Increased migraine risk in osteoporosis patients: a nationwide population-based study

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Abstract

Background: Osteoporosis and migraine are both important public health problems and may have overlapping pathophysiological mechanisms. The aim of this study was to use a Taiwanese population-based dataset to assess migraine risk in osteoporosis patients.

Methods: The Taiwan National Health Insurance Research Database was used to analyse data for 40,672 patients aged ≥20 years who had been diagnosed with osteoporosis during 1996–2010. An additional 40,672 age-matched patients without osteoporosis were randomly selected as the non-osteoporosis group. The relationship between osteoporosis and migraine risk was estimated using Cox proportional hazard regression models.

Results: During the follow-up period, 1110 patients with osteoporosis and 750 patients without osteoporosis developed migraine. After controlling for covariates, the overall incidence of migraine was 1.37-fold higher in the osteoporosis group than in the non-osteoporosis group (3.72 vs. 1.24 per 1000 person-years, respectively). Migraine risk factors included high Charlson Comorbidity Index score, female gender, hypertension, depression, asthma, allergic rhinitis, obesity, and tobacco use disorder.

Conclusions: Our results indicate that patients with a history of osteoporosis had a higher risk of migraine.

Keywords: Osteoporosis, Migraine, Nationwide population-based study

Background

Both osteoporosis and migraine are common conditions that can affect quality of life and can impose large social and economic burdens (Kuo et al. 2015; Manandhar et al. 2015a, b; Mbewe et al. 2015; Rao et al. 2015; Steiner et al. 2015; Lampil et al. 2016). The National Institutes of Health Consensus Development Conference Statement defines osteoporosis as a skeletal disorder characterized by diminished bone strength resulting in increased fracture risk. Bone strength is measured in terms of both bone mineral density (BMD) and bone quality (Nih Consensus Development Panel on Osteoporosis Prevention and Therapy 2001). In elderly populations, osteoporosis affects approximately 30 % of women and 12 % of men (Rachner et al. 2011). Migraine is a neurological disorder that manifests as a debilitating headache associated with altered sensory perception (Goadsby et al. 2002; Charles 2013; Baykan et al. 2015; Manandhar et al. 2015a, b). The International Headache Society defines migraine as a headache that lasts for 4–72 h and has at least two of the following characteristics: pulsating quality, unilateral localization, moderate-to-severe pain intensity, and aggravation by movement (Headache Classification Subcommittee of the International Headache 2004). Previous studies have identified interacting relationships among migraine, various sleep disorders, depression, psoriasis, restless legs syndrome and cardiovascular disease (Kelman and Rains 2005; Pompili et al. 2009; Schurks et al. 2009; Cho et al. 2015; Egeberg et al. 2015; Kim et al. 2016; Risal et al. 2016). Migraine is associated with episodes of local sterile meningeal inflammation, hypersensitized pain pathways, and increased inflammatory cytokines that contribute to the pathogenesis of osteoporosis, such...
as interleukins (ILs) or tumor necrosis factor-α (Braun and Schett 2012; Egeberg et al. 2015). Like osteoporosis and other inflammatory conditions, migraine is also apparently associated with systemic endothelial dysfunction (Vanmolkot et al. 2007; Sacco et al. 2013; Steyers and Miller 2014). Although no recent studies have suggested a link between osteoporosis and migraine, both conditions are independent risk factors for cardiovascular disease (Sumino et al. 2008; Bigal et al. 2010; Hyder et al. 2010), and both are comorbid with pain-related and psychiatric conditions (Kalaydjian and Merikangas 2008; Radaei et al. 2014). We therefore investigated the impact of osteoporosis on migraine risk in a nationwide cohort in Taiwan.

Methods

Database

This population-based cohort study used data obtained from the Taiwan National Health Insurance Research Database (NHIRD) maintained by the national health care system of Taiwan. The NHIRD is an encrypted secondary database containing medical data for approximately 99% of the 23.74 million residents of Taiwan. The Taiwan national health insurance program allows researchers to access this database of administrative data for patients. The NHIRD files are composed of comprehensive use and enrollment information of the patients. Besides, under regulations of the Personal Electronic Data Protection Law of Taiwan, all citizens and hospital identities in the NHIRD database were decoded. This retrospective cohort study analysed 1996–2010 data contained in a subset of the NHIRD, the Longitudinal Health Insurance Database 2010, which comprises data for 1 million beneficiaries randomly sampled from the primary NHIRD. In this study, diseases were identified and classified according to the diagnostic codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Ethical approval

The study was performed in accordance with the Declaration of Helsinki guidelines and was also evaluated and approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT (II)-20160016).

Study population

The study cohort included 40,672 patients aged 20 years or older who had been diagnosed with osteoporosis (ICD-9-CM code 733.0) during 1996–2010. To maximize accuracy, the analysis was limited to patients who had a record of ≥2 osteoporosis diagnoses during ambulatory visits or ≥1 diagnoses during inpatient care, an ICD-9 code assigned by an orthopaedist, and at least one BMD examination. The index date was defined as the date of the first clinical visit for osteoporosis. A migraine (ICD-9-CM code 346) was defined as a history of two or more migraine diagnoses in ambulatory visits or one or more migraine diagnoses in inpatient care as well as a record of an ICD-9 code for migraine assigned by a neurologist. The date of diagnosis was defined as the date of the first diagnosis of osteoporosis. Matching control subjects were assigned an identical “pseudo date of diagnosis”, which was the date of diagnosis in matched cases. The exclusion criteria were diagnosis of migraine before or on the index date, incomplete information, and age younger than 20 years.

The ratio of osteoporosis to non-osteoporosis patients was kept at 1:1 to enhance the power of statistical tests and to obtain a sufficient number of migraine cases for stratified analyses. The patients in the non-osteoporosis cohort were selected by a simple random sampling method in which one insured patient without osteoporosis was randomly selected and frequency matched with each person in the osteoporosis cohort in the same period by age, gender, and year of osteoporosis diagnosis. A post hoc sample size was calculated to determine statistical power. Logistic regression analysis was used to obtain a 4-digit match of the propensity score for each patient with the covariates, including age and gender. As a result, 40,672 subjects were enrolled in the non-osteoporosis cohort. Figure 1 shows a flowchart of the study procedure.

Outcome and comorbidities

The patients in both the osteoporosis and non-osteoporosis cohorts were followed up until diagnosis with
migraine, withdrawal from insurance, or the end of 2010, whichever occurred first. Baseline comorbidities identified by ICD-9-CM codes in the claims records before the index date included hypertension (ICD-9-CM codes 401-405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM codes 296.2, 296.3, 300.4 and 311), asthma (ICD-9-CM code 493), allergic rhinitis (ICD-9-CM code 477), psoriasis (ICD-9-CM code 696.1), obesity (ICD-9-CM code 278), tobacco use disorder (ICD-9-CM code 350.1), and alcohol attributed disease (ICD-9-CM codes 291.0-9, 303, 305.0, 357.5, 425.5, 535.3, 571.0-3, 980.0 and V11.3). The Charlson Comorbidity Index (CCI) score was used to assess the severity of comorbidities, i.e., myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease (mild, moderate, or severe), diabetes (with or without chronic complication), hemiplegia or paraplegia, renal disease, any malignancy (including lymphoma and leukemia but excluding skin malignancy), metastatic solid tumor, human immunodeficiency virus infection and acquired immune deficiency syndrome. The CCI scores were then categorized into four levels: 0, 1–2, 3–4 and ≥5.

Statistical analyses
Chi square test was used to compare distributions of categorical demographics and clinical characteristics between the osteoporosis and non-osteoporosis cohorts. The Student t test and Wilcoxon rank-sum test were used as appropriate to compare mean age and follow-up time (y) between the two cohorts. The Kaplan–Meier method was used to estimate cumulative incidence, and the differences between the curves were tested by 2-tailed log-rank test. For osteoporosis patients, survival was calculated until hospitalization, an ambulatory visit for migraine, or the end of the study period (December 31, 2010), whichever occurred first. Incidence rates of migraine estimated in 1000 person-years were compared between the two cohorts. Univariable and multivariable Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95 % confidence intervals (CIs) for migraine if the proportional hazards assumption was satisfied. The multivariable Cox models were adjusted for age, gender, CCI score, and relevant comorbidities. A 2-tailed P value of <0.05 was considered statistically significant. All data processing and statistical analyses were performed using Statistical Analysis Software, version 9.4 (SAS Institute, Cary, NC, USA).

Results
Baseline characteristics of patients with and without osteoporosis
The baseline demographic characteristics and comorbidities in the two cohorts are presented in Table 1. In the osteoporosis cohort, 82.48 % patients were female. Compared to the non-osteoporosis cohort, the osteoporosis cohort had significantly higher percentages of patients with hypertension (70.12 vs. 54.07, P < 0.001), diabetes mellitus (38.58 vs. 27.71, P < 0.001), hyperlipidemia (61.28 vs. 43.96, P < 0.001), depression (21.21 vs. 11.71, P < 0.001), asthma (28.77 vs. 19.20, P < 0.001), allergic rhinitis (44.62 vs. 32.38, P < 0.001), psoriasis (2.15 vs. 1.43, P < 0.001), obesity (2.64 vs. 2.11, P < 0.001), tobacco use disorder (1.91 vs. 1.04, P < 0.001) and alcohol-attributable disease (2.63 vs. 1.92, P < 0.001). The osteoporosis cohort also had higher CCI scores. During a median observation time of 3.5 years, 2.73 % (1110) of the osteoporosis patients had migraine (interquartile range [IQR] 1.5–6.2). The migraine incidence of osteoporosis cohort was significantly (P < 0.001) higher than that in the non-osteoporosis patients (751 with migraine out of 40,672 age- and gender-matched controls [1.85 %]) during a median observation time of 7.2 years [IQR 4.8–10.5]). Migraine development was significantly faster in the osteoporosis group (3.5 years) compared to the non-osteoporosis group (7.2 years) for the respective observation periods.

Migraine incidence and risk
The migraine incidence and HRs by gender, age and comorbidity are stratified in Table 2. During the follow-up period, migraine developed in 2.73 % (1110) of the osteoporosis patients and in 1.85 % (750) of the non-osteoporosis patients. The overall migraine risk was 1.37 times greater in the osteoporosis group compared to the non-osteoporosis group (3.72 vs. 1.24 per 1000 person-years, respectively) after adjusting for age, gender, CCI, and related comorbidities (hypertension, diabetes mellitus, hyperlipidemia, depression, asthma, allergic rhinitis, psoriasis, obesity, tobacco use disorder and alcohol-attributable disease).

The gender-specific analyses showed that, in both cohorts, the incidence of osteoporosis was higher in women than in men (3.61 vs. 2.28 per 1000 person-years, respectively, in the osteoporosis cohort; 1.35 vs. 0.73 per 1000 person-years, respectively, in the non-osteoporosis cohort). Additionally, the osteoporosis group had a significantly higher migraine risk in both genders (adjusted HR 1.34, 95 % CI 1.19–1.49 for women; adjusted HR 1.66, 95 % CI 1.19–2.31 for men).

Although the incidence of migraine was consistently higher in all age groups in the osteoporosis cohort
compared to the non-osteoporosis cohort, the migraine risk decreased with age. Age-specific risk comparisons showed that, compared to the non-osteoporosis cohort, the osteoporosis cohort had a significantly higher migraine risk in patients under 50 years old (adjusted HR 1.46, 95 % CI 1.17–1.82, P < 0.001) than in patients over 50 years old (HR 1.34, 95 % CI 1.20–1.50, P < 0.001). Regardless of comorbidities, migraine risk was higher in osteoporosis patients than in non-osteoporosis patients. However, the migraine risk contributed by osteoporosis decreased in the presence of comorbidity.

The Kaplan–Meier curves for the cumulative incidence of migraine between the osteoporosis and non-osteoporosis groups at the 15-year follow up are compared in Fig. 2. The Kaplan–Meier curves showed a significantly higher cumulative incidence of migraine in the osteoporosis cohort compared to the non-osteoporosis cohort (log-rank test P < 0.001).

### Table 1 Baseline characteristics of patients with and without osteoporosis

| Variables                        | Osteoporosis                        | No (N = 40,672) | P value |
|----------------------------------|-------------------------------------|----------------|---------|
| Migraine patients, n (%)         | Yes (N = 40,672)                     |                | <0.001  |
| Period of developing migraine, median (IQR), years | 3.5 (1.5–6.2) | 7.2 (4.8–10.5) | <0.001  |
| Mean age at diagnosis of migraine, years | 57.9 (10.4) | 62.6 (10.3) | <0.001  |
| Age group, n (%)                 |                                     |                |         |
| 20–49                            | 7361 (18.10)                        | 7361 (18.10)   | 1.000   |
| ≥50                              | 33,311 (81.90)                      | 33,311 (81.90) |         |
| Gender, n (%)                    |                                     |                |         |
| Men                              | 7125 (17.52)                        | 7125 (17.52)   | 1.000   |
| Women                            | 33,547 (82.48)                      | 33,547 (82.48) |         |
| Charlson Comorbidity Index, n (%)|                                     |                |         |
| 0                                | 1912 (4.70)                         | 7744 (19.04)   | <0.001  |
| 1–2                              | 9667 (23.77)                        | 14,437 (35.50) | <0.001  |
| 3–4                              | 11,911 (29.29)                      | 9861 (24.25)   | <0.001  |
| ≥5                               | 17,182 (42.25)                      | 8630 (21.22)   | <0.001  |
| Co-morbidity, n (%)              |                                     |                |         |
| Hypertension                     | 28,521 (70.12)                      | 21,991 (54.07) | <0.001  |
| Diabetes mellitus                | 15,693 (38.58)                      | 11,272 (27.71) | <0.001  |
| Hyperlipidemia                   | 24,923 (61.28)                      | 17,879 (43.96) | <0.001  |
| Depression                       | 8,625 (21.21)                       | 4,764 (11.71)  | <0.001  |
| Asthma                           | 11,700 (28.77)                      | 7,807 (19.20)  | <0.001  |
| Allergic rhinitis                | 18,146 (44.62)                      | 13,168 (32.38) | <0.001  |
| Psoriasis                        | 874 (2.15)                          | 583 (1.43)     | <0.001  |
| Obesity                          | 1073 (2.64)                         | 857 (2.11)     | <0.001  |
| Tobacco use disorder             | 776 (1.91)                          | 422 (1.04)     | <0.001  |
| Alcohol attributed disease       | 1069 (2.63)                         | 780 (1.92)     | <0.001  |

Risks factors for migraine in osteoporosis patients

The Cox regression analysis revealed the following risk factors for migraine in the osteoporosis group: high CCI score, female gender, hypertension, depression, asthma, allergic rhinitis, obesity, and tobacco use disorder. Risk factors for migraine were female gender (adjusted HR 1.51, 95 % CI 1.23–1.85), hypertension (adjusted HR 1.19, 95 % CI 1.02–1.38), depression (adjusted HR 2.36, 95 % CI 2.09–2.66), asthma (adjusted HR 1.28, 95 % CI 1.13–1.45), allergic rhinitis (adjusted HR 1.46, 95 % CI 1.29–1.66), obesity (adjusted HR 1.79, 95 % CI 1.40–2.28), tobacco use disorder (adjusted HR 2.30, 95 % CI 1.78–2.97) and high CCI (adjusted HR 1.57, 95 % CI 1.44–1.71) (Table 3).

Discussion

To our knowledge, this is the first nationwide population-based study of the relationship between osteoporosis and subsequent migraine in an Asian population. During the
follow-up period, migraine developed in 2.73 % (1110) patients with osteoporosis and in 1.85 % (750) patients without osteoporosis. After controlling for potential confounding factors, migraine risk was 1.37-fold higher in the osteoporosis group than in the non-osteoporosis group. Patients with osteoporosis, particularly those with high CCI score, female gender, hypertension, depression, asthma, allergic rhinitis, obesity, and tobacco use disorder, had a high migraine risk.

The exact mechanisms underlying the relationship between migraine and osteoporosis are likely to be elusive. However, several lines of evidence in the literature suggest that osteoporosis and migraine have a shared pathophysiology. First, bone density is significantly associated with magnesium, an essential micronutrient with a wide range of metabolic, structural and regulatory functions (Jahnen-Dechent and Ketteler 2012). In humans, magnesium deficiency contributes to osteoporosis. Low serum magnesium is a co-contributing factor in osteopenia in adults with sickle cell anemia (Elshal et al. 2012). Moreover, an association between serum magnesium and bone density has been identified in pre- and post-menopausal women (Saito et al. 2004; Song et al. 2007). Magnesium deficiency also has a strong association with migraine attacks (Welch and Ramadan 1995). Gallai et al. showed that individuals suffering from migraine

**Table 2** Incidence and hazard ratios of migraine by demographic characteristics and comorbidity among patients with or without osteoporosis

| Variables | Patients with osteoporosis | Patients without osteoporosis | Compared to non-osteoporosis |
|-----------|---------------------------|-----------------------------|----------------------------|
|           | Migraine PYs Rate         | Migraine PYs Rate           | CrudeHR* (95 % CI) | Adjusted HR* (95 % CI) |
| Overall   | 1110 324,126.20 3.42      | 751 604,550.99 1.24         | 2.48 (2.25–2.73)c 1.37 (1.23–1.51)c |
| Gender    |                           |                            |                           |
| Men       | 104 45,604.93 2.28        | 78 106,313.43 0.73         | 2.80 (2.04–3.85)c 1.66 (1.19–2.31)d |
| Women     | 1006 278,521.27 3.61      | 573 498,237.56 1.35        | 2.39 (2.17–2.66)c 1.34 (1.19–1.49)c |
| Stratify by age |                        |                            |                           |
| 20–49     | 252 64,474.34 3.91        | 130 109,506.02 1.19        | 2.97 (2.39–3.68)c 1.46 (1.17–1.82)c |
| ≥50       | 858 259,651.83 3.30        | 621 495,044.97 1.25        | 2.37 (2.12–2.64)c 1.34 (1.20–1.50)c |
| Comorbidityb |                      |                            |                           |
| No        | 19 20,949.87 0.91         | 43 127,923.68 0.34         | 2.41 (1.40–4.14)e 1.78 (1.03–3.06)f |
| Yes       | 1091 303,176.33 3.59       | 708 476,627.31 1.49        | 2.18 (1.97–2.41)c 1.34 (1.22–1.49)c |

PYs person-years, Rate incidence rate in per 1000 person-years, 95 % CI 95 % confidence interval, HR hazard ratio

- Model adjusted for age, gender, Charlson Comorbidity Index and relevant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, depression, asthma, allergic rhinitis, psoriasis, obesity, tobacco use disorder and alcohol attributed disease)
- Patients with any examined comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, depression, asthma, allergic rhinitis, psoriasis, obesity, tobacco use disorder and alcohol attributed disease, were classified as the comorbidity group
- P < 0.001
- P = 0.003
- P = 0.001
- P = 0.037

**Fig. 2** Cumulative incidence of migraine for adult patients with osteoporosis and the general population control cohort
Table 3 Cox regression model: significant predictors of migraine after osteoporosis

| Variables                        | Adjusted HRa (95% CI) | P value  |
|----------------------------------|------------------------|----------|
| Age                              | 0.76 (0.72–0.81)       | <0.001   |
| Charlson Comorbidity Index       | 1.57 (1.44–1.71)       | <0.001   |
| Female gender                    | 1.51 (1.23–1.85)       | <0.001   |
| Hypertension                     | 1.19 (1.02–1.38)       | 0.027    |
| Depression                       | 2.36 (2.09–2.66)       | <0.001   |
| Asthma                           | 1.28 (1.13–1.45)       | 0.001    |
| Allergic rhinitis                | 1.46 (1.29–1.66)       | <0.001   |
| Obesity                          | 1.79 (1.40–2.28)       | <0.001   |
| Tobacco use disorder             | 2.30 (1.78–2.97)       | <0.001   |

The adjusted HR and 95% CI were estimated by a stepwise the Cox proportional hazards regression method. HR: hazard ratio, 95% CI: 95% confidence interval.

a Model adjusted for age, gender, Charlson Comorbidity Index and relevant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, depression, asthma, allergic rhinitis, psoriasis, obesity, tobacco use disorder and alcohol attributed disease).

Conclusions

In summary, this nationwide population-based cohort study revealed that adult patients with osteoporosis had a significantly higher risk of developing subsequent migraine compared to controls without osteoporosis. Clinicians should be aware that osteoporosis is a potential risk factor for migraine. Further studies are recommended to confirm this association and to explore its mechanisms.

Abbreviations

BMD: bone mineral density; CGRP: calcitonin gene-related peptide; CCI: Charlson Comorbidity Index; CI: confidence interval; HR: hazard ratio; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; IL: interleukin; NHIRD: National Health Insurance Research Database.

Authors’ contributions

CHW participated in study design, interpreted result and drafted the manuscript. ZHZ participated in study design and performed the statistical analysis. MKW participated in study design and helped to draft the manuscript. CHW helped to perform the statistical analysis and coordination. YYL and CLL conceived of the study, participated in its design, coordination and revising the manuscript. All authors read and approved the final manuscript.
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Competing interests
All authors declare that they have no competing interests.

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