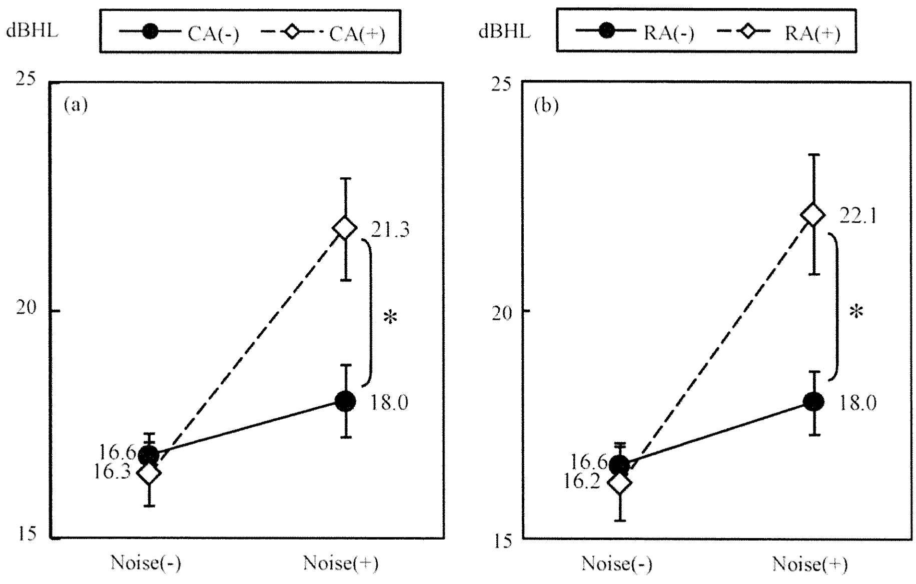


Fig. 1. (a) Comparative plotting of mean pure-tone thresholds at 500 Hz by occupational noise exposure and carotid atherosclerosis (CA) with adjustments for age. (b) Comparative plotting of mean pure-tone thresholds at 500 Hz by occupational noise exposure and retinal atherosclerosis (RA) with adjustments for age. Error bars show the standard error of the mean. Asterisk shows statistically significant difference ($p < 0.05$).

Study population [13]. They concluded that in an older population, retinopathy, a sign of retinal micro-vascular damage, was associated with hearing loss in women, particularly low-frequency losses.

We found that a significant main effect of CA was present at 8000 Hz even after controlling for the strong association of noise and age with hearing. The proximal portion of the cochlea, where high-frequency sounds are transduced, is vulnerable to many factors, such as age, noise exposure, ototoxic drugs, and therefore these risk factors are more frequently associated with high-frequency hearing loss [14]. As is shown in Table 4, $F$-values for noise and age at high-frequency thresholds were extremely high. Despite this disadvantageous condition, an independent effect of CA has persisted without being masked by the enormous effects of noise and age. The data suggest that the impact of arterial sclerosis on hearing is limited but significantly hazardous.

The interactive effects of noise exposure and arterial sclerosis were greater at low-frequency thresholds than at high-frequency thresholds. Possible interpretation is that the blood supply of the cochlea is most distal at the apex where low-frequency sounds are transduced [15,16]. It is also likely that diffuse vascular lesions affect low-frequency hearing [14]. Another explanation is that, because the respective effects of noise and age are enormous for high-frequency hearing loss, the interactive effects of noise and arterial sclerosis may be so small as to be masked by these predominant effects on high-frequency hearing loss.

An epidemiological approach has been performed to investigate the association between vascular risk factors and hearing loss. Hypertension and cardiovascular disease have been thought to have some relation to hearing loss [17,18]. Gates et al. reported that low-frequency hearing (250–1000 Hz) was related to cardiovascular disease events in both genders, especially women [17]. They proposed that noise-induced hearing loss may overshadow the effects of cochlear micro-vascular disease in men, while micro-vascular disease plays a greater role in low-frequency hearing loss in women. In this analysis, we assessed the impact of arterial sclerosis on hearing in men, taking account of the contribution of noise exposure. Our findings suggest that arterial sclerosis plays a role in hearing loss in men, and that the combined effects of noise exposure and arterial sclerosis in the cochlea could be synergistic. Determining if these combined risks also affect women will require additional studies.

Certain limitations should be noted. First, the present investigation on noise exposure was qualitative and not quantitative. The extent that noise affects cochlear blood flow appears to be heavily influenced by the length and intensity of noise exposure [19]. The variability in individual noise exposure could not be accounted for in this analysis. Second, neither the common carotid artery IMTs nor the stage of KWB classification is a direct indicator of cochlear blood flow. The inner ear artery (labyrinthine artery), which is usually a branch of the anterior inferior cerebellar artery (AICA), nourishes the inner ear, which is composed of the cochlea and the vestibular apparatus [16]. To date, there are no studies that have reported a useful and easily accessible marker for cochlear blood flow, and it was difficult to find direct evidence of impaired cochlear blood flow. This is because the cochlea, unlike the ocular fundus, is surrounded by bone, which prevents the direct observation of blood vessels [16].

We used both intima-media thickness of the carotid artery and narrowing of the retinal arterioles as indicators of cochlear blood flow. The IMT of the common carotid artery provides an index of general atherosclerosis in other vascular regions and has been shown to be associated with most atherosclerosis risk factors [20]. Recently, an increase in the carotid IMT has been directly associated with an increased risk of myocardial infarction and stroke in older adults with no history of cardiovascular disease [21]. The retinal microcirculation offers a unique opportunity to assess correlates and consequences of systemic micro-vascular disease in a non-invasive fashion, suggesting that retinal micro-vascular changes may reflect structural and functional damage elsewhere in end-organ tissues. Narrowing of the retinal arterioles has been associated with persistently elevated blood pressure and inflammation and predicts stroke independently of other risk factors [22,23]. Both the IMT of the common carotid artery, a marker of early atherosclerosis, and retinal arteriolar narrowing, a marker of arteriolosclerosis, are associated with a higher risk and greater pathogenesis of general atherosclerosis throughout the body. The advantages of these two markers have been shown when predicting vascular pathology, such as ischemic stroke and cardiovascular disease, even though the vascular source of each marker is different from that of the target organ; therefore, the IMT and the stage of KWB classification are representative and non-invasive risk indicators of arterial sclerosis. In the present study, both atherosclerosis and arteriolosclerosis were associated with increased effects of noise exposure on hearing, implying that these vascular markers could predict the pathology of cochlear blood flow.

The advantages of the current analysis are that it is a large, population-based study with a careful assessment of study factors and outcome factors. In addition, we used two risk indicators to assess arterial sclerosis; IMT and the stage of KWB classification.

Whether there is a relationship between impaired cochlear blood flow and damage in a hearing frequency domain remains an important question. However, our findings suggest that reduced blood flow does contribute to hearing loss as the impact of arterial sclerosis at high-frequency, and as the interactive effects of noise exposure and arterial sclerosis at low frequencies. Underlying arterial sclerosis potentially results in increased susceptibility for many risk factors for hearing loss. Early recognition of arterial sclerosis found in carotid artery and retinal changes might be contributory to the hearing prognosis after middle age, especially for noise-exposed men.

## 5. Conclusions

The main effect of arterial sclerosis and the combined effect with noise exposure on hearing were investigated in a community-dwelling middle-aged and elderly sample of men. A significant main effect of CA on pure-tone threshold was observed at 8000 Hz. The presence of CA and RA aggravated the hearing thresholds in noise-exposed subjects, especially at low frequencies. The present study suggests that the impact of arterial sclerosis alone was limited but significantly hazardous on hearing, and that the harmful effects of noise exposure on hearing were enhanced by arterial sclerosis. Early recognition of general atherosclerosis might be contributory to the hearing prognosis after middle age, especially for noise-exposed men.

## Conflicts of interest

There are no conflicts of interest.

## Acknowledgements

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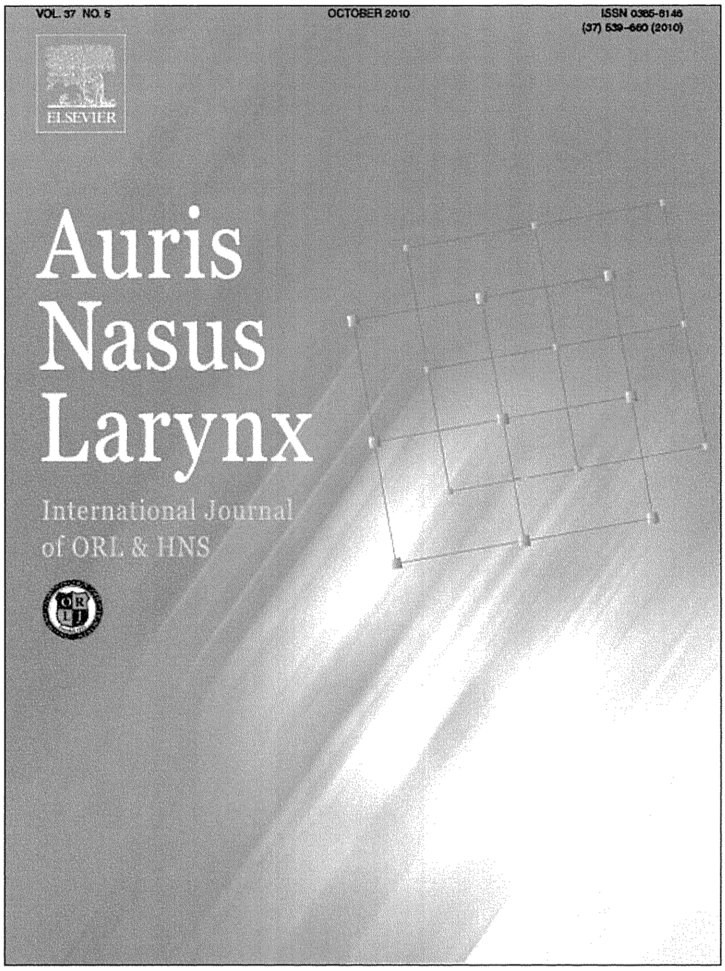
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# Diabetes reduces auditory sensitivity in middle-aged listeners more than in elderly listeners: A population-based study of age-related hearing loss



**Authors' Contribution:**
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

**Yasue Uchida[1ACDEF], Saiko Sugiura[1BF], Fujiko Ando[2,3BD], Tsutomu Nakashima[4DF], Hiroshi Shimokata[3BCDG]**

[1] Department of Otorhinolaryngology, National Center for Geriatrics and Gerontology, Aichi, Japan
[2] Faculty of Medical Welfare, Aichi Shukutoku University, Aichi, Japan
[3] Department of Epidemiology, National Center for Geriatrics and Gerontology, Aichi, Japan
[4] Department of Otorhinolaryngology, Nagoya University School of Medicine, Nagoa, Japan

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## Summary

**Background:** Diabetes mellitus (DM) and hearing impairment are both highly prevalent in older adult populations, but how the impact of diabetes on hearing varies by age is not well-studied.

**Material/Methods:** The subjects were 2306 adults aged 40 to 86 years who participated in a population-based study of aging, and were divided into 2 age groups, 40–64 years and 65–86 years, for cross-sectional analysis. Air-conduction pure-tone thresholds at octave intervals from 125 to 8000 Hz were obtained. Outcomes were categorized in relation to presence or absence of DM. Hearing levels at 7 frequencies were set in the general linear model as objective variables with adjustment for confounders. Explanatory variables were age (<65 years vs. >65 years), DM (absence vs. presence), and interaction between age and DM.

**Results:** A statistically-significant adverse effect of DM on hearing was observed. This effect varied by age at the higher frequencies. The DM-age interaction was not synergistic at any test frequencies. No significant effects of the DM-age interaction were observed below 4000 Hz. In contrast, significant reciprocal effects of the DM-by-age interaction were found at 4000 Hz and 8000 Hz. Diabetes may accordingly affect higher-frequency hearing more strongly in the younger age-bracket.

**Conclusions:** This study demonstrated that diabetes detrimentally affected hearing in community-dwelling middle-aged and elderly people, and that the effect of diabetes on higher-frequency hearing might be stronger in middle age. Screening for hearing impairment in diabetic patients may provide benefits for intervention or prevention of early presbycusis, particularly in this age group.

**key words:** **diabetes • aging • hearing • interaction • population-based study**

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**Author's address:** Yasue Uchida, Department of Otorhinolaryngology. National Center for Geriatrics and Gerontology, 36-3 Gengo, Morioka, Obu, Aichi 474-8511, Japan, e-mail: yasueu@ncgg.go.jp

## BACKGROUND

Diabetes mellitus (DM) is a prevalent disease in older people. DM in older adults has become a major public health problem, affecting an increasing number of individuals worldwide. According to a 2006 national nutrition survey in Japan, the rates of likely DM (HbA1c >6.1% or in treatment) were 3.2%, 10.2%, 13.6%, and 18.0% for people in their 40s, 50s, 60s, and 70s or over, respectively. The rates of subclinical DM (HbA1c 5.6–6.1%) were 14.2%, 19.0%, 23.1%, and 24.7% for people in their 40s, 50s, 60s, and 70s or over, respectively [1].

Hearing loss is also highly prevalent in older adult populations [2,3]. Research has shown that presbycusis affects about 30% of people aged 65 and over [4,5], and that about half of the population aged over 75 years has significant hearing loss [6].

A relationship between DM and hearing loss was first proposed in a case report by Jordao in 1857 [7]. Although this potential association has been investigated ever since then [8–13], it has not been as firmly established as the association between DM and its known complications affecting the renal, visual, and peripheral nervous systems. Several factors, such as noise exposure, presbycusis, and syndromic hearing loss, might confound the association between DM and hearing impairment. Although aging is thought to be a key factor in both glucose metabolism and cochlear function, it is difficult to demonstrate the interrelated contribution of DM and aging to hearing impairment.

We aimed to investigate the impact of DM on hearing, and the relationship between this and age, in middle-aged and elderly community-dwelling individuals.

## MATERIAL AND METHODS

### Subjects

The present study was conducted as part of the comprehensive 'Longitudinal Study of Aging (NILS-LSA)' conducted by the National Institute for Longevity Sciences of the National Center for Geriatrics and Gerontology. The NILS-LSA is a population-based biennial survey of a cohort of approximately 2200 people, which started in November 1997. The subjects of the NILS-LSA were randomly selected from resident registrations, stratified by both age and sex. Details of the methodology used in the NILS-LSA have been reported elsewhere [14]. The study protocol was reviewed by the Ethical Committee of the National Center for Geriatrics and Gerontology, and written informed consent was obtained from all participants.

Data obtained from the 4$^{th}$ wave examination of NILS-LSA were analyzed cross-sectionally in the present study. Participants were 2383 adults aged 40 to 86 years who took part in the NILS-LSA between May 2004 and July 2006. Demographic characteristics, personal history, family history, lifestyle habits, and medical history were obtained from detailed questionnaires filled out before the examination visit. Venous blood was collected early in the morning after at least 12 hours' fasting.

The definition of DM was based on medical history obtained from questionnaires, or defined as a fasting plasma glucose concentration greater than 126 mg/dl and an HbA1c of more than 6.5%, or the taking of medication to lower the blood glucose level. In this way, participants were classified into a DM (+) group and a DM (–) group. Histories of ear disease and occupational noise exposure were obtained from the self-reported questionnaire. Occupational noise was defined in our questionnaires as background noise in a work environment over which the worker could not hold a conversation in a normal voice. Former and current noise exposures were combined. History of ear disease and history of occupational noise exposure were treated as binary variables (presence =1, absence =0).

Those who did not undergo blood testing, had incomplete hearing measurements, or provided invalid questionnaire responses were eliminated from the analysis. Accordingly, 2306 participants with complete data were selected for the present analysis. The subjects were divided into 2 groups for analysis: 40–64 and 65–86 years (Table 1).

### Audiometric measurements

Audiometric measurements were examined in a soundproof compartment by laboratory technicians on the same day of the blood draw. Air-conduction pure-tone thresholds at octave intervals from 125 to 8000 Hz were obtained using diagnostic audiometers (AA-73A and AA-78; Rion, Tokyo, Japan). The thresholds over the predetermined output level, according to the Japanese Industrial Standards T 1201 calibration, were treated as that level plus an additional 5 dB; that is to say, over 70 dB at 125 Hz was treated as 75 dB. For analyses of supraliminal levels we used 90 dB at 250 Hz, 105 dB at 500 to 4000 Hz, and 100 dB at 8000 Hz. Pure-tone averages (PTAs) were calculated for the better ear (BE) and the worse ear (WE) in order not to overlook subjects with at least 1 affected ear. The low-frequency PTA was calculated as the average threshold across the 125-, 250- and 500-Hz thresholds. The high-frequency PTA was calculated as the average across the 2000-, 4000- and 8000-Hz thresholds. The mid-frequency PTA was calculated as the average across the 500-, 1000-, 2000- and 4000-Hz thresholds. Hearing impairment was defined as PTAs greater than 25 dB.

### Statistical analyses

Statistical analyses were conducted using the Statistical Analysis System (SAS) version 9.13 (SAS Institute, Cary, NC, USA). All values are expressed as mean ± standard error if not specified otherwise. Comparisons of hearing impairment rates between the DM (–) group and DM (+) group by age were performed using the chi-square test. In multivariable analyses, general linear model (GLM) analyses were performed to assess both the individual and the interactive impacts of age and DM on hearing of the BE and WE, based on the mid-frequency PTA. Hearing levels at 7 frequencies were set in the GLM as objective variables. Explanatory variables were age (binary variable; <65 years vs. >65 years), DM (binary variable; absence vs. presence), and interaction between age and DM. Moderator variables were sex, history of ear disease, and history of occupational noise exposure.

## RESULTS

Table 1 shows the clinicodemographic profile of the subjects by age group and DM status. A total of 2306 participants

**Table 1.** Clinicodemographic profile of the subjects by DM status and age group.

| (mean ± SE) | 40–64 years | | | 65–86 years | | |
|---|---|---|---|---|---|---|
| | DM (–) | DM (+) | *p* | DM (–) | DM (+) | *p* |
| N | 1349 | 67 | | 806 | 84 | |
| Male (%) | 50.1 | 64.2 | 0.0246 | 48.4 | 56.0 | NS |
| Fasting blood glucose (mg/dl) | 96.3±0.4 | 159.7±1.6 | <.0001 | 98.9±0.6 | 146.2±1.8 | <.0001 |
| HbA1c (%) | 5.2±0.01 | 7.4±0.06 | <.0001 | 5.3±0.02 | 7.2±0.06 | <.0001 |
| History of ear disease (%) | 41.4 | 34.3 | NS | 33.3 | 33.3 | NS |
| History of occupational noise exposure (%) | 19.4 | 16.4 | NS | 18.9 | 25.0 | NS |

DM – diabetes mellitus.



**Table 2.** The prevalence of hearing impairment based on the low-frequency, high-frequency and mid-frequency PTA.

| Hearing impairment (%) | | 40–64 years | | | 65–86 years | | |
|---|---|---|---|---|---|---|---|
| | | DM (–) | DM (+) | p | DM (–) | DM (+) | p |
| Better ear | Low-frequency PTA$_{125,250,500}$ >25 dB | 5.6 | 13.4 | 0.0087 | 37.0 | 44.1 | NS |
| | High-frequency PTA$_{2000,4000,8000}$ >25 dB | 16.8 | 44.8 | <.0001 | 75.1 | 79.8 | NS |
| | Mid-frequency PTA$_{500,1000,2000,4000}$ >25 dB | 7.3 | 13.4 | NS | 52.0 | 59.5 | NS |
| Worse ear | Low-frequency PTA$_{125,250,500}$ >25 dB | 19.2 | 31.3 | 0.0149 | 60.3 | 66.7 | NS |
| | High-frequency PTA$_{2000,4000,8000}$ >25 dB | 29.0 | 59.7 | <.0001 | 87.3 | 88.1 | NS |
| | Mid-frequency PTA$_{500,1000,2000,4000}$ >25 dB | 15.7 | 40.3 | <.0001 | 66.4 | 75.0 | NS |

PTA pure tone averages; DM – diabetes mellitus; NS – not significant.

ages 40 through 86 years were analyzed in 4 subject groups: in the younger age bracket (40-64 years), 67 had diabetes and 1349 did not; in the older age-bracket (65–86 years) 84 had diabetes and 806 did not. The prevalence of DM was 4.7% in the younger participants, and 9.4% in the older participants.

Table 2 provides the results from chi-square analysis regarding the prevalence of hearing impairments (based on low-frequency, high-frequency and mid-frequency PTAs) according to age group and DM status. In the younger group, participants with DM had a significantly higher prevalence of hearing impairment than those without DM, for all frequency criteria except mid-frequency in the BE. In contrast, in the older age bracket, no significant differences were observed in the prevalence rates of any defined hearing impairments according to DM status.

The individual and interactive effects of age and DM on the hearing levels at 7 frequencies, from the GLM analysis, are shown in Table 3. The statistically significant main effect of DM was more moderate than that of age, but it was observed from low to high frequencies in both the BE and WE. The direction of each main effect was confirmed for the BE and WE in the lower sections of Table 3, which provide the mean hearing levels in the 4 groups: DM (–) and DM (+) in the younger and the older age-brackets. The main effect of DM was to impair hearing levels at all frequencies except 125 Hz in the BE and 500Hz in the WE. Moreover, the interactive effect of age and DM was statistically significant at 4000 Hz and 8000 Hz in both the BE and WE. The adverse effect of DM on hearing varied according to age.

For the purpose of visual comparison, the interactive effect of age and DM in the BE at 8000 Hz are graphically presented in the Figure 1. The solitary main effect of DM on hearing level was strong in the younger age bracket but less obvious in the older age bracket.

## Discussion

We found a statistically significant harmful effect of DM on hearing and noted that this effect varied by age in the high frequencies. The effects of the DM-age interaction were not synergistic at any of the test frequencies; in other words, aging did not intensify the deleterious effects of DM on hearing. The DM-age interaction was additive at below 4000 Hz, but reciprocal at 4000 Hz and 8000 Hz. The impact of DM on hearing at 4000 Hz and 8000 Hz was more severe in the younger than the older participants. Hearing sensitivity at the higher frequencies is particularly vulnerable to ototoxic insults such as aging [4, 6], hazardous noise exposure [14], and ototoxic agents. Accordingly the present results can be explained by the fact that the effect of DM on

**Table 3.** Relationship between hearing level, age, and DM status as assessed by general linear model analyses.

| | | Hearing level at 125 Hz | | Hearing level at 250 Hz | | Hearing level at 500 Hz | | Hearing level at 1000 Hz | | Hearing level at 2000 Hz | | Hearing level at 4000 Hz | | Hearing level at 8000 Hz | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Better ear based on the mid-frequency** | | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** |
| | DM | 3.13 | NS | 4.41 | 0.0359 | 6.41 | 0.0114 | 6.98 | 0.0083 | 5.35 | 0.0208 | 11.68 | 0.0006 | 18.96 | <0.0001 |
| | Age | 496.5 | <0.0001 | 445.3 | <0.0001 | 509.1 | <0.0001 | 648.4 | <0.0001 | 907.7 | <0.0001 | 1094 | <0.0001 | 1536 | <0.0001 |
| | DM × age | 1.49 | NS | 1.21 | NS | 1.39 | NS | 1.04 | NS | 0.89 | NS | 5.62 | 0.0179 | 8.39 | 0.0038 |
| | | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** |
| 40–64 years | DM (–) | 20.5 | 19.9–21.1 | 18.3 | 17.7–18.9 | 14.3 | 13.7–14.9 | 10.9 | 10.3–11.6 | 15.3 | 14.5–16.0 | 18.0 | 17.1–19.0 | 23.2 | 22.0–24.3 |
| | DM (+) | 22.9 | 20.7–25.0 | 20.9 | 18.6–23.2 | 17.4 | 15.1–19.8 | 14.3 | 11.7–16.8 | 18.6 | 15.7–21.6 | 25.7 | 22.0–29.3 | 34.7 | 30.3–39.2 |
| 65–86 years | DM (–) | 29.3 | 28.6–30.0 | 26.9 | 26.2–27.7 | 23.8 | 23.1–24.6 | 22.6 | 21.8–23.4 | 30.9 | 30.0–31.9 | 39.8 | 38.7–41.0 | 54.5 | 53.1–55.9 |
| | DM (+) | 29.8 | 27.8–31.7 | 27.8 | 25.8–29.8 | 25.0 | 22.9–27.1 | 24.1 | 21.8–26.3 | 32.4 | 29.8–35.0 | 41.4 | 38.2–44.7 | 57.1 | 53.2–61.0 |
| **Worse ear based on the mid-frequency** | | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** | **F value** | **p value** |
| | DM | 6.93 | 0.0085 | 9.74 | 0.0018 | 3.56 | NS | 4.26 | 0.039 | 9.14 | 0.0025 | 11.88 | 0.0006 | 16.49 | <0.0001 |
| | Age | 460.6 | <0.0001 | 408.8 | <0.0001 | 411.9 | <0.0001 | 523.6 | <0.0001 | 753 | <0.0001 | 926.32 | <0.0001 | 1364 | <0.0001 |
| | DM × age | 0.21 | NS | 0.18 | NS | 1.29 | NS | 1.01 | NS | 2.47 | NS | 6.61 | 0.0102 | 10.47 | 0.0012 |
| | | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** | **Mean** | **95% CI** |
| 40–64 years | DM (–) | 22.8 | 22.1–23.6 | 21.1 | 20.3–22.0 | 18.4 | 17.5–19.3 | 15.6 | 14.7–16.6 | 20.4 | 19.5–21.4 | 24.2 | 23.1–25.3 | 23.2 | 26.3–28.8 |
| | DM (+) | 26.0 | 23.1–28.9 | 25.2 | 21.9–28.4 | 22.2 | 18.7–25.8 | 19.6 | 16.0–23.3 | 26.6 | 22.8–30.3 | 33.6 | 29.3–37.9 | 34.7 | 35.7–45.5 |
| 65–86 years | DM (–) | 34.0 | 33.1–34.9 | 32.7 | 31.7–33.8 | 31.3 | 30.2–32.4 | 30.5 | 29.4–31.7 | 38.8 | 37.7–40.0 | 48.1 | 46.7–49.4 | 54.5 | 59.1–62.2 |
| | DM (+) | 36.3 | 33.7–38.8 | 35.8 | 33.0–38.7 | 32.3 | 29.2–35.5 | 32.0 | 28.7–35.2 | 40.9 | 37.6–44.2 | 49.7 | 45.9–53.5 | 57.1 | 58.1–66.9 |

Objective variables: Hearing level at respective frequencies; Explanatory variables: DM, age, DM × age; Moderator variables: sex, history of ear disease (presence=1), history of occupational noise-exposure (presence=1).
The degrees of freedom were 1 for all F values. DM – diabetes mellitus; presence vs. absence; age: <65 years vs. ≥65 years;
CI – confidence interval; NS – not significant.

hearing in the higher frequencies might be more emphatic in the younger age bracket because this type of hearing is generally better preserved in younger than in older people.

Regarding the association of diabetes with hearing, Bainbridge et al. reported the risk for hearing loss in people with self-reported DM in a recent study examining a large sample of 5140 non-institutionalized adults in the US National Health and Nutrition Examination Surveys [15]. They found that people with DM were at increased risk for hearing loss. The literature also contains some discussion about the cross-contribution of DM and aging to hearing impairment [9,15–17]. Although Bainbridge et al. mentioned that the relative contribution of DM to hearing impairment might have been stronger among their study group (age 20 to 69 years) than in a previously reported older group, they did not analyze the DM-by-age interaction as it relates to hearing in a straightforward manner. They demonstrated that the prevalence of hearing impairment among people with diagnosed DM statistically exceeded the prevalence among those without DM in all groups except people aged 60 to 69 years. They therefore speculated that hearing of younger people, before the cumulative effects of aging, noise exposure, and other factors have made substantial contributions to hearing impairment, is potentially affected by DM more than in older people. Vaughan et al. tested audiometric measures including ultra-high-frequency range in 342 veterans with DM and 352 without DM. They concluded that patients aged 60 or younger with DM may show early high-frequency hearing loss similar to early presbycusis, while there was less difference in hearing loss between patients with and without DM after age 60 [17]. They found a significant effect of DM in both ears after adjusting for age, but only in the ultra-high-frequency range (10–16 kHz), and the DM-age interaction was significant in the right ear but not in the left at this frequency range. They also demonstrated that differences between patients with and without DM diminished or disappeared at 10, 12.5, 14 and 16 kHz in the right ear as age increased. Vasilyeva et al. prospectively assessed hearing abilities in middle-aged mice with Type 1 DM or Type 2 DM, and found that induction of diabetes in middle-aged CBA/CaJ mice promoted amplification of age-related peripheral hearing loss [18].

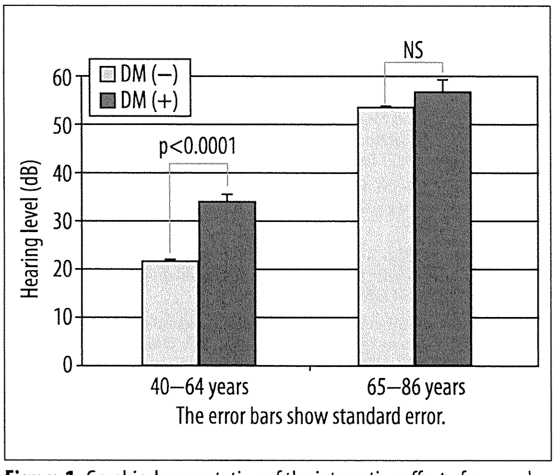


**Figure 1.** Graphical presentation of the interactive effect of age and DM in BE at 8000 Hz.

The pathophysiological mechanism of hearing impairment in DM has been investigated for years in temporal bone studies using animal models of DM and in human post-mortem cases; however, it has not been completely clarified [19–21]. Some investigators have observed findings of DM-related cochlear microangiopathy, such as vessel wall thickening or atrophy of the stria vascularis, the organ responsible for generating endolymph, which serves as the driving force for hair cell mechanotransduction. However, others have failed to find these changes in DM. Recently, possible biochemical pathways involved in the detrimental effects of DM on sensory end-organs have been advocated [10,22]. The auditory system requires glucose and high-energy utilization for its complex signal processing. The high metabolic demands of the inner ear and the auditory pathway could make them a target of the disease, even before evidence of microvascular complications. This could occur through hyperglycemia, which has effects including oxidative stress, hypoxia and ischemia, activation of the polyol pathway, and increased levels of advanced glycation end products (AGEs), which play an important role in development of atherosclerosis in diabetes.

A recent study provided evidence that various forms of oxidative stress increase in the aging cochlea, while cellular antioxidant defense systems are reduced [23]. The findings mean that, irrespective of the presence of DM, oxidative stress during the aging process leads to dysfunctional degeneration of the cochlear tissue. Another study demonstrated that increased vulnerability of outer hair cells from the base of the cochlea, which responds to higher frequency auditory stimuli compared with those at the apex, was associated with lower levels of the antioxidant glutathione in the basal hair cells [24]. This finding may explain the current result that DM could potentially accelerate early presbycusis, high-frequency sensorineural hearing loss, in the younger age-bracket.

Some limitations of the present study should be mentioned. Although the definition of DM in the present study was based on multiple criteria, medical history and medication taken to lower blood glucose level were obtained by questionnaires. We could not distinguish between type 1 and type 2 DM, and did not take into account severity or duration since DM diagnosis. Additionally, the participants of the NILS-LSA are potentially more health-conscious than average Japanese. Residents selected from resident registrations were invited by mail to an explanatory meeting at which the objectives of NILS-LSA, study design, and detailed procedures of examinations were described. Only those who understood the project and signed a written informed consent form became participants. Employed people would have to get time off to take part in the examination, and those with seriously impaired activities of daily living, rarely attend. Therefore, the present subjects may have been healthier than the subjects in other analyses in the clinical setting.



Despite these possible limitations, however, the present findings that diabetes reduces auditory sensitivity in middle-aged people may indicate potential benefits of early intervention. Yoshikawa et al. has prospectively examined the effect of short-term intervention with lifestyle modification, and has clearly demonstrated that lifestyle modification can significantly reduce circulating AGE levels [25]. Screening for hearing impairment in diabetic patients may be valuable for intervention or prevention, especially in early middle-age.

## Conclusions

The present study demonstrated that DM adversely affected hearing in the community-dwelling middle-aged and elderly population. Although the DM-age interaction appeared additive at below 4000 Hz, significant reciprocal effects of this interaction were found at 4000 Hz and 8000 Hz. This suggests that DM could potentially accelerate early presbycusis, high-frequency sensorineural hearing loss. Screening for hearing impairment in patients with DM may provide benefits for prompt intervention or primary prevention, especially in early middle-age.

### Acknowledgments

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### Declaration of interest

Nothing declared.

### Conflict of interest

None. The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

### Ethical approval

Ethical Committee of the National Center for Geriatrics and Gerontology.

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# 特集 甲状腺疾患：診断と治療の進歩

## トピックス

### I. 診療の進歩
### 1. 地域住民における潜在性甲状腺機能異常の頻度と実態

下方　浩史　　安藤富士子　　北村伊都子

要　旨

無作為抽出された40歳以上の地域住民について潜在性甲状腺機能異常の頻度，4年間の変化，各検査結果との関連について検討した．潜在性甲状腺機能低下症は3.3%，亢進症は2.3%に認められた．潜在性機能低下症は女性に多く，加齢とともに増加していた．4年間の追跡で潜在性甲状腺機能低下症の10%が顕在性の低下症となった．潜在性甲状腺機能低下症・亢進症ともに，動脈硬化，喫煙との関連が示唆された．

〔日内会誌　99：686〜692，2010〕

**Key words**：潜在性甲状腺機能異常，地域住民，縦断研究，動脈硬化，喫煙

## はじめに

甲状腺刺激ホルモン（TSH）の測定は1970年代から行われ，その後，簡易な測定法が開発されて検査が一般的に行われるようになった．TSHの測定が広く行われるようになり，血中の甲状腺ホルモン値は正常であるが，TSHが高値もしくは低値である人が数多く見つかるようになった．これを潜在性甲状腺機能異常症という．そしてTSHが高値である場合を潜在性甲状腺機能低下症，TSHが低値である場合を潜在性甲状腺機能亢進症といい，その臨床的な意義が注目されている．しかし，わが国においては地域住民での甲状腺機能異常症の実態とその意義についての検討は数少ない．本稿では，無作為抽出された一般地域住民を対象に，潜在性甲状腺機能異常症の有病率，性・年齢別の分布，追跡による変化，また臨床所見や生活習慣との関連などについて報告する．

## 1．地域住民におけるデータの収集

国立長寿医療センター研究所疫学研究部では，1997年より「国立長寿医療センター研究所・老化に関する長期縦断疫学研究（NILS-LSA：National Institute for Longevity Sciences-Longitudinal Study of Aging）」を実施している[1〜3]．この調査は日本人の老化および老年病に関する詳細な縦断的データを収集し老化像を明らかにし，老化および老年病に関する危険因子を解明することを目的としている．調査の対象者は国立長寿医療センター周辺の地域住民から性・年齢を層化，無作為抽出を行い，調査参加への同意の得られた男女2,267名であり，観察開始年齢は40〜79歳である（表1）．第1次調査は

しもかた　ひろし：国立長寿医療センター研究所疫学研究部
あんどう　ふじこ：愛知淑徳大学医療福祉学部
きたむら　いつこ：愛知学院大学教養部

表 1. 調査参加者の性別・年齢階級別分布 (NILS-LSA 第 1 次調査)

| 年齢 | 男性 | 女性 | 合計 |
|---|---|---|---|
| 40～49 | 291 | 282 | 573 |
| 50～89 | 282 | 279 | 561 |
| 60～69 | 283 | 285 | 568 |
| 70～79 | 283 | 282 | 565 |
| 合計 | 1,139 | 1,128 | 2,267 |

男女各年代が同数になるように性・年齢を層化し住民基本台帳から無作為抽出した. 調査に同意した者のみを対象にしているため対象者の人数に多少のバラツキが生じている.

1997 年 11 月より開始し, 2 年ごとに追跡調査を繰り返し行っている. 調査地域は地理的に日本の中心に位置し, 気候風土が日本全国のほぼ平均であるとともに, 縦断調査開始前に行った全国郵送調査で, この地域に在住する人々の食習慣を含めた生活習慣全般が全国平均に近いことを確認している[4].

## 2. 潜在性甲状腺機能異常の有病率

### 1) ホルモン測定値の性別・年代別分布

NILS-LSAの第 1 次調査参加者のうち, 採血可能であった者から甲状腺疾患の内服治療を受けている 13 名を除いた 2,251 名を対象として検討を行った. 早朝空腹時に採血を行い, 遊離トリヨードサイロニン ($FT_3$), 遊離サイロキシン ($FT_4$) および甲状腺刺激ホルモン (TSH) を電気化学発光免疫測定法 (ECLIA : electrochemiluminescence immunoassay) により測定した. FT3 は男性では年代が上がるとともに低下し (Cochran-Mantel-Haenszel検定, p trend<0.001), 女性では年代が上がるとともに増加した (p trend = 0.003). $FT_4$ は男女とも年代上昇にともなう有意な変動傾向はなかった. TSHは男女とも年代が上がるとともに有意に増加していた (男性p trend<0.001, 女性p trend = 0.003). 各ホルモン濃度の性差は年代が若い群で顕著で, $FT_3$, $FT_4$ は 40 代, 50 代では男性のほうが高値であったが, 60 代, 70 代では性差はなく, TSHは 40 代, 50 代, 60 代では女性のほうが高値であったが, 70 代では性差はなかった (図 1).

### 2) 潜在性甲状腺機能異常症の有病率

各ホルモン濃度の基準値 ($FT_3$ : 2.3～4.3 pg/ml, $FT_4$ : 0.9～1.7 ng/dl, TSH : 0.5～5.0 μIU/ml) にしたがって, ①正常 (TSH, $FT_3$, $FT_4$ のすべてが基準値内), ②潜在性甲状腺機能低下症 ($FT_3$, $FT_4$ がともに基準値内でTSHが高値), ③潜在性甲状腺機能亢進症 ($FT_3$, $FT_4$ がともに基準値内でTSHが低値), ④顕性甲状腺機能低下症 ($FT_3$, $FT_4$ の一方もしくは両方が低値), ⑤顕性甲状腺機能亢進症 ($FT_3$, $FT_4$ の一方もしくは両方が高値) の 5 群に分類した. 第 1 次調査の参加者では, 正常 89.2% (2,007 名) 潜在性甲状腺機能低下症 3.3% (75 名), 潜在性甲状腺機能亢進症 2.3% (52 名), 顕性甲状腺機能低下症 3.4% (77 名), 顕性甲状腺機能亢進症 1.8% (40 名) の割合であった.

潜在性甲状腺機能異常の性, 年代別の分布を検討した (図 2). 40 代から 70 代にかけての潜在性甲状腺機能低下症の有病率は, 男性では 0.7% (2 名), 0.7% (2 名), 3.5% (10 名), 5.0% (14 名), 女性では 1.8% (5 名), 3.3% (9 名), 5.7% (16 名), 6.1% (17 名) と, 男女とも年代上昇とともに有意な増加傾向を示した (男女ともp trend<0.001). 一方, 潜在性甲状腺機能亢進症の有病率は, 男性 3.8% (11 名), 1.1% (3 名), 3.5% (10 名), 2.5% (7 名), 女性では 1.9% (5 名), 1.5% (4 名), 1.4% (4 名), 2.9% (8 名) と年代による有意な変動傾向を示さなかった. 性別で有病率を比べると, 潜在性甲状腺機能低下症は男性 2.5%, 女性 4.2% であり, 女性のほうが有意に有病率が高く (p = 0.02), 潜在性甲状腺機能亢進症は男性 2.7%, 女性 1.9% で, 有病率に男女間での有意な差はなかった.

潜在性甲状腺機能低下症の有病率は, 閉経後女性を対象としたオランダのRotterdam Study[5] で 10.8% (TSH 4.0 μIU/ml以上を基準), アメリ

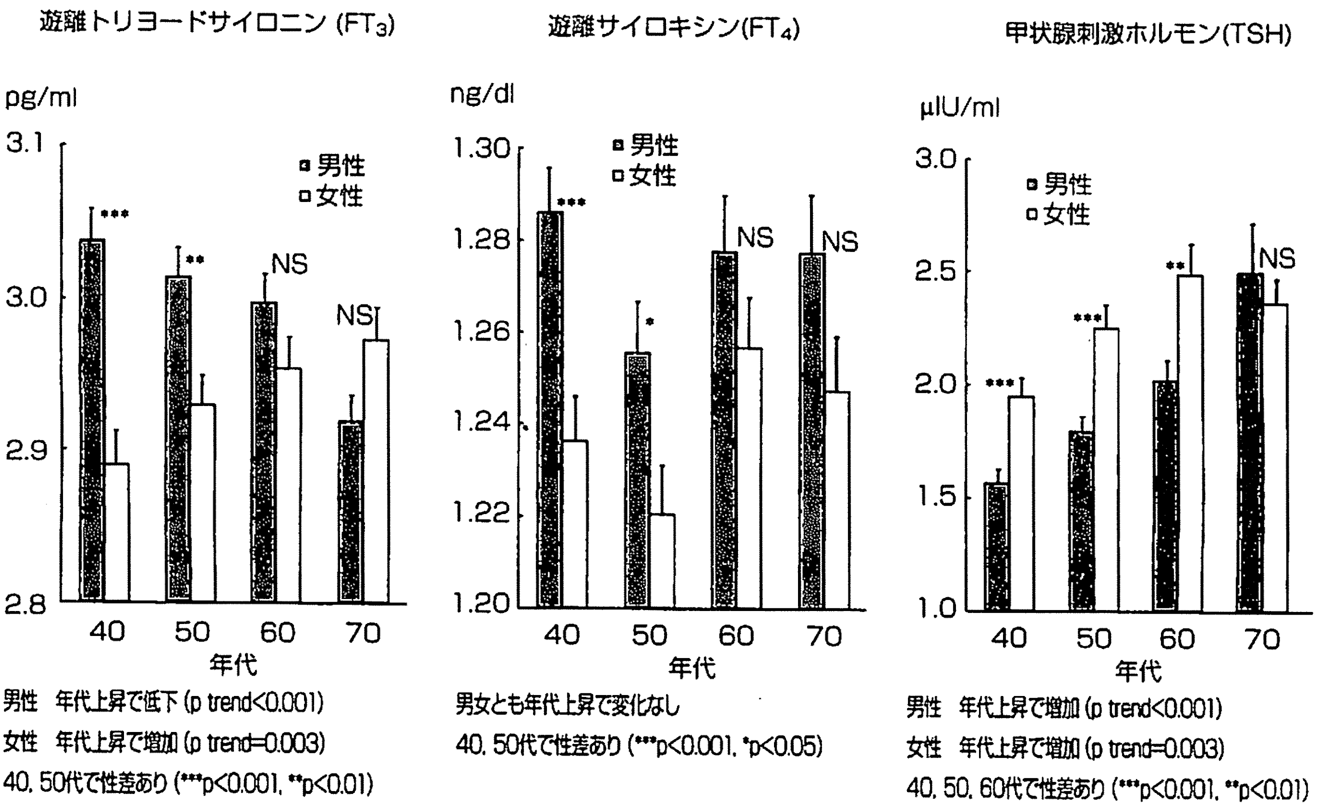


**図 1.　性・年代別の $FT_3$, $FT_4$, TSH の値．性差の検定は $\chi^2$ 検定で，年齢群による傾向性の検定は Cochran-Mantel-Haenszel 検定で行った．**

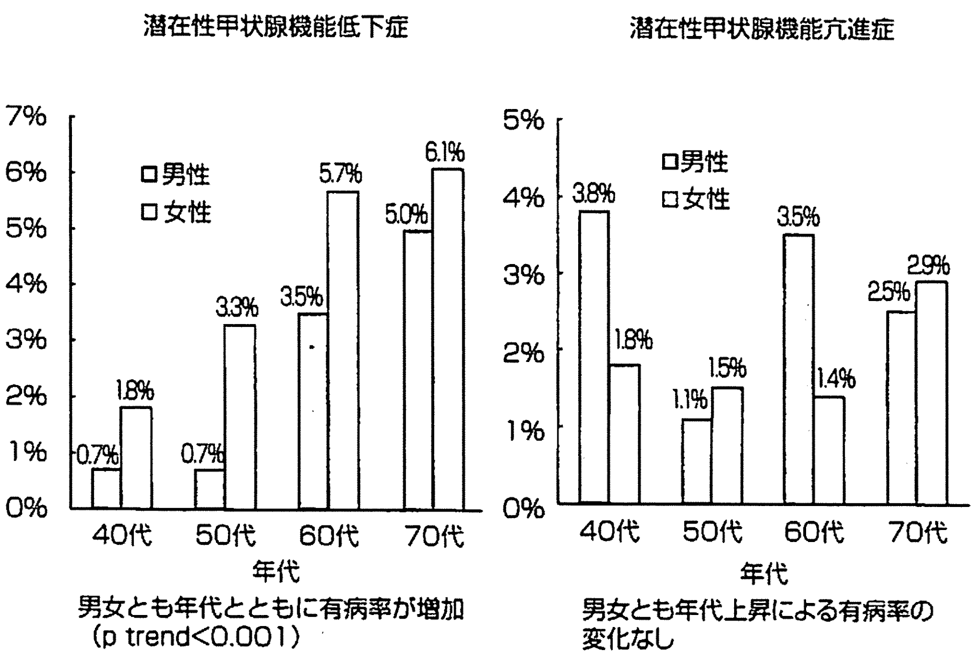


**図 2.　性・年代別の潜在性甲状腺機能異常症の有病率**

カのNHANESIIIstudy[6]で 4.3%（TSH 4.6 μIU/ml 以上を基準），コロラドの調査[6]でのデータでは 8.5%（TSH 5.1 μIU/ml以上を基準），長崎の原爆被爆者での調査では男性 9.8%，女性 10.5%（TSH 5.0 μIU/ml以上を基準）に認められている[8]．これらの報告に比べると，NILS-LSAでの潜在性甲状腺機能低下症頻度は，全体で 3.3%，男性 2.5%，女性 4.2% とやや低い値となっている．一方，潜

表2. 4年間の追跡による甲状腺機能の変化

| 第1次調査 | | 第3次調査 | | | | |
|---|---|---|---|---|---|---|
| | | 正常 | 潜在性甲状腺機能低下症 | 潜在性甲状腺機能亢進症 | 甲状腺機能低下症 | 甲状腺機能亢進症 |
| 正常 | 1,451 | 1,267 (87.0%) | 88 ( 6.1%) | 7 ( 0.5%) | 86 ( 5.9%) | 8 ( 0.6%) |
| 潜在性甲状腺機能低下症 | 50 | 10 (20.0%) | 35 (70.0%) | 0 ( 0.0%) | 5 (10.0%) | 0 ( 0.0%) |
| 潜在性甲状腺機能亢進症 | 36 | 27 (75.0%) | 0 ( 0.0%) | 6 (16.7%) | 2 ( 5.6%) | 1 ( 2.8%) |
| 顕性甲状腺機能低下症 | 55 | 38 (69.1%) | 6 (10.9%) | 0 ( 0.0%) | 11 (20.0%) | 0 ( 0.0%) |
| 顕性甲状腺機能亢進症 | 26 | 17 (65.4%) | 4 (15.4%) | 1 ( 3.9%) | 0 ( 0.0%) | 4 (15.4%) |

在性甲状腺機能亢進症の有病率はNHANESIIIstudy[6]で4.3% (TSH 0.4 μIU/ml未満を基準), 65歳以上の高齢者の集団[9]では1.5% (TSH 0.44 μIU/ml未満を基準) であった. 潜在性甲状腺機能異常症の有病率は, 基準値の設定, 対象集団の人種, 年齢, 地域の違いや対象コホートの性質の違いなどにより大きく異なっている.

## 3. 潜在性甲状腺機能異常の追跡による変化

第1次調査から4年後の第3次調査まで追跡できた1,618名について, 追跡での甲状腺機能の変化を表2に示す. 第1次調査で潜在性甲状腺機能低下症であった50名のうち, 35名 (70%) は持続して潜在性甲状腺機能低下症で, 10名 (20%) は正常に, 5名 (10%) は顕性甲状腺機能低下症に移行していた. 潜在性甲状腺機能亢進症では36名のうち, 6名 (17%) は持続して潜在性甲状腺機能亢進症であり, 27名(75%)は正常に, 2名(6%)は顕性甲状腺機能低下症に, 1名 (3%) は顕性甲状腺機能亢進症に移行していた. これらの追跡結果を正常群の追跡結果と比較した. 性・年齢を調整したCochran-Mantel-Haenszel検定では, 顕性の甲状腺機能低下症となる割合には正常群と潜在性甲状腺機能低下症とでは有意差はなかった. 同様に顕性の甲状腺機能亢進症となる割合に正常群と潜在性甲状腺機能亢進症では有意差はなかった. 追跡期間が4年間と比較的短いこと, 症例数が少ないことにより有意な結果が得られなかった可能性がある.

## 4. 潜在性甲状腺機能異常の臨床像

NILS-LSAでは頭部MRI (magnetic resonance imaging) 検査や心臓および頸動脈超音波断層検査, 骨密度測定, 腹部CT (computed tomography) 検査などの最新の機器を利用した医学検査だけでなく, 詳細な生活調査, 栄養調査, 運動機能調査, 心理検査など広汎で学際的な, しかも精度の高い調査・検査が行われている. NILS-LSAでの潜在性甲状腺機能異常とこれらさまざまな検査結果との関連について, 性・年齢を調整して網羅的な解析を行った.

### 1) 知能・鬱との関連

NILS-LSAでは知能検査としてWechsler成人知能検査WAIS-R-SF (Wechsler Adult Intelligence Scale-Revised-Short Form), 認知症のスクリーニングとしてMMSE: (Mini-Mental State Examination), 抑鬱のスクリーニングとしてCES-D (The Center for Epidemiologic Studies Depression Scale) を実施している. これらの成績との関連について検討を行ったが, 潜在性甲状腺機能低下症・亢進症と正常群との間で有意差のあるものはほとんどなかった. 海外での報告でも認知機能や抑鬱との関連を否定するものが多い[10~12]. しかし潜在性の甲状腺機能異常による認知機能・抑鬱への影響は年齢で異なる可能性も指摘されている[13].

2）頭部MRI所見との関連

MRIでの脳萎縮，脳室拡大（側脳室前角及び後角），PVH(脳室周囲高信号域)，ラクナ梗塞，脳梗塞の所見との関連を検討したところ，潜在性甲状腺機能亢進症ではラクナ梗塞，脳梗塞である者の割合が有意に多かった（p＝0.003 およびp＝0.01）．これまで潜在性甲状腺機能異常と脳血管疾患との関連についての報告は少ないが，潜在性甲状腺機能低下症では脳血管疾患の発症と関連を認めなかったとする報告がある[8,9]．

3）脂質代謝との関連

中性脂肪，総コレステロール，HDL(high density lipoprotein）コレステロール，LDL（low density lipoprotein)コレステロール，アポ蛋白，リポ蛋白(a)について正常群と比較したところ，潜在性甲状腺機能低下症・亢進症ともに脂質代謝のほとんどの指標で有意な関連が認められなかった．潜在性甲状腺機能低下症と脂質代謝との関連については多くの報告で示されている[7,14,15]．NILS-LSAでは潜在性甲状腺機能異常があった者の数は比較的多くなく，有意差を示すのに十分な検出力が得られなかった解析もあった．今後，更なる検討が必要であろう．

4）肥満との関連

体重，肥満度(BMI)，臍高腹囲，二重エネルギーX線吸収法（DXA法）による体脂肪率について検討を行ったが，正常群と潜在性甲状腺機能低下症・亢進症との間に有意な差はみられなかった．海外からの報告では，潜在性甲状腺機能異常と肥満については関連を認めるものと認めないものがあり結論は一定していない[16〜19]．

5）動脈硬化所見との関連

眼底検査，頸動脈超音波断層，心電図における虚血性変化との関連を調べたところ，潜在性甲状腺機能低下症では，眼底の高血圧性変化，心電図の虚血性変化のある者が有意に多かった(p＝0.04 及びp＝0.03)．潜在性甲状腺機能亢進症では頸動脈超音波断層検査による総頸動脈プラークを認める者が有意に多かった(p＝0.04)．閉経女性を対象とした報告[5]で，潜在性甲状腺機能低下症で大動脈石灰化と心筋梗塞である者が有意に多かったとしている．また，潜在性甲状腺機能低下症は男性で虚血性心疾患との関連があり，総死亡率も高値であるという本邦の報告[8]や虚血性心疾患のリスクを増大させるというメタアナリシスの報告[20]もある．ホルモン投与の効果についても潜在性甲状腺機能低下症では血管内皮の厚さが高値であったが，サイロキシン投与で改善をみとめたとする報告がある[21]．その一方で，潜在性甲状腺機能低下症での虚血性心疾患の発症率は有意に高くなかったとする高齢者を対象とした米国の調査[9]や，治療効果に対するエビデンスは不十分であるとするメタアナリシスもある[22]．

6）骨密度との関連

DXA法による腰椎，大腿骨頸部の骨密度と潜在性甲状腺機能異常症との関連について検討を行った．その結果，潜在性甲状腺機能低下症，潜在性甲状腺機能亢進症ともに骨密度との関連は認められなかった．甲状腺ホルモンの骨への影響は，罹病期間や他のリスクファクターとの関連など複雑であり，今までの報告でも結論は一定していない[23〜26]．

7）喫煙との関連

喫煙習慣について「喫煙している」，「禁煙した」，「喫煙したことがない」の３群に分けて潜在性甲状腺機能異常症と喫煙習慣との関連を検討した．「喫煙している」は潜在性甲状腺機能低下症で 6.7％，正常群で 23.1％，潜在性甲状腺機能亢進症で 38.5％ と潜在性甲状腺機能亢進症で割合が高く，一方，「喫煙したことがない」は潜在性甲状腺機能低下症で 70.7％，正常群で 55.1％，潜在性甲状腺機能亢進症で 48.2％ と潜在性甲状腺機能低下症で割合が高くなっていた．性別・年齢を調整した多重ロジスティック回帰による正常群に対する喫煙のオッズ比は潜在性甲状腺機能低下症で 0.3(95％ 信頼区間：0.1〜0.9)，潜在性甲状腺機能亢進症で 2.0(95％ 信頼区間：1.1〜

4.0）であった．しかし，これらの結果は横断的検討であり，因果関係は明らかすることはできない．これまでの報告でも喫煙が甲状腺機能に影響を与えている可能性が指摘されているが[27～29]，その機序については，まだはっきりしていない．

## おわりに

本報告での結果では，潜在性の甲状腺機能異常症と喫煙との関連や動脈硬化との関連が認められた．潜在性甲状腺機能異常症については，その臨床的な意義がまだまだはっきりしない．特に潜在性のうちに治療が必要かどうか，治療することによる危険性と有用性については，日本でのエビデンスがほとんどない．

本研究では一般地域住民から性，年齢を層化し無作為抽出された者を対象としている．日本の中高年地域住民のデータとして，本報告結果の意義は大きいと思われる．ただ，本コホートにおける潜在性甲状腺機能低下症および亢進症である者の数が十分でなかったことから，各検査結果との関連については，今後，縦断的研究を含めた十分な検討が必要であろう．

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〈原　著〉

# 在宅療養要介護高齢者の介護環境ならびに生命予後，入院，介護施設入所リスクの性差

葛谷　雅文[1)]　長谷川　潤[1)]　榎　裕美[2)]　井澤　幸子[3)]
平川　仁尚[4)]　広瀬　貴久[1)]　井口　昭久[5)]

**要　約　目的**：要介護認定を受けた在宅療養中の高齢者の性別による身体機能，疾病背景，介護環境（生活環境，介護者の有無ならびに続柄，サービス使用状況），さらに3年間の生命予後，入院，施設入所の相異を明らかにする．**方法**：名古屋市在住で要介護認定を受け在宅療養中の高齢者1,875名，さらにその主介護者1,568名を対象にした縦断調査（the Nagoya Longitudinal Study for Frail Elderly）の登録時のデータならびに3年間の死亡，入院，介護施設への入所に関する縦断的データを使用した．**結果**：登録された要介護者の性別構成は女性（66.3%）が男性（33.7%）の約2倍存在していた．男性に比較して女性要介護高齢者の平均年齢は高く（女性：81.5±7.5（SD）歳，男性：78.8±7.6（SD）歳，p<0.001），独居が多く（女性：26.2%，男性：14.6%，p<0.001），主介護者が配偶者である割合が男性要介護高齢者に比較して低かった（女性：22.1%，男性：73.6%，p<0.001）．女性要介護高齢者は訪問介護サービスの利用率が高く（女性：48.8%，男性：43.2%，p=0.021），また重篤な併存症の有病率は男性に比較して低く（男性vs女性，脳血管疾患：46.6% vs 28.3%，<0.001；慢性閉塞性肺疾患：9.9% vs 5.9%，p=0.003；悪性腫瘍：12.9% vs 7.3%，p<0.001），骨折の罹患率（過去5年間）が高かったが（27.4% vs 14.7%，p<0.001），3年間の死亡率，入院率は男性要介護高齢者よりも女性で低かった（男性vs女性%，死亡率：31.3% vs 20.6%，p<0.001；入院率：48.6% vs 39.9%，p<0.001）．介護施設への入所は男性よりも高かった（5.2% vs 8.4%，p=0.011）．Cox比例ハザード解析では男性と比較した女性要介護者の死亡，入院，施設入所のハザード・リスク（95%信頼区間）は単変量解析でそれぞれ0.61（0.51〜0.74），0.76（0.66〜0.88），1.48（1.00〜2.19）で，多変量解析ではそれぞれ0.51（0.39〜0.66），0.83（0.69〜0.99），1.19（0.73〜1.93）であった．**結論**：在宅療養中の要介護高齢者は女性が多く，主介護者の続柄など介護環境に性差が存在する．さらに女性要介護高齢者では男性よりも3年間の死亡率は低いものの，介護施設へ入所する率が多いことが明らかとなった．

**Key words**：介護保険，要介護高齢者，在宅療養，介護保険サービス，性差

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## 緒　言

平成21年版　高齢社会白書によると，日本における高齢化はとどまることを知らず，平成20年度には65歳以上の高齢者人口は，過去最高の2,822万人となり，総人口に占める割合（高齢化率）も22.1%（前年21.5%）となり，22%を超える結果となった[1)]．要介護高齢者の数も急速に増加しており，特に75歳以上の後期高齢者で顕著である．介護保険制度における要介護者又は要支援者と認定された者のうち，65歳以上の者の数についてみると，平成18（2006）年度末で425.1万人となっており，高齢者人口の16.0%を占めている．75歳以上の人口について，要支援，要介護の認定を受けた者のそれぞれの区分における人口に対する割合をみると，75歳以上の人口で要支援の認定を受けた者は6.6%，要介護の認定を受けた者は21.4%となっており，75歳以上人口の25%以上が要介護・支援状態である．介護保険制度のサービスを受給した65歳以上の被保険者は，平成21年1月審査分で約368万人となっており，男女比でみると男性が28.0%，女性が72.0%となっている（平成21年版　高齢社会白書より）[1)]．

1）M. Kuzuya, J. Hasegawa, T. Hirose：名古屋大学大学院医学系研究科（老年科学）
2）H. Enoki：東海学園大学人間健康学部管理栄養学科
3）S. Izawa：愛知学院大学心身科学部健康栄養学科
4）Y. Hirakawa：名古屋大学医学部附属病院卒後臨床研修・キャリア形成支援センター
5）A. Iguchi：愛知淑徳大学医療福祉学部
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これらより高齢者人口のかなりの数が要介護高齢者であり，さらにそのうち2/3以上を女性が占めていることがわかる．このように高齢者人口，要介護者集団においては数の上で明らかに性差があることが報告されている．しかし，その要介護高齢者の性別による背景（疾病構成，日常生活動作，精神心理的状態），介護環境（独居状態，主介護者の有無，主介護者の背景，介護保険サービスの使用状況）の相違，さらには性別による予後，病院への入院，介護施設への入所に対するリスクの相違などは明らかではない．今回1,875名の在宅療養中に要介護者，ならびにその主介護者たちを対象にしたコホート調査を基に上記の疑問を明らかにする．

## 対象と方法

1. 対象者

名古屋市で行われたthe Nagoya Longitudinal Study for Frail Elderly（NLS-FE）の登録時65歳以上であった高齢者のデータ（1,875名）を使用した．NLS-FEは名古屋市の17訪問看護ステーション併設居宅介護支援事業所を基盤とした訪問看護サービス利用者（65歳以上の高齢者），訪問看護未利用者に，訪問看護師または介護支援専門員から書面で研究内容に関する説明をし，文書での同意を得られた要介護高齢者（1,875名），さらにはその主介護者（1,568名）を調査対象（登録者）とする縦断的調査である．(登録は平成16年1月に終了)[2)～5)]．登録者に関し，登録時に行った基本調査は1年ごとに行われ，経過中3年間，3カ月ごとにイベントの有無を調査した．イベントとは1)病院への入院(処置，検査入院を含む)，2）介護施設（老人保健施設，特別養護老人ホーム，グループ・ホームなど）への入所，3）死亡，4）脱落（訪問看護サービスの中止）を示す．なお，本研究は平成19年1月に終了している．

2. 基本調査内容

基本調査内容はa）患者の属性　b）社会的背景　c）介護状態の把握　d）看護サービス内容　e）疾病背景　f）既往歴（特に転倒，骨折）　g）身体機能ならびに精神心理機能（基本的ADL：Barthel index（range：0～20）[6)]，認知症の有無，うつの有無：Geriatric depression scale short version（GDS-15，range：0～15）[7)]）　h）栄養状態（身体計測，摂取状況を含む　i）併存症の評価：Charlson index（range：0～9）[8)]　j）薬剤調査　k）主介護者の状態(健康状態，介護負担感(日本語版the Zarit Burden Interview：ZBI))，看護師の主観的調査（サービス利用状況，患者の健康状況，家族の介護状況，主介護者の健康状況ならびに負担)などである．慢性疾患(冠動脈疾患，心不全，脳血管障害，認知症，慢性閉塞性肺疾患，糖尿病，高血圧，悪性腫瘍）の有無はかかりつけ医からの情報を基に聴取された．さらに過去半年間の転倒歴，過去5年間の骨折歴を聴取した．これらの情報は本人または介護者，かかりつけ医からの情報を基にした．なお，GDS-15は認知症，またコミュニケーション不能者には実施しなかった．

3. 縦断調査

登録から3年間の経過中，イベント発生に関する報告書を看護師または介護支援専門員は記載し，3カ月ごとに名古屋大学に郵送した．イベントとは1）病院への入院（処置，検査入院を含む），2）介護施設（老人保健施設，特別養護老人ホーム，グループ・ホームなど）への入所　3）死亡　4）脱落を示す．

4. 解析

登録時基本調査内容の男性・女性の相違，ならびに3年間の観察中に起こったイベント（死亡，入院，介護施設への入所）の性差を検討した．使用する解析法はstudent-t test，カイ二乗検定，Kaplan-Meier検定，Cox比例ハザード検定などを使用した．女性要介護者の男性要介護者と比較した死亡，入院，介護施設入所のリスクをCox比例ハザード検定で解析した．多変量解析では単変量解析で統計的有意（$p<0.05$）な因子をモデルに投入した．

5. 倫理面への配慮

本研究は名古屋大学倫理委員会の承認を得て実施した．十分なインフォームド・コンセントの後，必ず要介護者本人，主介護者の書面による同意書をもって登録とした．匿名化された情報は名古屋大学で厳重に管理し，全て集団的に分析し，個々のデータの提示などは行わず，個人のプライバシー保護に努めた．

## 結　果

表1に男女別登録された要介護高齢者ならびに主介護者背景を示す．登録された要介護高齢者は女性が明らかに多く（66.3%），男性（33.7%）のほぼ2倍であった．年齢は女性81.5歳と男性78.8歳に比較し有意に高齢であった（$p<0.001$）．登録者のうち，独居で在宅療養中の要介護高齢者は女性で26.2%であり，男性14.6%に比較し有意に多かった．8割以上の要介護高齢者には主介護者が存在していたが，配偶者が主介護者である割合は女性の要介護高齢者で22.1%，男性で73.6%であった．主介護者介護負担感（ZBI）は男性要介護者の主介護者で有意に高かった．

登録時の平均基本的ADLならびにGDS-15得点は性

**表1** 要介護者性別登録時の背景，居宅サービス使用状況ならびにその主介護者の背景

| | 男性 | 女性 | |
|---|---|---|---|
| | n = 632, 33.7% | n = 1,243, 66.3% | p |
| 年齢，mean（SD）* | 78.8 (7.6) | 81.5 (7.5) | < 0.001 |
| 独居，n（%） | 92 (14.6) | 326 (26.2) | < 0.001 |
| 主介護者有無（n = 1,568），n（%） | | | |
| 有り | 556 (88.0) | 1,012 (81.4) | < 0.001 |
| 無し | 76 (12.0) | 231 (18.6) | |
| 介護者女性，n（%） | 482 (86.7) | 697 (68.9) | < 0.001 |
| 介護者年齢，mean（SD）* | 67.9 (11.2) | 61.9 (12.7) | < 0.001 |
| 主介護者続柄，n（%） | | | |
| 配偶者 | 409 (73.6) | 224 (22.1) | < 0.001 |
| 嫁（孫嫁を含む） | 44 (7.9) | 274 (27.1) | |
| 子供 | 92 (16.5) | 467 (46.1) | |
| 兄弟（姉妹） | 4 (0.7) | 30 (3.0) | |
| 主介護者 ZBI, ** mean（SD）* | 31.2 (17.2) | 27.6 (16.8) | < 0.001 |
| 居宅サービス使用（%） | | | |
| デイ・ケア（サービス） | 43.5 | 43.9 | 0.865 |
| 訪問看護サービス | 56.2 | 48.0 | 0.001 |
| 訪問介護サービス | 43.2 | 48.8 | 0.021 |
| 定期的受診 | 61.7 | 58.4 | 0.164 |
| ショートステイサービス | 8.5 | 9.7 | 0.402 |
| 訪問入浴サービス | 11.7 | 11.2 | 0.734 |
| 訪問リハビリテーションサービス | 9.3 | 5.3 | 0.001 |
| 福祉用具レンタルサービス | 65.8 | 56.3 | < 0.001 |

*：student t-test，それ以外はカイ二乗検定
**：日本語版 the Zarit Burden Interview（range：0～88，n = 1,257）

差を認めなかった（表2）．併存症の重症度のスケールとして使用したCharlson comorbidity indexの平均得点は男性で高得点であり，より生命予後に係る併存症の集積が男性に認められた．定期的なかかりつけ医への受診率は性差を認めなかったが，男性で多剤服用（6種類以上）が多かった（表2）．慢性疾患の有病率では脳血管障害，慢性閉塞性肺疾患，悪性腫瘍は男性での有病率が有意に高かったが，認知症は逆に女性で有意に高かった．過去半年間の転倒経験率は男女間で差を認めなかったが，過去5年間の骨折の既往率は女性で有意に高かった（表2）．

図1に男女別，要介護度を示した．男女とも要介護1をピークとする分布を示し，ほぼ同様の分布であった．登録時の居宅サービスの使用率はデイケア（デイサービスを含む），ショートステイ，訪問入浴サービスでは男女差を認めなかった（表1）．一方，訪問看護サービス，訪問リハビリテーション，福祉用具レンタルサービスの使用は男性でより高率で使用されていた．逆に訪問介護サービスは女性の要介護高齢者でより高率に使用されていた（表1）．

3年間の観察期間中に要介護者1,875名のうち，454人死亡し，そのうち107名が在宅での看取りであった．男性の死亡率は3年間で31.3%，女性は20.6%で有意に男性の死亡率が高かった（表3）．在宅死の率は男女の差を認めなかった．一方，3年間で一度でも入院を経験した要介護高齢者は1,875名のうち803名あり，男女別では男性では48.5%と女性（39.9%）に比較し有意に高かった．介護施設への入所は逆に女性で高率（男性：5.2% vs 女性：8.4%）であった（表3）．

図2に男女別，累積生存率，累積入院率，累積入所率を示す（Kaplan-Meierのプロット）．死亡，入院に関しては有意に男性が女性に比較して高率であった．一方逆に女性の方が高い率で介護福祉施設に入所した．

性による3年間の観察期間における死亡，入院，介護施設入所に対するリスク差を明らかにするために，Cox比例ハザード検定を行った．男性要介護者に比較し女性の死亡，入院のハザード・リスク（HR）は単変量解析ではそれぞれ0.61（95%信頼区間（95%CI）：0.51～0.74），0.76（0.66～0.88）で，多変量解析ではそれぞれ0.51（0.39～0.66），0.83（0.69～0.99）であった（表4）．一方，介護施設入所の女性要介護者のHR（95%CI）は単変量解析では1.48（1.00～2.19）と有意差を認めたが，多重