hearing level], 123.5 dB SPL [sound pressure level], 500 Hz) delivered monoaurally at a repetition rate of 2.1 Hz. The responses to up to 80 stimuli were averaged, and the amplitude difference between the initial positive peak (p13) and the subsequent negative peak (n23) was measured. For each ear, cVEMPs were recorded twice and averaged, with amplitudes <50 μV considered to indicate unresponsiveness. We recorded the sternocleidomastoid muscle activity simultaneously during the test, obtained the rectified peak-to-peak amplitude, and calculated the mean tonic muscular activity using surface electrodes, an analog-to-digital converter (NI PCI-4461, National Instruments), and the LabVIEW program (National Instruments). Finally, the normalized cVEMP amplitudes were derived by dividing the absolute cVEMP amplitude by the mean tonic activation of the sternocleidomastoid muscle. In selected patients who were nonresponders to the sound stimulus, forehead tap-induced cVEMPs were tested.

For the oVEMP testing, the patient was seated in a chair and instructed to look up at a target positioned 2 meters above the floor. The stimuli consisted of 60 forehead taps over 1 minute using an electric reflex hammer (VIASYS Healthcare). The induced inferior oblique muscle activity was recorded simultaneously on both sides from surface electrodes placed just below the lower eyelids. After averaging the responses, we measured the amplitude difference between the initial negative peak (n1) and the following positive peak (p1). The oVEMPs were obtained twice and averaged for each patient, with an average amplitude <5 μV classified as indicating unresponsiveness.

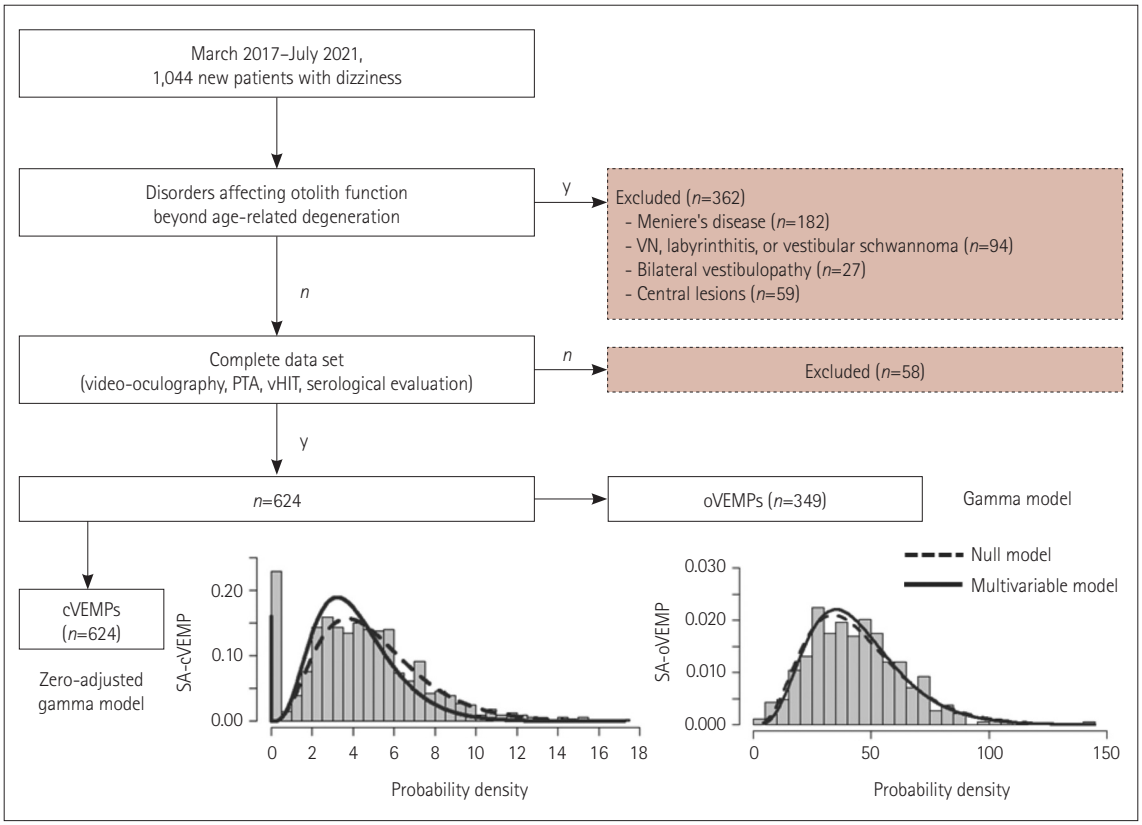

Fig. 1. Flowchart of patient inclusion. cVEMPs, cervical vestibular evoked myogenic potentials; oVEMPs, ocular vestibular evoked myogenic potentials; PTA, pure tone audiometry; SA-cVEMP, summated amplitudes of cVEMPs; SA-oVEMP, summated amplitudes of oVEMPs; vHIT, video head impulse test; VN, vestibular neuritis.

Summated amplitudes of cVEMPs and oVEMPs

Abnormalities of cVEMPs and oVEMPs can be defined in various ways, but in clinical practice the most widely used measure is the asymmetry index, calculated as the difference between the amplitudes for the two ears divided by their summation. In our institute, the reference range for the asymmetry index is <23%. Since the asymmetry index was not applicable to cases of bilateral hypofunction, we adopted the following reference ranges for each ear: >2 (unitless) for the sound-induced normalized cVEMP amplitude and >10 μV for the tapping-induced oVEMP amplitude.

However, since this study aimed to identify risk factors for otolith deterioration, the conventional clinical parameters for lesion localization were inadequate. We therefore introduced new parameters of saccular and utricular functions by summing bilateral responses for cVEMPs and oVEMPs, respectively. For the summated amplitude of cVEMPs (SA-cVEMP), we used air-conducted (sound-induced) cVEMPs only. The normalized p13−n23 amplitude was measured twice in each ear, averaged, and then summed across both ears. For the summated amplitude of oVEMPs (SA-oVEMP), the n1−p1 amplitude obtained from forehead tapping was averaged for each ear and then summed across both ears. To provide a normative reference, we retrieved data from a healthy control group at our institute (28 subjects, mean age 52.3±10.2 years) and presented these normative SA-cVEMP and SA-oVEMP values alongside those calculated from our patient cohort.

Statistical analyses

Continuous variables were expressed either as means with standard deviations or as medians with interquartile ranges, while categorical variables were expressed as numbers and percentages.

The associations between otolith function and systemic factors were investigated using generalized linear models with SA-cVEMPs and SA-oVEMPs set as the dependent variables. We first examined the distributions of SA-cVEMPs and SA-oVEMPs, then compared their Akaike information criterion values to identify the most-suitable distributions for generalized linear regression. Since the SA-cVEMP data contained a large number of zeros and were right-skewed, we compared normal, zero-adjusted gamma, and Tweedie distributions, which revealed that the zero-adjusted gamma distribution provided the best fit because it appropriately handled zero inflation. The Tweedie model also offers flexibility for zero-inflated and mixed data, but it did not outperform the zero-adjusted gamma model for our data. Conversely, the SA-oVEMP data exhibited right-skewness without substantial numbers of zero values, and after comparing normal and gamma distributions, we selected the latter. We subsequently conducted univariable analyses of all variables, and those with $p<0.2$ were included in the multivariable regression analyses. Model residuals were assessed through histograms and the Shapiro−Wilk test, and model fit was evaluated by comparing Akaike information criterion values between the null model (without independent variables) and the multivariable model.

The zero-adjusted gamma model used for SA-cVEMPs in this study independently estimates and presents three parameters (μ, σ, and ν), whereas the standard gamma model used for SA-oVEMPs simultaneously estimates the mean (μ) and variance (σ). Given our interest in identifying systemic factors affecting otolith function deterioration in linear relationships, we focused on parameter μ (the mean) during the interpretation. In both the zero-adjusted gamma model and the standard gamma model, β coefficients are expressed on a logarithmic scale, meaning that the effect of a one-unit increase in a predictor corresponds to multiplying the dependent variable by e^{β}. Equivalently, $(e^{\beta}-1)\times100$ provides the percentage change in the dependent variable. Therefore, the results from the regression analyses are presented using β coefficients with 95% confidence intervals (CIs), along with their logarithmic transformations to represent the actual effects in the model.

After applying generalized linear regression analyses to the entire dataset, the same analyses were repeated in subgroups dichotomized by the median age of 55 years (younger [<55 years] vs. older [≥55 years]) and sex (male vs. female). All statistical analyses were conducted using R software (version 4.2.2, R Foundation for Statistical Computing).

RESULTS

Baseline characteristics of included patients

Table 1 summarizes the demographic and laboratory characteristics of the 624 patients included in the study. The patients were aged 54.5±13.6 years, and approximately 70% of them were female. The values from the serological tests were within the normal ranges, except for a mildly decreased total vitamin D level (22.1±11.1 ng/mL, reference range=30−50 ng/mL). All of the included patients underwent cVEMP testing, but oVEMP testing was performed in only 349 patients. The results for cVEMPs and oVEMPs are presented in Table 1. The normalized cVEMP amplitudes were 2.30±1.57 μV and 2.23±1.54 μV in the right and left ears, respectively (reference=4.43±2.60 μV for each ear), and SA-cVEMP was 4.52±2.92 μV (reference=9.31±5.34 μV). The oVEMP amplitudes were 21.81±10.63 μV and 21.79±11.17 μV in the right and left ears, respectively (reference=28.5±14.3 μV for each ear),

Table 1. Demographic and laboratory characteristics of the enrolled patients

Variable	Value (*n*=624)
Demographic and laboratory characteristics	
Sex, female	440 (70.5)
Age (yr)	54.5±13.6
Total cholesterol (mg/dL)	192.8±38.5
LDL cholesterol (mg/dL)	113.7±29.2
HDL cholesterol (mg/dL)	56.4±13.2
Triglycerides (mg/dL)	124.9±74.2
HbA1c (%)	5.5±0.6
eGFR (mL/min/1.73 m^2)	97.2±20.2
Hematocrit (%)	41.7±3.5
White blood cells (10^3/μL)	6.2±1.8
ESR (mm/h)	12.8±6.9
Procalcitonin (ng/mL)	0.3±0.1
Albumin (g/dL)	4.4±0.3
Osteocalcin (ng/mL)	18.4±8.2
Alkaline phosphatase (U/L)	72.2±24.7
C-terminal telopeptide (ng/mL)	0.4±0.2
Total vitamin D (ng/mL)	22.1±11.1
PTH (pg/mL)	32.1±14.0
TSH (mU/L)	2.2±1.7
Free thyroxine (ng/dL)	1.3±0.2
Otolith function	
cVEMPs (*n*=624)	
Right normalized amplitude (μV)	2.30±1.57
Left normalized amplitude (μV)	2.23±1.54
Asymmetry index (%)	18.1±28.1
SA-cVEMP (μV)	4.52±2.92
oVEMPs (*n*=349)	
Right amplitude (μV)	21.81±10.63
Left amplitude (μV)	21.79±11.17
Asymmetry index (%)	13.58±20.70
SA-oVEMP (μV)	43.60±20.80
Canal function (video head impulse test)	
Right horizontal canal gain	1.03±0.09
Right anterior canal gain	0.98±0.08
Right posterior canal gain	0.96±0.08
Left horizontal canal gain	1.06±4.71
Left anterior canal gain	1.00±0.09
Left posterior canal gain	0.97±0.10

Data are mean±standard deviation values for continuous variables and number (percentage) values for categorical variables.
cVEMPs, cervical vestibular evoked myogenic potentials; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; oVEMPs, ocular vestibular evoked myogenic potentials; PTH, parathyroid hormone; SA-cVEMP, summated amplitudes of cVEMPs; SA-oVEMP, summated amplitudes of oVEMPs; TSH, thyroidstimulating hormone.

and SA-oVEMP was 43.60±20.80 μV (reference=56.90±28.36 μV).

Potential risk factors for deterioration of saccular function

In the univariable analyses using the zero-adjusted gamma model (Table 2), age, female sex, HbA1c, alkaline phosphatase, and free thyroxine were negatively associated with SA-cVEMP. In contrast, SA-cVEMP was positively associated with the high-density lipoprotein (HDL) cholesterol and albumin levels.

The multivariable regression analyses identified four independent variables, with SA-cVEMP being negatively associated with age (β=-0.012, 95% CI=-0.016 to -0.009; effect=-1.23%, 95% CI=-1.59% to -0.90%), female sex (β=-0.110, 95% CI=-0.219 to -0.001; effect=-10.42%, 95% CI=-19.67% to -0.10%), and free thyroxine (β=-0.298, 95% CI=-0.461 to -0.135; effect=-25.74%, 95% CI=-36.93% to -12.63%), and positively associated with HDL cholesterol (β=0.005, 95% CI=0.002 to 0.007; effect=0.46%, 95% CI=0.20% to 0.70%) (Fig. 2A).

The subgroup analyses revealed that while SA-cVEMP was negatively associated only with age in males, in females it was negatively associated with age, HbA1c, and free thyroxine. In the older subgroup (age ≥55 years), SA-cVEMP was negatively associated with free thyroxine but positively associated with albumin. In the younger subgroup (age <55 years), SA-cVEMP was negatively associated with free thyroxine but positively associated with HDL cholesterol. Detailed results for the multivariable zero-adjusted gamma regression model according to subgroups are presented in Table 3.

Potential risk factors for deterioration of utricular function

In the univariable analyses using the standard gamma model (Table 4), SA-oVEMP was negatively associated with age and positively associated with female sex. In addition, both the eGFR and procalcitonin level were positively associated with SA-oVEMP.

The multivariable regression analyses identified two independent variables associated with SA-oVEMP: a negative association with age (β=-0.008, 95% CI=-0.012 to -0.004; effect=-0.84%, 95% CI=-1.24% to -0.44%) and a positive association with female sex (β=0.141, 95% CI=0.029 to 0.253; effect=15.19%, 95% CI=2.98% to 28.85%) (Fig. 2B).

The subgroup analyses revealed that age was negatively associated with SA-oVEMP in both males and females. Unexpectedly, the total vitamin D level was negatively associated with SA-oVEMP in males. In the older subgroup (age ≥55

Table 2. Risk factors associated with deterioration of saccular function (*n*=624)

Variable	β	Effect (%)	*p*
Univariable analyses (zero-adjusted gamma model)			
Sex†	-0.088 (-0.180 to 0.004)	-8.42 (-16.47 to 0.40)	0.061
Age*†	-0.012 (-0.015 to -0.009)	-1.19 (-1.49 to -0.90)	<0.001
LDL cholesterol	0.000 (-0.002 to 0.001)	0.00 (-0.20 to 0.10)	0.608
HDL cholesterol*†	0.004 (0.001 to 0.007)	0.40 (0.10 to 0.70)	0.013
Total cholesterol	-0.001 (-0.002 to 0.001)	-0.10 (-0.20 to 0.10)	0.297
Triglycerides	0.000 (-0.001 to 0.000)	0.00 (-0.10 to 0.00)	0.570
HbA1c*†	-0.136 (-0.218 to -0.054)	-12.72 (-19.59 to -5.26)	0.001
eGFR	0.001 (-0.001 to 0.003)	0.10 (-0.10 to 0.30)	0.306
Hematocrit§	0.010 (-0.002 to 0.022)	1.01 (-0.20 to 2.22)	0.115
White blood cells	0.004 (-0.025 to 0.033)	0.40 (-2.47 to 3.36)	0.782
Procalcitonin†	0.662 (-0.146 to 1.470)	93.87 (-13.58 to 334.92)	0.109
Albumin*†	0.227 (0.070 to 0.383)	25.48 (7.25 to 46.67)	0.005
Osteocalcin	-0.001 (-0.006 to 0.003)	-0.10 (-0.60 to 0.30)	0.624
Alkaline phosphatase*†	-0.002 (-0.004 to 0.000)	-0.20 (-0.40 to 0.00)	0.044
C-terminal telopeptide	-0.045 (-0.210 to 0.120)	-4.40 (-18.94 to 12.75)	0.593
Total vitamin D	0.000 (-0.004 to 0.004)	0.00 (-0.40 to 0.40)	0.849
PTH	-0.002 (-0.005 to 0.002)	-0.20 (-0.50 to 0.20)	0.323
TSH†	-0.020 (-0.042 to 0.001)	-1.98 (-4.11 to 0.10)	0.068
Free thyroxine*†	-0.235 (-0.408 to -0.062)	-20.94 (-33.50 to -6.01)	0.008
Multivariable regression analyses (zero-adjusted gamma model)			
Sex*	-0.110 (-0.219 to -0.001)	-10.42 (-19.67 to -0.10)	0.048
Age*	-0.012 (-0.016 to -0.009)	-1.23 (-1.59 to -0.90)	<0.001
HDL cholesterol*	0.005 (0.002 to 0.007)	0.46 (0.20 to 0.70)	0.002
HbA1c	0.018 (-0.058 to 0.094)	1.82 (-5.64 to 9.86)	0.642
Hematocrit	-0.001 (-0.016 to 0.014)	-0.11 (-1.59 to 1.41)	0.881
Procalcitonin	0.110 (-0.674 to 0.893)	11.57 (-49.03 to 144.24)	0.784
Albumin	0.024 (-0.143 to 0.190)	2.41 (-13.32 to 20.92)	0.780
Alkaline phosphatase	0.000 (-0.002 to 0.002)	0.00 (-0.20 to 0.20)	0.960
TSH	-0.014 (-0.035 to 0.007)	-1.35 (-3.44 to 0.70)	0.206
Free thyroxine*	-0.298 (-0.461 to -0.135)	-25.74 (-36.93 to -12.63)	<0.001

95% confidence intervals are within parentheses. The effect of each variable was calculated using $(e^{\beta}-1)\times100$, which indicates the percentage change in SA-cVEMP for a unit increase in the variable.
*Statistically significant in multivariable regression. Units are the same as in Table 1; †Included in multivariable regression.
eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone; SA-cVEMP, summated amplitudes of cervical vestibular evoked myogenic potential; TSH, thyroidstimulating hormone.

years), age and female sex were associated with SA-oVEMP, following the same direction of the associations observed in the entire cohort. In the younger subgroup (age <55 years), only the PTH level showed a negative association with SA-oVEMP. Detailed results for the multivariable standard gamma regression model according to subgroups are presented in Table 5.

DISCUSSION

This study explored potential risk factors for the deterioration of saccular and utricular functions, as measured by SA-cVEMPs and SA-oVEMPs, respectively. Age emerged as a consistent and significant risk factor across both otolith organs, highlighting the role of age-related degeneration in vestibular function. In addition to aging, the free thyroxine level and female sex were negatively associated with saccular function, whereas a higher HDL-cholesterol level demonstrated a protective role. These findings indicate that metabolic and vascular factors potentially affect saccular function. It was particularly interesting that female sex exerted a protective effect on utricular function while having a negative impact on saccular function. Furthermore, the subgroup analyses revealed that the associations of the identified risk

factors differed depending on sex and age subgroups, suggesting the presence of complex interactions between demographic characteristics, metabolic status, and vestibular function.

Aging-related otolith degeneration

The decreases in SA-cVEMPs and SA-oVEMPs with aging, as observed in this study, likely result from various degenerative changes in the neural pathways originating from the

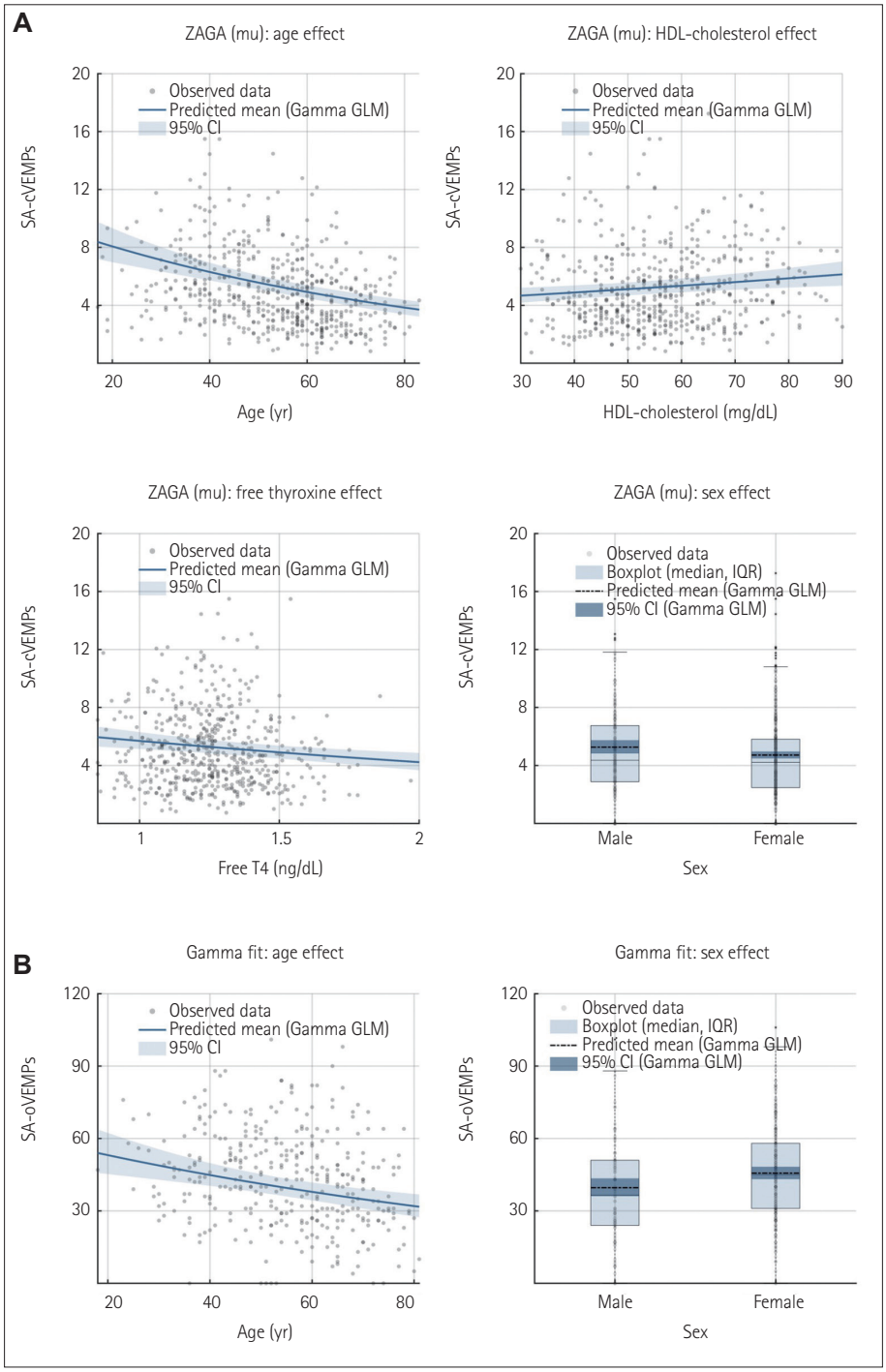

Fig. 2. Associations between risk factors for otolith deterioration. A: Age, HDL cholesterol, free thyroxine, and sex showed significant associations with the SA-cVEMP. B: Age and sex were significantly associated with the SA-oVEMP. ZAGA denotes a zero-adjusted gamma model, whereas gamma denotes a standard gamma model; both were generalized linear models. For SA-cVEMPs, only the μ parameter (the mean of the gamma distribution for the positive values) from the ZAGA model is presented. CI, confidence interval; GLM, generalizes linear regression; HDL, high-density lipoprotein; IQR, interquartile range; SA-cVEMP, summated amplitudes of cervical vestibular evoked myogenic potential; SA-oVEMP, summated amplitudes of ocular vestibular evoked myogenic potential.

Table 3. Results from subgroup analyses of risk factors for the deterioration of saccular function

Variable	β	Effect (%)	*p*
Males (*n*=184)			
Age*	-0.009 (-0.014 to -0.003)	-0.85 (-1.43 to -0.26)	0.005
HDL cholesterol	0.004 (-0.001 to 0.008)	0.36 (-0.07 to 0.79)	0.102
eGFR	0.002 (-0.003 to 0.006)	0.19 (-0.25 to 0.63)	0.406
Albumin	0.008 (-0.255 to 0.272)	0.81 (-22.54 to 31.22)	0.952
PTH	-0.004 (-0.009 to 0.001)	-0.40 (-0.92 to 0.12)	0.129
TSH	-0.017 (-0.055 to 0.020)	-1.72 (-5.31 to 2.01)	0.364
Females (*n*=440)			
Age*	-0.009 (-0.014 to -0.005)	-0.92 (-1.38 to -0.46)	<0.001
HDL cholesterol	0.004 (0.000 to 0.008)	0.37 (-0.02 to 0.77)	0.066
Triglycerides	0.000 (-0.001 to 0.001)	-0.02 (-0.09 to 0.06)	0.701
HbA1c*	-0.087 (-0.167 to -0.007)	-8.33 (-15.39 to -0.68)	0.034
Procalcitonin	0.041 (-0.924 to 1.005)	4.14 (-60.29 to 173.12)	0.934
Albumin	0.110 (-0.097 to 0.317)	11.58 (-9.29 to 37.24)	0.300
Alkaline phosphatase	-0.001 (-0.003 to 0.002)	-0.06 (-0.31 to 0.20)	0.654
C-terminal telopeptide	-0.046 (-0.273 to 0.181)	-4.49 (-23.91 to 19.87)	0.692
Free thyroxine*	-0.226 (-0.370 to -0.082)	-20.20 (-30.91 to -7.83)	0.002
Older (*n*=322)			
Age	-0.006 (-0.015 to 0.003)	-0.62 (-1.49 to 0.30)	0.173
HDL cholesterol	0.003 (-0.001 to 0.007)	0.33 (-0.10 to 0.72)	0.110
Albumin*	0.269 (0.047 to 0.491)	30.93 (4.82 to 63.49)	0.018
Osteocalcin	0.006 (-0.002 to 0.013)	0.55 (-0.20 to 1.30)	0.141
C-terminal telopeptide	0.072 (-0.192 to 0.335)	7.43 (-17.50 to 39.83)	0.594
Free thyroxine*	-0.407 (-0.734 to -0.079)	-33.47 (-51.56 to -7.61)	0.015
Younger (*n*=302)			
Sex	-0.107 (-0.224 to 0.010)	-10.16 (-20.08 to 1.01)	0.072
Age	-0.006 (-0.012 to 0.001)	-0.55 (-1.19 to 0.09)	0.089
HDL cholesterol*	0.004 (0.000 to 0.008)	0.41 (0.02 to 0.81)	0.044
Osteocalcin	-0.006 (-0.012 to 0.002)	-0.57 (-1.19 to 0.20)	0.105
Total vitamin D	0.005 (-0.001 to 0.010)	0.47 (-0.12 to 1.01)	0.112
Free thyroxine*	-0.255 (-0.442 to -0.069)	-22.50 (-35.70 to -6.67)	0.008

95% CIs are within parentheses. For simplicity, only results from multivariable regression analyses are presented. The effect of each variable was calculated using $(e^{\beta}-1)\times 100$, which indicates the percentage change in SA-cVEMP for a unit increase in the variable.
*Statistically significant in multivariable regression. Units are the same as in Table 1.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone; SA-cVEMP, summated amplitudes of cervical vestibular evoked myogenic potential.

otolith organs. The otolithic membrane comprises a gel layer and a mesh-like network that contains collagen fibers and collagen-like otolin-1 to form its structural framework, as well as noncollagenous glycoproteins such as otogelin and α- and β-tectorin that contribute to membrane anchoring and stability.[25] This membrane serves as an anchoring matrix for otoconia and facilitates the transmission of mechanical forces to the underlying hair cells.[25] Notably, the elevation of serum otolin-1 in older individuals suggests that it degenerates with aging,[26] with the age-related degradation of key structural proteins such as otolin-1 and otogelin in turn weakening the integrity of this matrix. This change can induce instability in the overlying otoconial layer and alter the viscoelastic properties of the membrane itself.[2,27]

Moreover, the otoconial layer—the topmost layer of the otolithic membrane—undergoes significant morphological changes with aging. Histological evaluations have shown that although the volume of the aging otolith is relatively preserved, it exhibits a decrease in density, indicating a reduction in mass[28] and hence changes in the inertial properties of the otolithic membrane.[2] Additionally, otoconia fragment into smaller particles with aging, while also forming enlarged, irregularly shaped structures.[29] The resulting uneven weight distribution may reduce the efficiency of mechanical force

Table 4. Risk factors associated with deterioration of utricular function (*n*=349)

Variable	β	Effect (%)	*p*
Univariable analyses (standard gamma model)			
Sex*†	0.136 (0.030 to 0.243)	14.62 (3.04 to 27.51)	0.012
Age*†	-0.010 (-0.013 to -0.006)	-0.99 (-1.33 to -0.64)	<0.001
LDL cholesterol†	0.001 (0.000 to 0.003)	0.12 (-0.04 to 0.28)	0.139
HDL cholesterol†	0.003 (0.000 to 0.007)	0.31 (-0.05 to 0.66)	0.089
Total cholesterol†	0.001 (0.000 to 0.002)	0.10 (-0.03 to 0.22)	0.124
Triglycerides†	-0.001 (-0.001 to 0.000)	-0.06 (-0.13 to 0.01)	0.097
HbA1c	-0.035 (-0.105 to 0.035)	-3.46 (-10.01 to 3.57)	0.327
eGFR*†	0.003 (0.001 to 0.005)	0.30 (0.06 to 0.54)	0.017
Hematocrit	-0.007 (-0.021 to 0.007)	-0.68 (-2.08 to 0.74)	0.345
White blood cells	0.001 (-0.028 to 0.031)	0.13 (-2.79 to 3.13)	0.933
Procalcitonin*†	1.313 (0.422 to 2.205)	271.80 (52.48 to 806.60)	0.004
Albumin	0.087 (-0.078 to 0.253)	9.12 (-7.54 to 28.78)	0.302
Osteocalcin	-0.003 (-0.009 to 0.003)	-0.33 (-0.93 to 0.28)	0.288
Alkaline phosphatase†	-0.002 (-0.004 to 0.000)	-0.16 (-0.35 to 0.04)	0.119
C-terminal telopeptide	-0.069 (-0.272 to 0.135)	-6.62 (-23.83 to 14.48)	0.510
Total vitamin D†	-0.003 (-0.007 to 0.001)	-0.31 (-0.70 to 0.09)	0.132
PTH†	-0.002 (-0.006 to 0.001)	-0.25 (-0.56 to 0.07)	0.123
TSH	-0.001 (-0.027 to 0.024)	-0.14 (-2.66 to 2.44)	0.913
Free thyroxine	-0.126 (-0.405 to 0.153)	-11.83 (-33.29 to 16.53)	0.377
Multivariable regression analyses (standard gamma model)			
Sex*	0.141 (0.029 to 0.253)	15.19 (2.98 to 28.85)	0.014
Age*	-0.008 (-0.012 to -0.004)	-0.84 (-1.24 to -0.44)	<0.001
LDL cholesterol	0.004 (-0.005 to 0.013)	0.39 (-0.52 to 1.32)	0.402
HDL cholesterol	0.002 (-0.005 to 0.009)	0.19 (-0.50 to 0.88)	0.594
Total cholesterol	-0.002 (-0.010 to 0.005)	-0.21 (-0.97 to 0.54)	0.580
Triglycerides	0.000 (-0.001 to 0.001)	-0.04 (-0.13 to 0.06)	0.428
eGFR	0.001 (-0.002 to 0.003)	0.07 (-0.19 to 0.33)	0.599
Procalcitonin	0.657 (-0.286 to 1.600)	92.89 (-24.91 to 395.49)	0.173
Alkaline phosphatase	0.000 (-0.002 to 0.002)	-0.01 (-0.22 to 0.19)	0.888
Total vitamin D	-0.001 (-0.006 to 0.003)	-0.14 (-0.57 to 0.29)	0.518
PTH	-0.002 (-0.005 to 0.001)	-0.21 (-0.53 to 0.11)	0.201

95% CIs are within parentheses. The effect of each variable was calculated using $(e^{\beta}-1)\times 100$, which indicates the percentage change in SA-oVEMP for a unit increase in the variable.
*Statistically significant in multivariable regression. Units are the same as in Table 1; †Included in multivariable regression.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone; SA-oVEMP, summated amplitudes of ocular vestibular evoked myogenic potential; TSH, thyroidstimulating hormone.

transmission to the underlying hair cells.[27]

In addition to otolith degeneration itself, experimental studies have documented the aging-related loss of otolith hair cells.[30] The number of type I hair cells, which are concentrated in the striolar region, progressively decreases with aging.[31] The structural integrity of these hair cells and their synaptic connectivity with afferent neurons deteriorate over time.[31] Furthermore, recent observations suggest the occurrence of age-related narrowing in the striolar region that could further affect the precision of signal processing.[28] Lastly, the number of cells in Scarpa's ganglion, which transmits signals to the central nervous system, also decreases after middle age.[32]

Therefore, the combined effects of otolith degeneration and the loss of hair cells and primary afferent neurons will reduce the mechanoelectrical transduction efficiency, which in turn will reduce the cVEMP and oVEMP responses observed in aging individuals.

Elevated free thyroxine as a metabolic risk factor for saccular dysfunction

Elevated free thyroxine is known to accelerate osteoclastic activity, increase bone-turnover rates, and influence the bal-

Table 5. Results from subgroup analyses of risk factors for the deterioration of utricular function

Variable	β	Effect (%)	*p*
Males (*n*=98)			
Age*	-0.009 (-0.017 to -0.001)	-0.89 (-1.65 to -0.12)	0.026
eGFR	0.003 (-0.003 to 0.009)	0.32 (-0.28 to 0.93)	0.292
Total vitamin D*	-0.014 (-0.025 to -0.003)	-1.43 (-2.52 to -0.33)	0.013
Females (*n*=251)			
Age*	-0.009 (-0.014 to -0.005)	-0.93 (-1.38 to -0.48)	<0.001
LDL cholesterol	0.005 (-0.004 to 0.013)	0.48 (-0.38 to 1.35)	0.272
HDL cholesterol	0.005 (-0.001 to 0.010)	0.46 (-0.13 to 1.05)	0.132
Total cholesterol	-0.003 (-0.010 to 0.004)	-0.27 (-0.95 to 0.42)	0.445
HbA1c	0.033 (-0.061 to 0.127)	3.34 (-5.91 to 13.49)	0.493
Procalcitonin	0.331 (-0.646 to 1.308)	39.18 (-47.60 to 269.69)	0.508
Albumin	0.052 (-0.136 to 0.239)	5.31 (-12.69 to 27.02)	0.589
Osteocalcin	-0.002 (-0.011 to 0.008)	-0.16 (-1.09 to 0.78)	0.741
C-terminal telopeptide	-0.035 (-0.343 to 0.272)	-3.48 (-29.04 to 31.29)	0.822
PTH	-0.002 (-0.006 to 0.001)	-0.25 (-0.58 to 0.09)	0.145
Older (*n*=176)			
Sex*	0.192 (0.005 to 0.379)	21.18 (0.55 to 46.04)	0.045
Age*	-0.017 (-0.029 to -0.006)	-1.71 (-2.81 to -0.59)	0.003
LDL cholesterol	0.005 (-0.003 to 0.014)	0.55 (-0.27 to 1.38)	0.193
Total cholesterol	-0.003 (-0.009 to 0.004)	-0.25 (-0.87 to 0.37)	0.428
Hematocrit	-0.016 (-0.043 to 0.010)	-1.60 (-4.18 to 1.05)	0.237
Procalcitonin	0.473 (-0.963 to 1.908)	60.42 (-61.81 to 573.79)	0.520
Younger (*n*=173)			
HDL cholesterol	0.002 (-0.003 to 0.007)	0.18 (-0.31 to 0.68)	0.468
Triglycerides	-0.001 (-0.002 to 0.000)	-0.10 (-0.20 to 0.00)	0.061
eGFR	0.002 (-0.002 to 0.005)	0.15 (-0.17 to 0.48)	0.350
Procalcitonin	0.938 (-0.177 to 2.054)	155.60 (-16.21 to 679.65)	0.101
PTH*	-0.005 (-0.009 to -0.001)	-0.49 (-0.92 to -0.06)	0.026

95% CIs are within parentheses. For simplicity, only results from multivariable regression analyses are presented. The effect of each variable was calculated using $(e^{\beta}-1)\times100$, which indicates the percentage change in SA-oVEMP for a unit increase in the variable.
*Statistically significant in multivariable regression. Units are the same as in Table 1.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone; SA-oVEMP, summated amplitudes of ocular vestibular evoked myogenic potential.

ance between bone formation and resorption.[33] Otoconia primarily consist of calcium carbonate crystals, and their formation is dynamically regulated by systemic bone metabolism.[34] Increased free thyroxine might affect saccular function by disrupting these calcium-dependent processes so as to decrease the otoconial mass. Indeed, previous studies have found significant associations between osteoporosis and BPPV, which is an otolith-related disorder.[18] For example, a nationwide population-based cohort study found that osteoporosis significantly increased the risk of developing BPPV.[35] Furthermore, biochemical studies have demonstrated that osteoporotic patients with BPPV exhibit higher levels of systemic bone-turnover markers such as osteocalcin.[36] Therefore, although direct evidence linking elevated free thyroxine to structural damage in the saccule or utricle is still inadequate, elevated free thyroxine may impair otoconia homeostasis by increasing bone resorption and altering calcium metabolism, which could be a plausible underlying mechanism for BPPV as a reflection of otoconia degeneration. Our subgroup analyses also indicated that the negative associations between elevated free thyroxine and saccular dysfunction were stronger in females and older individuals. This finding may be explained by more-pronounced osteoclastic effects of thyroid hormones in postmenopausal females and older individuals undergoing osteopenia,[37] potentially promoting otolith dysfunction.

HDL cholesterol as a microvascular protective factor for saccular function

HDL cholesterol is well known for its antiatherosclerotic ef-

fect and is linked to favorable cardio- and cerebrovascular outcomes. The underlying mechanism involves surplus cholesterol removal, restoration of endothelial function, and antioxidative and anti-inflammatory functions.[38] Specifically, HDL cholesterol is associated with small-vessel disease. A study using Mendelian randomization found that a genetic predisposition to elevated HDL cholesterol reduces the risk of small-vessel stroke and the volumes of white-matter hyperintensities, probably by improving endothelial function.[39] We previously posited that microangiopathic changes can influence saccular function as assessed by measuring cVEMPs. This suggests that the positive association between the HDL-cholesterol level and SA-cVEMP observed in the present study could similarly be related to improved endothelial function.[21] The protective effects of HDL cholesterol extend beyond the cerebrovascular system to other small-vessel systems such as the retina, kidneys, and auditory system. In the retina, HDL cholesterol has been shown to increase blood flow and protect against oxidative stress, which are critical for preventing retinopathy.[40] In the kidneys, HDL cholesterol helps preserve the microvasculature and reduces the risk of chronic kidney disease via antioxidative actions that prevent endothelial damage.[41] Similarly, HDL cholesterol is suggested to improve the functioning of the cochlea in the auditory system as well as the vestibular system.[41] Given this background, the positive association between the HDL-cholesterol level and SA-cVEMP implies that HDL cholesterol supports the microvascular integrity of the saccule, thereby exerting a protective effect.

Sex-specific effects on the saccule and utricle

Female sex emerged as a significant risk factor for saccular dysfunction in this study. This may be due to the inherent susceptibility of females—particularly with aging—to osteopenic processes that reduce the mass of the otoconial layer and to collagen degradation that stiffens the otoconial membrane.[42] Both of these mechanisms may contribute to lower SA-cVEMP responses. Paradoxically, female sex appeared protective for the utricle, which contradicts our explanation. However, two key factors should be considered. First, unlike cVEMPs, which are potentials in the neck muscles, oVEMPs reflect the activity of the inferior oblique muscle.[43] Additionally, experiments in mice suggest that the otolith–ocular reflex is stronger in females than in males.[28,44] Second, when a standardized tapping force is applied during oVEMP testing, the lower head mass in females may result in their utricular stimulation being greater than that in males. Together these factors could mask potential utricular weakening, ultimately leading to a net protective effect in female subjects.

Potential risk factors revealed by subgroup analyses

The subgroup analyses revealed distinct associations between systemic factors and otolith function across different demographic and laboratory characteristics. In females, the HbA1c level was negatively associated with SA-cVEMP. Glycemic dysregulation in diabetes mellitus is a well-established risk factor for microvascular damage across various end organs, including the kidneys, eyes, and nerves.[45] Similarly, the otolithic organs show diabetes-induced remodeling of the inner ear capillary bed, along with changes in subneuroepithelial structures such as increases in secondary lysosomes, accumulations of intracellular lipid droplets, depositions of extracellular matrix, and losses of type I hair cells.[46] It is especially noteworthy that the saccule appears to be more vulnerable than the utricle to these effects.[16] However, the relationship was not observed in males, suggesting that sex-specific mechanisms are involved in saccular dysfunction. The reduction in estrogen levels in aging females may increase their susceptibility to microvascular damage under hyperglycemic conditions, since estrogen plays a key role in vascular protection.[47] However, further studies are required to fully elucidate this sex-specific effect.

In the younger subgroup (<55 years), the PTH level was negatively associated with SA-oVEMP. There is a well-documented interaction between total vitamin D and PTH in calcium homeostasis, which may influence the otoconial integrity and stability.[34,48] Vitamin D insufficiency impairs calcium absorption in the intestine, leading to compensatory PTH secretion, which in turn increases bone resorption to maintain the calcium level.[49] This mechanism may explain the inverse relationship between PTH and SA-oVEMP found in the younger subgroup of the present study.

Meanwhile, in males, total vitamin D also showed a negative association with SA-oVEMP, which contradicts the previous explanation, since elevated total vitamin D is not typically linked to increased bone turnover.[50] One possible explanation is that males, who generally have a lower SA-oVEMP—potentially due to sex-related differences in head mass—also have a higher total vitamin D due to spending more time outdoors, which could contribute to this conflicting finding. Further investigations are needed to confirm and explain this finding.

Limitations and summary

This study had several limitations. First, otolith function was assessed using VEMPs, which current guidelines indicate might not truly represent otolith function.[6] Although VEMP responses might be confounded by the integrity of the vestibular nerve and central pathways, we excluded those conditions that are known to alter VEMPs. In addition, the guide-

line statement on the limitations of VEMP testing was primarily based on its diagnostic utility for specific vestibular disorders. Since age-related changes in VEMPs were not the focus of that evaluation, the present findings may offer a different perspective on the role of VEMPs in assessing otolith function, which could be substantiated by comparisons with normal subjects. Second, selection bias may have been present due to the single-center retrospective design of this study, which would have also restricted the generalizability of the findings. Third, the study population was predominantly female (70%) and had an average age of 55 years. Therefore, the findings of the subgroup analyses may be less robust in males due to the smaller sample, meaning that the disappearance of risk factors other than age should be interpreted with caution. In addition, the included population showed diagnostic heterogeneity (BPPV, PPPD, and benign recurrent vertigo, which encompasses various disorders including vestibular migraine, cardiac arrhythmia, and possible Ménière's disease), which may further restrict interpretations of the findings. Fourth, unlike the cVEMP testing using a quantitative tone-burst stimulus, oVEMP testing was performed using an electrical tapping device. As noted above, the latter method may result in the acceleration input varying with the head size and mass, potentially leading to larger inaccuracies in identifying risk factors for SA-oVEMPs than for SA-cVEMPs. Fifth, information on the use of medications such as antidiabetics or lipid-lowering agents was not available in our dataset. Sixth, while our findings and the previous literature suggest that the microvascular integrity influences otolith function, the direct causal relationships between microvascular changes and otolith degeneration remain to be clarified through histopathological and longitudinal studies. Notwithstanding these limitations, this study has provided valuable insights into how systemic factors influence otolith function by analyzing the largest patient cohort (to the best of our knowledge) while performing detailed statistical analyses.

In summary, systemic factors beyond sex and age may affect dizziness that is potentially related to otolith dysfunction via their effects on the microvascular system and bone metabolism. Assessing otolith function from different perspectives using different forms of VEMP testing while also controlling risk factors may help in patient management. Further validation of the present findings is warranted through population-based studies as well as clinical trials aimed at preserving or restoring otolith function.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflicts of Interest

J-Y Choi serves on the editorial board of the *Journal of Clinical Neurology*. J-S Kim serves as an associate editor of *Frontiers in Neuro-Otology* and on the editorial boards of the *Journal of Clinical Neurology, Frontiers in Neuro-ophthalmology, Journal of Neuro-Ophthalmology, Journal of Vestibular Research, Journal of Neurology, and Medicine*. Other authors have nothing to disclose.

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