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# Age-related deterioration of saccule-related neural function is associated with decreased estimated glomerular filtration rate and increased free thyroxine

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HIGHLIGHTS

- Amplitude of cervical vestibular-evoked myogenic potentials (cVEMP) representing saccule-related neural function decreases with ageing.
- Decreased estimated glomerular filtration rate (eGFR) is associated with reduced cVEMP amplitudes.
- The deleterious effect of free T4 on cVEMP amplitude occurs in younger subjects but not in older ones.

ABSTRACT

*Objective:* This study attempted to identify systemic factors for age-related decline in neural function originating from the saccule using cervical vestibular-evoked myogenic potentials (cVEMP) parameters.
*Methods:* We recruited 129 symptomatic vertiginous patients who did not have known disorder affecting the cVEMP pathway (mean age = 52.4 ± 13.9). The indicators of saccule-related neural function were the sum of normalized cVEMP amplitude (SNA) and the average of p13 latency on both sides (average latency, AL). Any associations between cVEMP and systemic factors were evaluated using a linear regression.
*Result:* SNA decreased with ageing ($p < 0.001$) in univariable regression. The estimated glomerular filtration rate (eGFR) was positively associated with SNA ($p = 0.002$). Hematocrit, C-reactive protein, vitamin D, and free thyroxine (T4) showed a trend of association with SNA ($p < 0.2$). SNA was associated with ageing, increased free T4, and decreased eGFR in multivariable analysis. In the subgroup analysis, SNA was significantly associated with free T4 in younger patients (mean age = 41.5 ± 9.91) but not in the older ones (mean age = 63.5 ± 6.54). AL did not show any significant associations with systemic factors.
*Conclusion:* Decreased eGFR and increased free T4 as well as aging may be risk factors for decline of saccule-related neural function.
*Significance:* Neural function originating from the saccule may be affected by systemic factors.


## 1. Introduction

The saccule is the otolith organ that lies in the vertical plane of the head in an upright position (Leigh and Zee, 2015). Along with the utricle, the saccule senses linear acceleration, which is the

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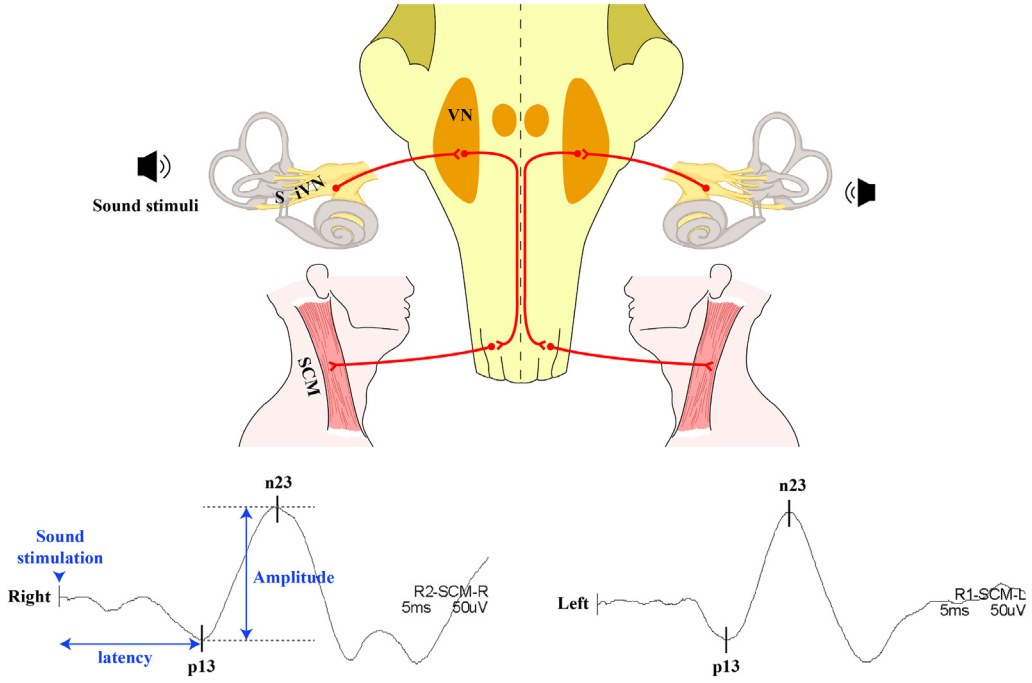


**Fig. 1.** Saccule-related pathways and cervical vestibular-evoked myogenic potentials elicited by sound stimulus.

sum of gravitational and inertial acceleration applied to the head, and provides information to the brain via the vestibular nerve (Buttner-Ennever, 1999; Uchino and Kushiro, 2011).

Clinically, saccular function and its central processing in the vestibular nucleus and vestibulospinal tract can be evaluated with cervical vestibular-evoked myogenic potentials (cVEMP) elicited by loud sound or bone vibration (Colebatch et al., 1994; Rosengren et al., 2010) (Fig. 1). The abnormality of cVEMP can be found in various central and peripheral vestibular disorders that involve the saccular pathways (Shin et al., 2009; Chiarovano et al., 2011; Huang and Young, 2012; Oh et al., 2013; Choi et al., 2014; Kim et al., 2015; Chang et al., 2017; Maheu et al., 2017; Okumura et al., 2017). Moreover, cVEMP abnormality unrelated to other audio-vestibular or neuro-otological signs (isolated cVEMP abnormality) has drawn attention; for example, abnormal cVEMP may predict evolution of isolated recurrent vertigo into Meniere's disease (Lee et al., 2017). Isolated cVEMP abnormality may be also implicated in idiopathic otolithic vertigo, which is characterized by tilting or translational false motion sense from unknown causes (Murofushi et al., 2013; Fujimoto et al., 2018).

There are two representative parameters of cVEMP, amplitude and latency (Fig. 1). Interestingly, cVEMP amplitude decreases with age, which infers that ageing affects the neural function originating from the saccule (Colebatch et al., 2013; Zu Eulenburg et al., 2017). On the other hand, there is little known about the effect of ageing on cVEMP latency. The ageing process is influenced not only by genetic predisposition but also by acquired systemic conditions (Rodriguez-Rodero et al., 2011). Indeed, various acquired disorders, such as hypertension, diabetes, dyslipidemia, and smoking, may exacerbate certain vestibular and balance disorders (Agrawal et al., 2009; Jeong et al., 2009, 2013; Li et al., 2015; Wu et al., 2017). Hence, systemic factors may accelerate the decline of neural function derived from the saccule. However, the association between saccule-related neural function and systemic factors has been poorly understood in vertiginous disorders of unclear causes. Therefore, this study aimed to identify systemic factors possibly affecting the neural function derived from the saccule using the air-conducted cVEMP.

## 2. Methods

### 2.1. Patients & evaluation

We retrospectively recruited 1471 consecutive vertiginous patients, who visited the Dizziness Center at the Seoul National University Bundang Hospital from March to November 2017. Firstly, the patients diagnosed with benign paroxysmal positional vertigo (n = 236), vestibular neuritis (n = 77), Meniere's disease (n = 126), and central vestibular lesions (n = 188), such as stroke, tumor, or cerebellar ataxia were excluded from this study. The remaining 844 patients were diagnosed as having benign recurrent vertigo with undetermined causes (n = 380), persistent postural-perceptual dizziness (n = 353), or vestibular migraine (n = 111). Of the 844 patients, 129 who had a complete set of video head impulse tests, cVEMP, pure tone audiometry, and serological results were included (Fig. 2). The evaluation of systemic disorders included a history of hypertension, stroke, and coronary artery disease and a laboratory assessment, such as complete blood cell counts, lipid profiles, estimated glomerular filtering rate (eGFR), and serum levels of hemoglobin A1c (HbA1c), C-reactive protein (CRP), thyroid and parathyroid hormone, c-telopeptide, osteocalcin, and vitamin D. The institutional review board of Seoul National University Bundang Hospital approved the protocol of this retrospective, observational study (IRB number: B-1808-484-104) and waived patient consent.

### 2.2. Cervical VEMPs

The detailed method and normalized data for cVEMP in our institute were described previously (Lee et al., 2017). Briefly, cVEMP was recorded using a Nicolet Viking Select unit (Nicolet-Biomedical, Madison, WI, USA). The stimulus, a burst tone sound (110 dB nHL, 123.5 dB SPL, 500 Hz, linear envelope with 2 ms of rise and fall time and 3 ms of plateau), was applied at 2.1 Hz monoaurally via a headphone. The responses of up to 80 stimuli were averaged for each test, and two trials were obtained from each ear. During the evaluation of cVEMP, the sternocleidomastoid

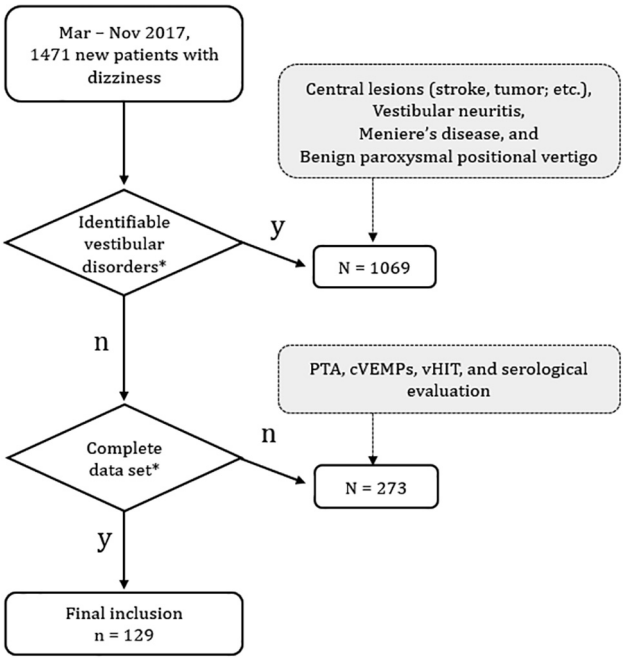


**Fig. 2.** Flow diagram of patient inclusion. PTA, pure tone audiometry; cVEMP, cervical vestibular-evoked myogenic potentials; vHIT, video head impulse test.

muscular activities were simultaneously recorded via surface electrodes and digitalized with 1 kHz intervals using an analog-to-digital converter (NI PCI-4461, National Instruments, Austin, TX, USA). Then we used the LabVIEW program (National Instruments) that automatically measures and rectifies the peak-to-peak amplitudes of the sternocleidomastoid muscular activities and calculates the mean tonic muscular activation during the recording. The amplitude of raw cVEMP response was then normalized using the mean tonic activation of the sternocleidomastoid muscle (normalized cVEMP amplitude). The ratio of interaural difference was defined as $[(NAR - NAL)/(NAR + NAL) \times 100]$. NAR and NAL are the normalized amplitude of cVEMP during right and left ear stimulation, respectively.

### 2.3. Sum of normalized cVEMP amplitude (SNA) and average latency (AL)

In the present study, we used the amplitude and latency of cVEMP as parameters to evaluate systemic risk factors possibly affecting saccule-related neural function. The amplitude parameter was defined as the sum of normalized cVEMP amplitude (SNA) by adding the normalized cVEMP amplitudes of the two ears. For the latency parameter, we used average of p13 latency of the two ears (AL).

### 2.4. Statistical analysis

Data are presented as mean and standard deviation or median and interquartile range for continuous variables and number and percentage for categorical variables. To investigate the association between cVEMP parameters and possible risk factors, we adopted univariable and multivariable linear regression analysis. In regression analysis, the six patients with no response in the test were included in the analysis of SNA with a value of zero but were excluded from the analysis of AL. Covariables with p value less than 0.2 in the univariable analysis were included in the multivariable regression analysis. Beta coefficient (β) was presented with 95% confidence interval (CI). Statistical analyses were performed using SPSS Statistics for Windows (version 20.0, IBM, US) and Statistics and Machine Learning Toolbox of MATLAB version R2018a (MathWorks, Natick, MA, US).

## 3. Results

### 3.1. Baseline characteristics of included patients

Clinical characteristics of 129 patients are presented in Table 1. The mean age was 52.4 ± 13.9, and about three-quarters of the patients were women. Among them, 124 (83.7%) patients were diagnosed with either benign recurrent vertigo from an undetermined cause (n = 70, 54.3%) or persistent postural-perceptual dizziness (n = 58, 45.0%). Four were considered to have overlapping symptoms of persistent postural-perceptual dizziness and benign recurrent vertigo. The remaining five patients were diagnosed with vestibular migraine.

The prevalence of hypertension and cerebrovascular/cardiovascular disease (such as stroke and myocardial infarction) was 18.6% and 6.1%, respectively. Serological blood tests indicated that patients had controlled blood sugar (5.5% of HbA1c) and lipid levels (187.9 and 103.0 mg/dl of total and low-density lipoprotein cholesterol, respectively) as well as normal renal (95.0 ml/min/1.73 $m^2$ of eGFR) and euthyroid function (1.37 ng/dL of free T4; reference range, 0.89 ± 1.79 ng/dL). The levels of parathyroid hormone,

**Table 1**
Demographic characteristics and audio-vestibular function of patients (n = 129).

| | | | |
|---|---|---|---|
| Demographic characteristics | | | |
| Age (years) | 52.4 ± 13.9 | Sex (female) | 95 (73.6%) |
| HTN | 24 (18.6%) | Stroke or MI | 8 (6.1%) |
| ALP (IU/L) | 71.0 ± 23.1 | CRP (mg/dL) | 0.12 ± 0.26 |
| Calcium (mg/dL) | 9.3 ± 0.4 | C-telopeptide (μg/L) | 0.448 ± 0.247 |
| eGFR (mL/min/1.73 $m^2$) | 95.0 ± 19.6 | Hematocrit (%) | 41.5 ± 3.8 |
| Hemoglobin A1c (%) | 5.5 ± 0.6 | Free T4 (ng/dL) | 1.37 ± 0.30 |
| Total-Cholesterol (mg/dL) | 187.9 ± 39.5 | Triglyceride (mg/dL) | 111.8 ± 73.2 |
| HDL-Cholesterol (mg/dL) | 55.6 ± 12.4 | LDL-Cholesterol (mg/dL) | 103.0 ± 28.5 |
| Osteocalcin (ng/mL) | 22.3 ± 9.1 | PTH (pg/mL) | 29.4 ± 11.6 |
| Phosphorus (mg/dL) | 3.7 ± 0.5 | Vitamin D (ng/mL) | 19.6 ± 8.2 |
| Cervical VEMP | | | |
| R Normalized amplitude (μV) | 2.06 ± 1.19 | R p13 latency (ms) | 15.25 ± 1.20 |
| L Normalized amplitude (μV) | 2.34 ± 1.47 | L p13 latency (ms) | 15.33 ± 1.50 |
| Normalized IAD (%) | 14.5 ± 19.7 | AL (ms) | 15.31 ± 1.22 |
| SNA | 4.40 ± 2.53 | | |
| Video-HITs | | | |
| R HC gain | 1.05 ± 0.04 | L HC gain | 1.02 ± 0.06 |
| R AC gain | 1.02 ± 0.05 | L AC gain | 1.02 ± 0.05 |
| R PC gain | 0.99 ± 0.05 | L PC gain | 0.98 ± 0.06 |
| Pure tone audiometry | | | |
| R PTA 250 Hz (dB) | 9.2 ± 6.4 | L PTA 250 Hz (dB) | 8.5 ± 6.5 |
| R PTA 500 Hz (dB) | 10.4 ± 7.3 | L PTA 500 Hz (dB) | 10.5 ± 6.6 |
| R PTA 1000 Hz (dB) | 12.7 ± 7.4 | L PTA 1000 Hz (dB) | 12.3 ± 7.8 |
| R PTA 2000 Hz (dB) | 14.2 ± 9.4 | L PTA 2000 Hz (dB) | 14.2 ± 10.4 |
| R PTA 4000 Hz (dB) | 20.2 ± 16.3 | L PTA 4000 Hz (dB) | 21.9 ± 18.1 |
| R PTA 8000 Hz (dB) | 29.3 ± 21.8 | L PTA 8000 Hz (dB) | 29.0 ± 21.9 |

Data are presented as mean and standard deviation or median and interquartile range for continuous variables and a number and percentage for categorical variables.
AC, anterior canal; AL, average of p13 latency on both sides; ALP, alkaline phosphatase; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HC, horizontal canal; HDL, high density lipid; HTN, hypertension; IAD, interaural difference; L, left; LDL, low density lipid; MI, myocardial infarction; PC, posterior canal; PTA, pure tone audiometry; PTH, parathyroid hormone; R, right; SNA, sum of normalized cVEMP amplitude; VEMPs, vestibular evoked myogenic potentials; video-HIT, vide head impulse test.

calcium, phosphorus, alkaline phosphate, osteocalcin, and c-telopeptide were within respective reference ranges. However, the mean value of total vitamin D was decreased in these patients (19.6 ng/dl; reference range, 30–50 ng/dl).

Of 129 patients, 72 (55.8%) had abnormal cVEMP. Specifically, 62 showed a decreased normalized amplitude, 2 had an increased interaural difference, and 8 had both decreased normalized amplitude and increased interaural difference. Mean normalized cVEMP amplitude was 2.06 ± 1.19 and 2.34 ± 1.47 in the right and left ears (reference range, >2.1). The interaural difference of normalized cVEMP amplitudes was 14.5 ± 19.4% (reference range, <20%). The p13 latency of cVEMP was 15.25 ± 1.20 and 15.33 ± 1.50 in the left and right ears, respectively. Therefore, SNA was 4.40 ± 2.53, and AL was 15.31 ± 1.22.

The mean gain for the video head impulse test was normal in all six semicircular canals (>0.9). The mean threshold levels of pure tone audiometry up to 2000 Hz were normal (<25 dB) but were slightly increased at 4000 and 8000 Hz in both ears.

### 3.2. Potential risk factors for deterioration of cVEMP

In terms of SNA, univariable analysis revealed that SNA was negatively associated with age (β = −0.066; 95% CI = −0.095 to −0.036) and HbA1c (β = −0.850; 95% CI = −1.597 to −0.104) and was positively associated with eGFR (β = 0.034; 95% CI = 0.013–0.056) ($p < 0.05$) (Table 2). Therewithal, SNA showed a trend of association with hematocrit, CRP, vitamin D, and free T4 ($p < 0.2$).

In multivariable analysis with all those variables entered simultaneously, SNA was significantly associated with age, free T4, and eGFR ($p < 0.05$) (Table 3, Model 1) (Fig. 3). However, vitamin D, HbA1c, CRP, and hematocrit did not have any association with SNA. The results were reaffirmed through regression with the method of backward selection because age, free T4, and eGFR were finally remained (Table 3, Model 2) (Fig. 3).

The main and interaction effects of the variables associated with SNA were also analyzed (Table 3). In that, free T4 and age had a significant association (β = 0.196; 95% CI = 0.031–0.360). In the subgroups divided by median age (55.2 years), SNA was significantly associated with free T4 in younger patients [mean age = 41.5 ± 9.91; 47 (72.3%) women; β = −1.631; 95% CI = −3.174 to −0.088] but not in older ones [mean age = 63.5 ± 6.54; 48 (73.8%) women; β = −1.082; 95% CI = −5.277 to 3.113). In contrast, no meaningful interaction was observed between free T4 and eGFR (β = −0.001; 95% CI = −0.042 to 0.049) or between age and eGFR (β = 0; 95% CI = −0.001 to 0.002).

With regard to AL, univariable analysis showed that AL had no significant association with any variable ($p < 0.05$). There was a trend of association between AL and age (β = 0.008; 95% CI = −0.006 to 0.022), between AL and alkaline phosphate (β = 0.005; 95% CI = −0.036 to 0.013), and between AL and free T4 (β = −0.377; 95% CI = −0.958 to 0.204) ($p < 0.2$). In multivariable analysis, however, AL was not significantly associated with any of those variables (Supplementary Table S1).

**Table 2**
Potential risk factors for deterioration of cervical VEMP in terms of SNA in univariable regression analysis.

| Variables | Beta coefficient (95% CI) | *P*-value |
|---|---|---|
| Age (years) | −0.066 (−0.095 to −0.036) | <0.001 |
| Sex (female) | 0.067 (−0.938 to 1.071) | 0.896 |
| HTN | 0.144 (−0.993 to 1.281) | 0.802 |
| Stroke or MI | 0.470 (−1.363 to 2.303) | 0.613 |
| ALP (IU/L) | −0.004 (−0.023 to 0.015) | 0.694 |
| Calcium (mg/dL) | 0.246 (−1.017 to 1.510) | 0.700 |
| C-telopeptide (μg/L) | −0.913 (−2.707 to 0.880) | 0.316 |
| CRP (mg/dL) | −1.442 (−3.109 to 0.225) | 0.089 |
| eGFR (mL/min/1.73 $m^2$) | 0.034 (0.013–0.056) | 0.002 |
| Free T4 (ng/dL) | −1.149 (−2.626 to 0.329) | 0.126 |
| HbA1c (%) | −0.850 (−1.597 to −0.104) | 0.026 |
| Hct (%) | 0.114 (−0.001 to 0.229) | 0.052 |
| Osteocalcin (ng/mL) | −0.023 (−0.072 to 0.026) | 0.354 |
| PTH (pg/mL) | 0.001 (−0.037 to 0.040) | 0.938 |
| Phosphorus (mg/dL) | 0.205 (−0.652 to 1.061) | 0.637 |
| Total-Cholesterol (mg/dL) | −0.001 (−0.012 to 0.010) | 0.843 |
| Triglyceride (mg/dL) | 0.001 (−0.005 to 0.007) | 0.843 |
| HDL-Cholesterol (mg/dL) | 0.009 (−0.027 to 0.045) | 0.607 |
| LDL-Cholesterol (mg/dL) | −0.006 (−0.021 to 0.010) | 0.473 |
| Vitamin D (ng/mL) | −0.048 (−0.101 to 0.005) | 0.077 |

CI, confidence interval. Other abbreviations are same in Table 1.

**Table 3**
Potential risk factors for deterioration of cervical VEMP in terms of SNA in multivariable regression analysis.

| Variables | Beta coefficient (95% CI) | *P*-value |
|---|---|---|
| *Model 1* | | |
| Age (years) | −0.045 (−0.083 to −0.007) | 0.021 |
| CRP (mg/dL) | −1.221 (−2.782 to 0.340) | 0.124 |
| eGFR (mL/min/1.73 $m^2$) | 0.024 (0.000–0.049) | 0.049 |
| Free T4 (ng/dL) | −1.606 (−3.019 to −0.194) | 0.026 |
| HbA1c (%) | −0.083 (−0.875 to 0.709) | 0.836 |
| Hct (%) | 0.077 (−0.032 to 0.187) | 0.164 |
| Vitamin D (ng/mL) | −0.008 (−0.061 to 0.045) | 0.763 |
| *Model 2* | | |
| Age (years) | −0.053 (−0.087 to −0.020) | 0.002 |
| eGFR (mL/min/1.73 $m^2$) | 0.023 (−0.001 to 0.047) | 0.063 |
| Free T4 (ng/dL) | −1.738 (−3.144 to −0.331) | 0.016 |
| *Main and interaction effects of age and free T4 on SNA* | | |
| Age (years) | −0.337 (−0.565 to −0.109) | 0.004 |
| Free T4 (ng/dL) | −11.379 (−19.869 to −2.889) | 0.009 |
| Age * Free T4 | 0.196 (0.031–0.360) | 0.020 |
| *Main and interaction effects of age and eGFR on SNA* | | |
| Age (years) | −0.081 (−0.246 to 0.083) | 0.331 |
| eGFR (mL/min/1.73 $m^2$) | −0.001 (−0.093 to 0.095) | 0.981 |
| Age * eGFR | 0.000 (−0.001 to 0.002) | 0.747 |
| *Main and interaction effects of eGFR and free T4 on SNA* | | |
| eGFR (mL/min/1.73 $m^2$) | 0.043 (−0.022 to 0.107) | 0.192 |
| Free T4 (ng/dL) | −1.711 (−7.826 to 4.403) | 0.581 |
| eGFR * Free T4 | −0.001 (−0.042 to 0.040) | 0.970 |

In the multivariable model 1, all variables were entered simultaneously, but in the multivariable model 2, the method of stepwise backward selection was used. Abbreviations are same in Table 1.

## 4. Discussion

In the present study, we investigated the associations between cVEMP parameters and systemic conditions. Decreased cVEMP amplitude was significantly associated with age and low eGFR. In addition, it was associated with a high level of free T4 only in the younger group. In contrast, cVEMP latency had no definitive association with systemic conditions. The results suggest that age-related deterioration of saccule-related neural function measured as cVEMP amplitude could be hastened by systemic factors such as chronic renal disease and hyperthyroidism. It also implies that saccular dysfunction should be managed according to the systemic conditions of patients.

In this study, ageing-related deterioration of saccule-related neural function was reaffirmed. Indeed, unlike the function of semicircular canal that yet remains controversial in term of ageing-effect (McGarvie et al., 2015; Kim and Kim, 2018), the deterioration of neural function originating from the saccule with ageing has been consistent across the studies (Colebatch et al., 2013; Zu Eulenburg et al., 2017). However, the different impact of ageing on the function of canal and saccule should be evaluated further. Though hypothetical, the vulnerability of saccule due to ageing

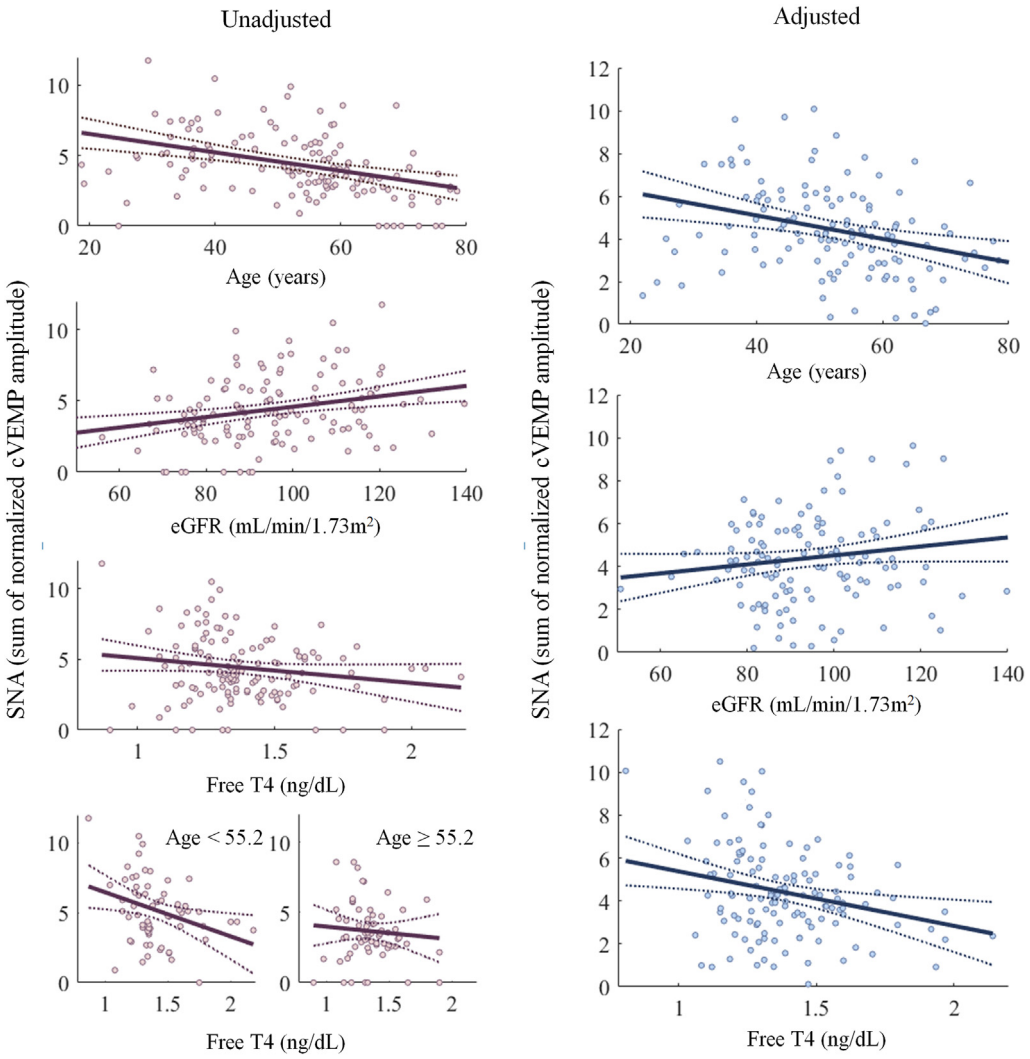


**Fig. 3.** The relationships between SNA and risk factors. The left column displays unadjusted associations of age, eGFR, and free T4 (marked on horizontal axis) with SNA. The bottoms of the left column present the different effects of free T4 on SNA according to the age groups. The right column shows the results of multivariable regression model 2, where the data distribution and slope of each risk factor were adjusted by other risk factors (i.e. the association of age with SNA was adjusted by eGFR and free T4). In all graphs, the thick line indicates the beta coefficient of each risk factor and the thin lines indicate 95% confidence interval. SNA = sum of normalized amplitude; eGFR = estimated glomerular filtration rate.

may be attributed to its structural characteristics. Saccule sense the gravito-inertial acceleration of the head mostly applied on the rostro-caudal and Naso-occipital axis (Baloh and Kerber, 2011). At head-upright and supine positions, the most common head positions of human being, the gravity constantly pulls down the otoconia on the saccular macule. Therefore, we assume that this constant mechanical force relayed on the saccule cause the otoconia easily detaching from the saccular macule, thereby exacerbates the saccular dysfunction in aging process.

In addition to ageing, we addressed whether the neural function derived from the saccule can be affected by vascular risk factors such as history of hypertension and myocardial infarction/stroke, low eGFR, and abnormal serum levels of HbA1c, triglyceride, and cholesterols. Multivariable regression analysis revealed that the eGFR was a vascular risk factor positively associated with cVEMP amplitude. The eGFR originally refers to the fluid volume filtered from the renal microvasculature per unit time and reflects global renal function (Stevens et al., 2006). Currently, the eGFR has been considered a serologic marker indicating arteriolar dysfunction in the brain, heart, and retina in addition to the kidney (Sarnak et al., 2003; Thompson and Hakim, 2009). The decline of eGFR especially in the brain is associated with small vessel disease, such as cerebral leukoaraiosis (Khatri et al., 2007; Ikram et al., 2008), lacuna infarction (Putaala et al., 2011), or microbleeds (Cho et al., 2009). The arteriole supplying blood to the saccular macule branches perpendicularly from the small saccular artery (Mazzoni, 1990). Hence, the sacculopathy manifested as decline of cVEMP amplitude may be small artery disease in the inner ear, and low eGFR can be a possible risk factor for ischemic saccular damage.

Though high frequency hearing (≥4 kHz) was mildly decreased, it is noteworthy that the canal or cochlea functions were relatively preserved in the studied patients. While the canal and cochlea are supplied by the circumflex artery such as the superior vestibular artery or main cochlear artery, the saccule has dual vascular supply from terminal branches of the posterior vestibular artery and the anterior vestibular artery (Mazzoni, 1990). Cerebral leukoaraiosis develops in the internal border-zone between the lenticulostriate perforators and the deep penetrating cortical branches of the middle cerebral artery (Ryu et al., 2014), and the border-zone area may

be more vulnerable to the hemodynamic changes or chronic ischemia. Because the saccule is localized in the vascular border-zone in the inner ear, the distinct vasculature may result in the decline of cVEMP amplitude, although the canal and cochlea functions are preserved.

Bone metabolism was also examined in this study using serum levels of vitamin D, parathyroid hormone, free T4, phosphorus, calcium, alkaline phosphatase, C-telopeptide, and osteocalcin. Vitamin D and free T4 showed a trend of association with cVEMP amplitude in univariable regression analysis, but only free T4 had a significant association with cVEMP amplitude in multivariable regression analysis. An increased free T4 causes osteoporosis by increasing the rate of bone turnover, shortening the cycle of bone remodeling, and disturbing the ratio between bone formation and resorption (Bassett and Williams, 2003; Tuchendler and Bolanowski, 2014). Otoconia mainly comprising calcium carbonate are in a dynamic state under bone metabolism (Ross, 1979; Vibert et al., 2008). In addition, some evidence suggests a sequential links between osteoporosis and benign paroxysmal positional vertigo (BPPV) (Jeong et al., 2009; Yamanaka et al., 2013), and between BPPV and abnormal cVEMP (Kim et al., 2015). Therefore, increased free T4 may affect homeostasis of otoconia and result in the decline of cVEMP amplitude in this study. Notably, a significant interaction was found between free T4 and age, and the effect of free T4 on cVEMP amplitude was only revealed after adjusting the age. This result may suggest that increased free T4 affects homeostasis of otoconia mainly in the young patients, but not in the old patients, considering that hyperthyroidism is an established risk factor for osteoporosis of younger population (Ferrari et al., 2012).

Two essential questions still remain in this study. One is whether the isolated saccular dysfunction can cause dizziness or vertigo. In fact, otolithic vertigo has referred to an episodic inertial (tilting or translational) sensation of the patients with otolithic dysfunction (Murofushi et al., 2013; Fujimoto et al., 2018), but the mechanism of vertiginous symptoms remains obscure. The saccule converts a physical variable (gravito-inertial acceleration) into an electrical signal (vestibular discharge). In this study, we assumed that the degeneration of saccule-related neural function might result in loss, delay, and noise of vestibular signal relaying gravito-inertial acceleration and finally cause a false linear motion sense. The second question is whether the included patients have other vestibular disorders besides otolithic dysfunction manifested by abnormal cVEMP. In fact, the disorders in the included patients could be classified into persistent postural-perceptual dizziness (Strupp et al., 2003), vestibular migraine (Radtke et al., 2012), or benign recurrent vertigo as a form of Meniere's disease without hearing loss (Haid et al., 1995). However, because cVEMP abnormality is not a diagnostic criterion for those disorders, it is still unclear what the final diagnoses in these patients are.

## 5. Limitation

This study has several limitations. The retrospective design had undetected selection biases. The sample size was relatively small in this study, and the association between cVEMP and other well-known cardiovascular and bone metabolic indicators could not be efficiently evaluated. Lastly, the utricular function could not be evaluated using ocular VEMP due to limitation of domestic health insurance policy. Future studies are needed to resolve these limitations.

## 6. Conclusion

Besides ageing, the neural function originating from the saccule determined by abnormal cVEMP can be affected by other systemic factors, and decreased eGFR and increased free T4 are potential risk factors. Appropriate management of these conditions may be important for patients with dizziness due to dysfunction of the saccular pathway.

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## Disclosures

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 disclosure.

## Author contributions

I.J. analyzed the data and drafted the manuscript; S.H.A, J.L, S.U.L, H.J.O, and H.J.K. acquired and analyzed the data; J.Y.C. conceptualized the study, acquired and analyzed the data and drafted the manuscript; J.S.K. analyzed the data and revised the manuscript.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.02.002.

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