Increased Risk of Sudden Sensorineural Hearing Loss in Patients With Osteoporosis: A Population-based, Propensity Score-matched, Longitudinal Follow-Up Study

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Context: Previous studies have reported an increased prevalence of sudden sensorineural hearing loss (SSNHL) in osteoporotic patients. However, the risk of SSNHL in this population remains unclear.

Objective: This study investigated the risk of SSNHL in osteoporotic patients.

Setting: Taiwan launched a single-payer National Health Insurance (NHI) program on March 1, 1995. NHI covers nearly all of Taiwan's residents.

Design: Using randomized representative sample of one million individuals from Taiwan's National Health Insurance claims database, we compared the data of 10 660 patients with newly diagnosed osteoporosis from 1998–2008 and with 31 980 patients without osteoporosis. All patients were tracked until SSNHL was diagnosed, death, or the end of 2011. Osteoporosis was identified based on a primary diagnosis of osteoporosis (ICD-9-CM code 7330) by dual-energy x-ray absorptiometry.

Intervention: Identified the diagnosis of osteoporosis and SSNHL by ICD-9CM code.

Main Outcome Measure: The identification of patients with newly diagnosed SSNHL by ICD-9CM code.

Results: The incidence rates of SSNHL in the osteoporosis cohort and comparison group were 10.43 and 5.93 per 10 000 person years. Patients with osteoporosis were at 1.76 times the risk of developing SSNHL than patients without osteoporosis. The incidence rate ratio (IRR) for SSNHL was significantly greater in older (50–64 y and ≥65 y), and female patients, and borderline greater in hypertensive patients with osteoporosis than the controls, IRRs being 1.50, 2.33, 1.87, and 1.59.

Conclusions: Patients with osteoporosis are at significantly greater risk of developing SSNHL. **(*J Clin Endocrinol Metab* 100: 2413–2419, 2015)**

Osteoporosis is a common skeletal condition characterized by systemic impairment of bone mass, strength, and microarchitecture, resulting in skeletal fragility and increased risk of fractures (1). The World Health Organization defines osteoporosis as a bone mineral density (BMD) T-score less than −2.5 measured by dual-emis-

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Abbreviations: BMD, bone mineral density; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IRR, incidence rate ratio; LHID2000, Longitudinal Health Insurance Database 2000; NF-κB, nuclear factor-κB; NHI, National Health Insurance; PY, person years; SSNHL, sudden sensorineural hearing loss.

sion x-ray absorptiometry. A growing body of evidence is showing a correlation between skeletal disease and systemic inflammatory responses and endothelial dysfunctions. One cross-sectional study reported severe bone loss to be an independent risk factor for brain infarction (2). Another study suggested that lower BMD may be associated with increased risk of myocardial infarction (3). Therefore, osteoporosis is very probably a systemic disease rather than a disease affecting the bones only.

There are three types of hearing loss: sensorineural, conductive, and mixed. Conductive hearing loss involves the middle and outer ear whereas sensorineural hearing loss involves the inner ear, cochlea, or the auditory nerve (4). Sudden sensorineural hearing loss (SSNHL) is an acute, unexplained loss of hearing. The U.S. National Institute on Deafness and other Communication Disorders defined SSNHL as a loss of greater than 30 dB in three contiguous frequencies in less than 3 days. Most cases of SSNHL are idiopathic. There are several possible etiologies of SSNHL, including local vascular abnormalities, viral infection, immune-mediated mechanisms, chronic inflammation, and abnormalities of the inner ear (5–8). Previous studies have also shown that SSNHL increases the risk of subsequent stroke and myocardial infarction (9, 10).

Although osteoporosis and SSNHL are complex and heterogeneous disorders and are related to cerebrovascular and cardiovascular disease, the relationship between the two diseases remains undetermined. One study mentioned a possible association between idiopathic osteoporosis and decreased hearing function (11). Another study proposed an association between lower femoral neck bone mass and SSNHL (12). However, one study investigating 120 postmenopausal women, showed no statistical significance at low frequencies, irrespective of BMD values (13). These previous studies were of small sample sizes or cross-sectional designs and their results were inconclusive. Therefore, we used a nationwide population-based insurance dataset to conduct a follow-up study investigating the risk of SSNHL in 10 660 patients with osteoporosis compared with 31 980 age-matched unaffected individuals in Taiwan by propensity-score matching for underlying comorbidities.

Materials and Methods

Data sources

Taiwan launched a single-payer National Health Insurance (NHI) program on March 1, 1995. NHI claims database, which covers nearly all of Taiwan's residents (coverage rate >98% in 2009), is one of the largest and most complete population-based datasets in the world. Data used in this study were obtained from NHI's Longitudinal Health Insurance Database 2000 (LHID2000), a subdataset of NHI database, which contains all claims data (from 1996–2011) of one million beneficiaries who were systemic-randomly selected in 2000. There is no significant difference in age, sex, and health care costs between the sample group and all enrollees. The LHID2000 provides encrypted patient identification numbers, sex, date of birth, dates of admission and discharge, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of diagnoses and procedures, details of prescriptions, registry of catastrophic illness patient database, and costs covered and paid for by NHI. The institutional review board of Chi Mei Medical Center approved the study and waived the requirement of informed consent because the datasets we analyzed were devoid of identifiable personal information.

Study sample

A retrospective cohort study was conducted with two study groups—a newly onset osteoporosis group and a matched nonosteoporosis (comparison) group recruited 1999–2008. Osteoporosis was identified in patients with claims data containing a primary diagnosis of osteoporosis (ICD-9-CM code 7330) by dual-energy x-ray absorptiometry. In Taiwan, osteoporosis is defined as a T-score of −2.5 SD or less at the spine, hip, or forearm. Patients who were diagnosed as having osteoporosis before 1999 were excluded. Patients who were diagnosed as having SSNHL (ICD-9-CM code 388.2) before osteoporosis were also excluded.

From the same dataset, we randomly selected control patients (three per osteoporosis patient) who were not diagnosed with osteoporosis. They were matched using a propensity score by age, sex, area, income and comorbid diabetes mellitus (DM), hypertension, chronic kidney disease, and coronary artery disease (CAD) status. Propensity-score matching was used to reduce selection bias because it can be used to bundle many confounding covariates that may be present in an observational study with this number of variables. Propensity scores were computed by modeling a logistic regression model with the dependent variable as the odds of diagnosis of osteoporosis, and the independent variables as the age at which DM was diagnosed (±30 d), sex, and selected comorbidities, area, and income. Then, a SAS matching macro "%OneToManyMTCH" was used following a recommendation proposed in the proceedings of the 29th SAS Users Group International (14). This macro matching allows propensity score matching from 1-to-1 to 1-to-N based on specifications from the user. The macro makes "best" matches first and "next-best" matches next, in a hierarchical sequence until no more matches can be made. Each control is selected at most once. The final matched-pair samples contain both closely matched individual pairs and balanced case and control groups. We also recorded claims data on comorbid disorders, including DM (250), hypertension (401–405), chronic kidney disease (582, 583, 585, 586, 588), and CAD (410–414) status. We counted these comorbid conditions if they were diagnosed in either an inpatient setting or in three or more ambulatory care claims coded 1 year before the index medical care date. Person years (PY) of follow-up time were calculated for each person until SSNHL was diagnosed, death, or the end of 2011. Information that identified patients with SSNHL was based on a minimum of three visits and a corresponding diagnosis provided by referral teaching hospitals and tertiary referral medical centers.

Table 1. Demographic Data for Patients with Osteoporosis and Controls (n = 42 640)

Category	Osteoporosis, n (%)	Controls, n (%)	Standardized Difference
N	10 660	31 980	
Age, y			
0∼49	1029 (9.653)	3062 (9.57)	0.003
50∼64	4883 (45.81)	14 910 (46.62)	0.016
≥65	4748 (44.54)	14 008 (43.80)	0.015
Female	9542 (89.51)	28 745 (89.88)	0.012
Comorbidity			
DM	1568 (14.71)	4775 (14.93)	0.006
HTN	3220 (30.21)	9777 (30.57)	0.008
CKD	230 (2.16)	622 (1.94)	0.016
CAD	1177 (11.04)	3445 (10.77)	0.009
Area			
North	5211 (48.88)	15 594 (48.76)	0.002
Center	1505 (14.12)	4442 (13.89)	0.007
South	3722 (34.92)	11 284 (35.28)	0.008
East	222 (2.08)	660 (2.06)	0.001
Income			
NT<15 840	6346 (59.53)	18 998 (59.41)	0.002
NT 15 841approximately 25 000	3117 (29.24)	9277 (29.01)	0.005
NT>25 001	1197 (11.23)	3705 (11.59)	0.011

Abbreviations: CKD, chronic kidney disease; HTN, hypertension.

Statistical analyses

All statistical operations were performed using the SAS 9.3 statistical package (SAS Institute, Inc). We used standardized difference, which was proposed by Ho (35), to assess the balance of measured variables between osteoporosis and nonosteoporosis subjects in the matched sample, because assessment of balance in baseline variables between treated and untreated cases should use methods that are not influenced by sample size and that are sample specific and do not refer to a hypothetical population (15). A standardized difference of 0.1 or more was considered indicative of imbalance (16). All following analyses were performed in the matched sample, using methods appropriate for the analysis of matched data in estimating the outcome effect. The incidence rate was calculated as the number of SSNHL cases during the followup divided by the total PY for each group by sex, age, and selected comorbidities. The risk of SSNHL between the osteoporotic subjects and matched controls was compared by estimating the incidence rate ratio (IRR) with conditional Poisson regression. Moreover, Cox proportional hazard regression was performed to compute the risk of SSNHL between the osteoporotic subjects and control groups after taking pair matching into account. To assess the effect of specific antiosteoporotic therapy on the association between SSNHL and osteoporosis, Cox proportional hazard regression was also performed to analyze osteoporotic patients who had received bisphosphonate therapy and without bisphosphonate therapy, which was used as a surrogate marker for severity of osteoporosis. In Taiwan, antiosteoporotic therapy, such as bisphosphonate, is covered by National Health Insurance only in the osteoporotic patients (T-score ≤ -2.5), who have at least one spine or hip fracture. The SAS procedures GENMOD (for conditional Poisson regression) and PHREG (for Cox proportional hazards regression on the matched pairs) can be used to analyze matched-pair cohort data. A Kaplan-Meier survival curve was estimated in both groups and stratified log-rank test was used to compare the difference between two cohorts by a test described by Klein and Moeschberger (17). A two-sided $P < .05$ was considered significant.

Results

Table 1 is a summary of the baseline characteristics and comorbid medical disorders in the study and comparison group. In total, we recruited 10 660 patients with osteoporosis and 31 980 controls matched by age, sex, baseline comorbidities (including DM, hypertension, chronic kidney disease, and CAD), resident area, and monthly income. Most of the enrolled subjects were female (89.51%) and more than 50 years old (91%), and 89% of patients with osteoporosis had a monthly income less than 25 000 NT dollars (USD 806).

The osteoporotic group had a significantly higher incidence of SSNHL than the control group (Table 2). A total of 91 of the 10 660 osteoporotic patients were diagnosed as having SSNHL during the follow-up period (10.43 per 10 000 PY). One hundred fifty-five of 31 980 of the controls developed SSNHL during the follow-up period (5.93 per 10 000 PY), making the incidence rate ratio (IRR) of 1.76 (95% confidence interval [CI], 1.36–2.28; $P < .0001$). Patients with osteoporosis aged 50 years or older were at higher risk of SSNHL, and the incidence rate ratio was 1.50 in those between 50 and 64 years old and 2.33 in those 65 years or older, respectively. Women with osteoporosis were at higher risk of SSNHL than those without osteoporosis (IRR = 1.87; 95% CI, 1.42–2.45; $P < .0001$). This tendency was not observed in men. Al-

Table 2. Risk of SSNHL for Osteoporotic Patients and Controls

	Osteoporosis				Controls					
Characteristics	**N**	**SSNHL**	**No. PY**	**Rate[a]**	**N**	**SSNHL**	**No. PY**	**Rate[a]**	**IRR (95% CI)**	***P* Value**
All	10 660	91	87 260.85	10.43	31 980	155	261 519.33	5.93	1.76 (1.36–2.28)	<.0001
Age, y										
0∼49	1029	6	9006.52	6.66	3062	13	26 687.96	4.87	1.36 (0.52–3.56)	.5274
50∼64	4883	46	42 348.17	10.86	14 910	92	127 603.31	7.21	1.50 (1.06–2.14)	.0234
≥65	4748	39	35 906.16	10.86	14 008	50	107 228.06	4.66	2.33 (1.53–3.55)	<.0001
Sex										
Male	1118	6	7687.67	7.80	3235	19	23 704.87	8.02	0.97 (0.39–2.44)	.9500
Female	9542	85	79 573.17	10.68	28 745	136	237 814.46	5.72	1.87 (1.42–2.45)	<.0001
Comorbidity										
DM	1568	12	12 765.92	9.40	4775	34	37 026.28	9.18	1.02 (0.52–1.99)	.9532
HTN	3220	28	24 517.73	11.42	9777	53	73 927.61	7.17	1.59 (1.01–2.51)	.0465
CKD	230	0	1524.66	—	655	5	4037.66	12.38	—	—
CAD	1177	10	8890.43	11.25	3445	26	26 011.82	10.00	1.13 (0.55–2.33)	.7445

Abbreviations: CKD, chronic kidney disease; HTN, hypertension.

[a] Rate per 10 000 PY.

though hypertensive patients with osteoporosis seemed to have higher risk of SSNHL than hypertensive patients without osteoporosis (IRR = 1.59; 95% CI, 1.01–2.51; $P = .0465$), the lower bound of the CI was essentially 1 and the *P* value was on the borderline of statistical significance.

In Table 3 we divided female patients into four groups by decades of age. We found an increasing trend in the IRR accompanying increases in age. Patients with osteoporosis aged 60 years or older were at higher risk of SSNHL. The IRR was 2.38 (95% CI, 1.50–3.75; $P = .0002$) in those between 60–70 years old and 2.59 (95% CI, 1.42–4.70; $P = .0018$) in those 70 years or older.

Table 4, the results of our Cox proportional hazard regressions, shows that the hazard ratio (HR) for SSNHL in patients with osteoporosis was 1.76, compared with those without osteoporosis (95% CI, 1.33∼2.34; $P < .0001$). To examine the effect of antiosteoporotic therapy on the association between osteoporosis and SSNHL, we also analyzed the effect of bisphosphonate therapy in Table 4. The HR for SSNHL in osteoporotic patients who has received bisphosphonate therapy was 2.46, compared with control group (95% CI, 1.52–3.99; $P = .0005$) and the HR for SSNHL in osteoporotic patients who had not received bisphosphonate therapy was 1.64, compared with control group (95% CI, 1.24–2.17; $P = .0003$). As can be seen in Figure 1, the Kaplan-Meier analysis revealed that patients with osteoporosis had a higher incidence of SSNHL than the control group (log-rank test $P < .0001$).

Discussion

This study found an approximately 1.76-fold increase in the incidence of SSNHL for patients with osteoporosis compared with the comparison group. The risk of SSNHL associated with osteoporosis remained high even after controlling for age, sex, medical comorbidities, geographical area, and monthly income. To the best of our knowledge, this is the first and largest population-based study to evaluate the risk of SSNHL in a national cohort of Asian patients with osteoporosis.

Several studies have suggested the risk factors for SSNHL include traditional cardiovascular risk factors, such as CAD, hypertension, chronic kidney disease, and DM (18, 19). In our study, hypertensive patients with osteoporosis had borderline higher risk of SSNHL than hypertensive pa-

Table 3. Risk of SSNHL for Osteoporotic Patients and Controls in Females

	Osteoporosis				Controls					
Characteristics	**N**	**SSNHL**	**No. PY**	**Rate[a]**	**N**	**SSNHL**	**No. PY**	**Rate[a]**	**IRR (95% CI)**	***P* Value**
Age										
0∼49	924	5	8176.83	6.11	2795	12	24 635.45	4.87	1.25 (0.44–3.54)	0.6680
50∼60	3239	27	28 289.6	9.54	9947	60	85 613.41	7.01	1.36 (0.86–2.13)	0.1844
60∼70	2721	33	23 461.34	14.07	8266	41	69 019.97	5.94	2.38 (1.50–3.75)	0.0002
≥70	2658	20	19 645.41	10.18	7737	23	58 545.63	3.93	2.59 (1.42–4.70)	0.0018

Abbreviation: CKD, chronic kidney disease.

[a] Rate per 10 000 PY.

Table 4. Cox Proportional Hazard Regressions and 95% confidence interval Stratified on the Matched Pairs for the Development of SSNHL for Study Cohorts

	HR	95% CI	*P*-Value
Controls	1.00		
Osteoporosis	1.76	1.33–2.34	<.0001
Osteoporosis without bisphosphonate therapy	1.64	1.24–2.17	.0003
Osteoporosis with bisphosphonate therapy	2.46	1.52–3.99	.0005

Adjusted by age group, sex, diabetes, hypertension, CAD, chronic kidney disease, income, and area.

tients without osteoporosis. The results should be interpreted with caution given that the lower bound of the CI was essentially 1. Additional studies are needed to clarify these results. One possible explanation for the association between osteoporosis and SSNHL is that osteoporosis contributes to the development of SSNHL via the effects of cardiovascular disease and risk factors. However, there remained a significant relationship between osteoporosis and SSNHL in our patients matched for these comorbidities after adjustment in our analysis. Therefore, cardiovascular disease and risk factors do not exclusively explain the relationship between osteoporosis and SSNHL.

Although the underlying mechanism contributing to the association between osteoporosis and SSNHL is likely complex, there are some possible explanations for our findings. One study concluded that dysfunction of cochlear capsule in osteoporotic patients might play a role in the development of SSNHL (20). One radiologic study of Paget's disease reported a significant association between demineralization of the cochlear capsule and the development of SSNHL (21). Demineralization of cochlear capsule was found to be correlated with hearing loss in patients with metabolic bone disorders such as Paget's disease and osteogenesis imperfecta. Hearing loss might also be caused

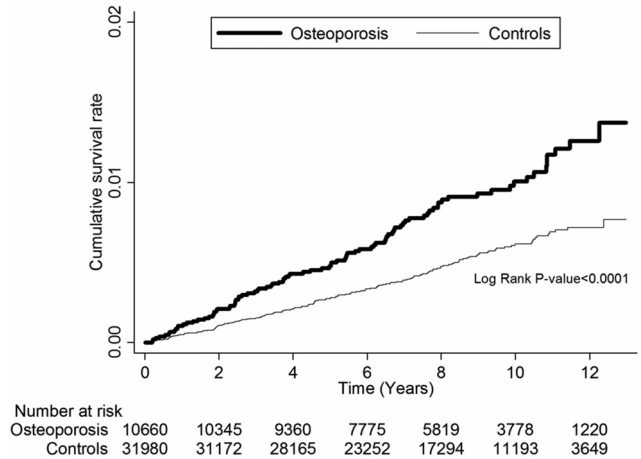

Figure 1. The cumulative incidence rate for SSNHL for patients with osteoporosis and without osteoporosis (log-rank $P < .0001$).

by internal auditory canal invasion and compression of the cochlear division of the cranial nerve (22, 23). Similar mechanisms might also underlie the relationship between osteoporosis and SSNHL. One study found an inverse association between BMD of the femoral neck and sensorineural hearing loss (12). They hypothesized that the bone mass of the femoral neck might reflect bone mass of the petrous temporal bone. Because osteoporosis is possibly a systemic metabolic disease with demineralization of skeletal system, it is reasonable to hypothesize that systemic demineralization may not spare the temporal bone, which contains the cochlea capsule and the conductive system.

There is a close link between inflammation and bone destruction. One study reported an increased level of inflammatory mediators such as interleukin IL-6, TNF-α, C-reactive protein (CRP), and soluble receptors (IL-2 sR, IL-6 sR, TNF sR1, and TNF sR2) in patients with osteoporosis (24). Cytokines play an important role in inflammatory bone destruction by up-regulating the receptor activator of nuclear factor-κB (NF-κB) ligand (25). There is also a close association between systemic inflammation and SSNHL. One study discovered that NF-κB activation in the cochlea can cause severe SSNHL, and the NF-κB activation can be induced by decreased natural killer cell activity, increased neutrophil count, and increased IL-6 level (26). Several studies have found increased systemic inflammation, represented by higher levels of mediators such as white cell count, neutrophil count, CRP or IL-6, to be associated with SSNHL (27, 28). Another recent study has proposed the markers of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio values can be used for the diagnosis and prognosis of SSNHL. Endothelial dysfunction might play a role in SSNHL and is associated with microvascular disturbances and inflammatory processes (29). Both osteoporosis and SSNHL are complex disorders and may be caused by multiple mechanisms, such as cardiovascular risk factors, bone demineralization, inflammation, and endothelial dysfunction.

This study found an association between osteoporosis and SSNHL in female but not male patients. It also found that osteoporotic patients aged 50 years or older were at higher risk of SSNHL, a tendency not found in those younger than 50 years. We subanalyzed the association between the onset of osteoporosis and SSNHL in women by decades of age. The association between osteoporosis and SSNHL was obvious in women age 60 years or older. Although the exact mechanism is not known, we speculate that estrogen may play a role in the development of SSNHL, however, in older women the lack of estrogen does not seem to be essentially connected with bone demineralization (30). Therefore, there might be other factors affecting

this relationship in women, such as genetic factors, aging, or lifestyle pattern. Additional studies investigating fine clinical details are needed to explore the possibilities.

It is worth noting that osteoporotic patients with antiosteoporotic therapy had higher HR. In Taiwan, antiosteoporotic therapy is covered by NHI only in the osteoporotic patients who have had at least one spine or hip fracture, and thus antiosteoporotic therapy is supported by NHI for severe osteoporotic patients only. Patients with more severe osteoporosis may have a higher risk of SSNHL than patients with osteoporosis of milder severity.

Our study has some limitations. One limitation was that the identification of osteoporosis and SSNHL diagnoses were based on diagnoses listed in an administrative database which may be less accurate. However, the Bureau of the NHI has formed different audit committees that randomly sample the claims data from every hospital and review charts on a regular basis to verify the diagnostic validity and quality of care. The NHI Research Database has acceptable validity for epidemiologic investigations (31). To further maximize case ascertainment, we selected only patients who fulfilled the dual-emission x-ray absorptiometry criteria for osteoporosis. Patients who had at least three ambulatory medical care visits and a principle diagnosis of SSNHL provided by an otolaryngologist in the referral teaching hospitals and tertiary referral medical centers to validate the diagnosis, which might be expected to provide adequate diagnostic accuracy. This method of identifying these diseases has been used extensively in various studies of Taiwan National Health Insurance Research Database, and many articles have been published (32–34). Another limitation is the difficulty in documenting the finer clinical details, such as cigarette smoking, alcohol consumption, family history, noise exposure, and changes in BMD in the analysis. Such data are not available in the NHI Research Database. Additional study is needed to clarify the effects of these factors.

In summary, this large population-based study reveals that patients with osteoporosis are at significantly increased risk of developing SSNHL. Additional studies should be performed to confirm our findings and determine the mechanism of the association between osteoporosis and SSNHL.

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