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Increased risk of osteoporosis in patients with erectile dysfunction

A nationwide population-based cohort study

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Abstract

In this study, we aimed to investigate the risk of osteoporosis in patients with erectile dysfunction (ED) by analyzing data from the Taiwan National Health Insurance Research Database (NHIRD). From the Taiwan NHIRD, we analyzed data on 4460 patients aged ≥40 years diagnosed with ED between 1996 and 2010. In total, 17,480 age-matched patients without ED in a 1:4 ratio were randomly selected as the non-ED group. The relationship between ED and the risk of osteoporosis was estimated using Cox proportional hazard regression models. During the follow-up period, 264 patients with ED (5.92%) and 651 patients without ED (3.65%) developed osteoporosis. The overall incidence of osteoporosis was 3.04-fold higher in the ED group than in the non-ED group (9.74 vs 2.47 per 1000 person-years) after controlling for covariates. Compared with patients without ED, patients with psychogenic and organic ED were 3.19- and 3.03-fold more likely to develop osteoporosis. Our results indicate that patients with a history of ED, particularly younger men, had a high risk of osteoporosis. Patients with ED should be examined for bone mineral density, and men with osteoporosis should be evaluated for ED.

Abbreviations: BNHI = Bureau of National Health Insurance, CCI = Charlson comorbidity index, CI = confidence interval, CKD = chronic kidney disease, CVD = cardiovascular disease, DM = diabetes mellitus, ED = erectile dysfunction, HR = hazard ratio, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, IL = interleukin, LHID 2010 = Longitudinal Health Insurance Database 2010, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database.

Keywords: erectile dysfunction, nationwide population-based cohort study, osteoporosis

1. Introduction

Erectile dysfunction (ED) is a neurovascular process dependent on the vascular health of the erectile tissue and the health of the central and peripheral nervous systems.[1] Thus, changes or alterations in the fibroelastic properties of the neural, vascular, and erectile tissue can cause. ED is defined as the inability to attain and maintain adequate erection for satisfactory sexual intercourse.[2] ED is the most common sexual problem in men, often causing serious distress and prompting them to seek medical attention. ED primarily affects men over 40 years of age.[3] Various medical, psychological, environmental, and lifestyle factors, such as cardiovascular disease (CVD), diabetes mellitus (DM), hyperlipidemia, hypertension, chronic kidney disease (CKD), metabolic syndrome, and psychological distress, have been suggested to contribute to the development of ED.[3–10] Osteoporosis has similar risk factors; hence, we postulate that osteoporosis and ED are related.

Osteoporosis is a systemic metabolic bone disease characterized by impaired bone strength caused by attenuated bone mineral density and compromised bone quality, which exposes patients to fragility fractures.[11] Previously, osteoporosis was generally considered to affect postmenopausal women; however, substantial bone loss occurs equally in men.[11] Osteoporosis and ED significantly affect the quality of life in men. The relationship between osteoporosis and ED has attracted attention since 2005. Keles et al[12] attempted to clarify a possible relationship between osteoporosis and ED; they reported that the frequencies of osteoporosis and ED increased with age; however, these conditions were independent of each other, and hormonal changes were not the major determinants for both conditions in elderly men. Recently, Dursun et al[13] investigated the relationship between ED and osteoporosis in 95 men with ED and 82 men with normal sexual function and reported that the men with ED had low bone mineral density and were at higher risk of

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osteoporosis than were their healthy counterparts. However, both these studies have a limited scope because they involved a small sample. Therefore, we conducted a nationwide population-based retrospective cohort study by using data from the Taiwan National Health Insurance (NHI) program database to clarify the relationship between ED and the subsequent risk of osteoporosis.

2. Methods

2.1. Database

The NHI is a mandatory single-payer health insurance program launched on March 1, 1995, by the Bureau of National Health Insurance (BNHI), covering approximately 99% of the 23.74 million residents of Taiwan. The National Health Research Institute is responsible for establishing the National Health Insurance Research Database (NHIRD), an encrypted secondary database, for medical research. This database contains administrative and health claims data collected through the NHI program, including comprehensive information on inpatient and ambulatory care and prescriptions dispensed at contracted pharmacies. The NHIRD provides researchers scrambled identification numbers associated with relevant claims information, including records of patient's sex, date of birth, registry of medical services, and medication prescriptions. In this study, we examined the ambulatory and inpatients care data in the Longitudinal Health Insurance Database 2010 (LHID 2010) between 1996 and 2010 for analysis and comparisons. The LHID 2010, a randomly sampled subset of the NHIRD, contains data on 1,000,000 beneficiaries during the period of January 1, 2010 to December 31, 2010. The database has a large sample size, thus facilitating the study of the risk of osteoporosis among ED patients. 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).

2.2. Ethical approval

The study was conducted in accordance with the Declaration of Helsinki guidelines and was evaluated and approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT (I)-20150032).

2.3. Study population

Our ED (psychogenic and organic ED, ICD-9-CM 302.72 and 607.84)[14,15] identification criteria was similar to those of similar studies[16–19] and are hence valid. To ensure the accuracy of the diagnostic data, we included only those patients receiving ≥2 diagnoses during ambulatory visits or ≥1 diagnosis in inpatient care according to the ICD-9-CM codes assigned exclusively by urologists. The date of first clinical visit for ED was considered the index date. To maximize accuracy, we only included cases if they received ≥2 osteoporosis diagnoses for ambulatory visits or ≥1 diagnosis in inpatient care, and the ICD-9 code was assigned by orthopedists and receiving bone mineral density examination.[20,21] Patients with previous osteoporosis (ICD-9-CM 733),[20,21] female patients, those with missing information, and those aged <40 years were excluded. The ratio of ED to non-ED patients was maintained at 1:4 for enhancing the power of statistical tests and ensuring an adequate number of patients with osteoporosis for performing stratified analyses. The patients in the non-ED group were selected using a simple random sampling method, in which 4 insured NHI beneficiaries without ED were randomly selected and frequency matched for age and index year (year of ED diagnosis) with each patient diagnosed with ED in the same period; thus, 17,480 non-ED patients were identified.

2.4. Outcome and comorbidities

The patients in the ED and non-ED groups were followed until they were diagnosed with osteoporosis, withdrawal from insurance or end of follow-up. Baseline comorbidities (ICD-9-CM codes are provided in Supplementary Table S1, http://links.lww.com/MD/B75)[15,22–25] were hypertension, DM, hyperlipidemia, CKD, chronic liver disease, chronic pulmonary disease, stroke, hyperthyroidism, and hyperparathyroidism before the index date. The Charlson comorbidity index (CCI) scores, categorized into 4 levels (0, 1–2, 3–4 and ≥5), were used for assessing the severity of comorbidities. Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild, moderate, and severe liver disease, diabetes with and without chronic complications, hemiplegia and paraplegia, renal disease, malignancy (including lymphoma and leukemia, except skin malignancy), metastatic solid tumors, human immunodeficiency virus infection, and acquired immune deficiency syndrome were the comorbidities included in the analysis. In addition, the use of oral corticosteroids or testosterone was analyzed.

2.5. Statistical analyses

The distributions of categorical and clinical variables between the ED and non-ED groups were compared using the Chi-square test. The paired *t* test and Wilcoxon rank-sum test were used for examining the differences in the mean age and follow-up period (years) between the 2 cohorts, as appropriately. Kaplan–Meier curves were used for estimating the cumulative incidence, and the differences between the curves were tested using 2-tailed log-rank tests. The survival period was calculated for patients with ED until a hospitalization event, an ambulatory visit for osteoporosis, or the end of the study (December 31, 2010), whichever occurred first. Osteoporosis incidence rates were estimated (in 1000 person-years) for both groups and compared. Univariable and multivariable Cox proportional hazard regression models were used for estimating the hazard ratios (HRs) and 95% confidence intervals (CIs) for osteoporosis if the proportional hazards assumption was satisfied. The multivariable Cox models were employed after controlling for age, CCI scores, and relevant comorbidities. A 2-tailed $P < 0.05$ was considered statistically significant. All data processing and statistical analyses were performed using Statistical Analysis Soft ware version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics of patients with and without ED

We enrolled 4460 men aged ≥40 years diagnosed with ED between 1996 and 2010 in our study cohort (Fig. 1).

The baseline demographic characteristics and comorbidity statuses in the ED and non-ED groups are presented in Table 1. The mean age was57.6 ± 10.7 and 57.7 ± 10.2 years in the non-ED and ED cohorts, respectively. Most patients were in the age

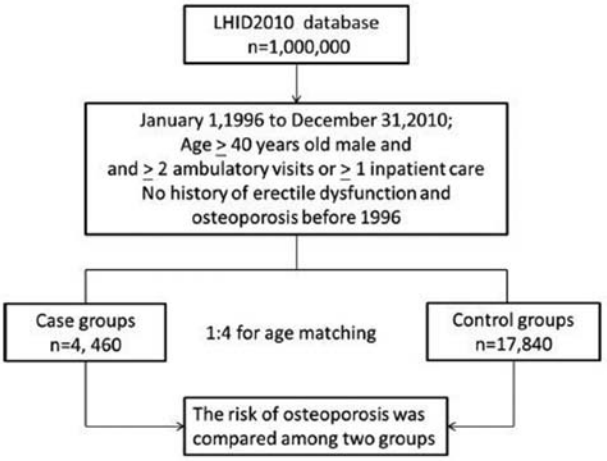

Figure 1. Flow diagram of the present study from the National Health Insurance Research Database. LHID = Longitudinal Health Insurance Database.

group of 50 to 59 years (34.26%) and 40 to 49 years (26.66%). The patients in the ED group were more likely to develop comorbidities than were those in the non-ED group. The comorbidities assessed were hypertension (67.13 vs 43.13, $P < 0.001$), DM (41.39 vs 21.43, $P < 0.001$), hyperlipidemia (61.46 vs 36.37, $P < 0.001$), stroke (14.06 vs 5.11, $P < 0.001$), CKD (22.53 vs 10.47, $P < 0.001$), chronic liver disease (54.71 vs 35.16, $P < 0.001$), chronic pulmonary disease (57.65 vs 35.67, $P < 0.001$), and hyperthyroidism (5.16 vs 2.27, $P < 0.001$). The CCI scores were higher in the ED group than in the non-ED group (40.5 vs 15.03, $P < 0.001$). Moreover, testosterone (2.62 vs 0.22, $P < 0.001$) and corticosteroid (11.19 vs 5.67, $P < 0.001$) use was higher in the ED group than in the non-ED group. A total 264 of 4460 patients with ED (5.92%) and 651 of 17,840 patients without ED (3.65%) were diagnosed with osteoporosis during a median observation time of 3.7 and 8.6 years, respectively (interquartile range = 1.7–6.5 and 5.5–12.2, respectively). Thus, the incidence of osteoporosis was significantly higher in the ED group than in the non-ED group ($P < 0.001$). Osteoporosis development was significantly faster in the ED group (3.7 years) than in the non-ED group (8.6 years) for the respective observation periods.

3.2. Incidence and risk of osteoporosis

The incidence densities and HRs of osteoporosis for different age groups and follow-up durations are presented in Table 2. During the follow-up period, 264 patients with ED (5.92%) and 651 patients without ED (3.65%) developed osteoporosis. The overall incidence of osteoporosis was 3.04-fold higher in the ED group than in the non-ED group (9.74 vs 2.47 per 1000 person-years, respectively) after controlling for age, CCI scores, related comorbidities of hypertension, DM, hyperlipidemia, stroke, CKD, chronic liver disease, chronic pulmonary disease, and hyperthyroidism, hyperparathyroidism, and testosterone and corticosteroid use.

In addition, the incidence of osteoporosis was consistently higher in the ED group for all age groups, and the incidence rate

Table 1

Baseline characteristics of patients with and without erectile dysfunction.

	Erectile dysfunction		
	Yes (N = 4460)	No (N = 17,840)	*P*
Osteoporosis patients, n (%)	264 (5.92)	651 (3.65)	<0.001
Period of developing osteoporosis median (IQR), y	3.7 (1.7–6.5)	8.6 (5.5–12.2)	<0.001
Age mean (SD), y	57.7 (10.2)	57.6 (10.7)	0.638
Age group, n (%)			
40–49	1189 (26.66)	4756 (26.66)	
50–59	1528 (34.26)	6112 (34.26)	
60–69	1087 (24.37)	4348 (24.37)	
70–79	597 (13.39)	2388 (13.39)	
≥80	59 (1.32)	236 (1.32)	1.000
Charlson comorbidity index, n (%)			
0	243 (5.45)	4536 (25.43)	
1–2	1151 (25.81)	6918 (38.78)	
3–4	1262 (28.30)	3704 (20.76)	
≥5	1804 (40.45)	2682 (15.03)	<0.001
Comorbidity, n (%)			
Hypertension	2994 (67.13)	7695 (43.13)	<0.001
Diabetes mellitus	1846 (41.39)	3824 (21.43)	<0.001
Hyperlipidemia	2741 (61.46)	6488 (36.37)	<0.001
Stroke	627 (14.06)	912 (5.11)	<0.001
Chronic kidney disease	1005 (22.53)	1867 (10.47)	<0.001
Chronic liver disease	2440 (54.71)	6272 (35.16)	<0.001
Chronic pulmonary disease	2571 (57.65)	6364 (35.67)	<0.001
Hyperthyroidism	230 (5.16)	405 (2.27)	<0.001
Hyperparathyroidism	5 (0.11)	25 (0.14)	0.648
Medication, n (%)			
Testosterone	117 (2.62)	40 (0.22)	<0.001
Corticosteroids	499 (11.19)	1012 (5.67)	<0.001

IQR = interquartile range, SD = standard deviation.

Table 2

Incidence and hazard ratios of osteoporosis among patients with or without erectile dysfunction stratified by age, and follow-up duration.

	Patients with ED			Patients without ED				
Variables	**Osteoporosis**	**PY**	**Rate***	**Osteoporosis**	**PY**	**Rate***	**IRR (95% CI)**	**Adjusted HR (95% CI)**
All	264	27099.51	9.74	651	263519.26	2.47	3.94 (3.42–4.55)‡	3.04 (2.57–3.58)‡
Stratify age								
40–59	69	16109.65	4.28	140	162202.38	0.86	4.96 (3.72–6.62)‡	3.59 (2.65–4.88)‡
≥60	195	10989.87	17.74	511	101316.88	5.04	3.52 (2.98–4.15)‡	2.89 (2.40–3.46)‡
Follow-up time,† y								
3	101	11526.73	8.76	34	53490.73	0.64	13.79 (9.35–20.33)‡	10.23 (6.74–15.54)‡
5	166	17438.12	9.52	137	88996.84	1.54	6.18 (4.93–7.75)‡	4.33 (3.39–5.53)‡

95% CI = 95% confidence interval, HR = relative hazard ratio, IRR = incidence rate ratio, PY = person-years.

* Rate, incidence rate in per 1000 person-years.

† Follow-up time, the follow-up time after the index date of ED diagnosis.

‡ $P < 0.001$.

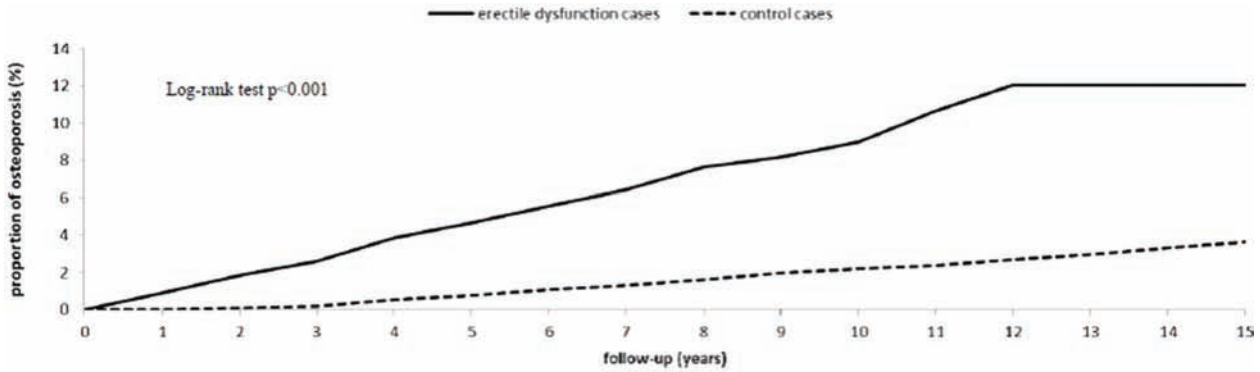

Figure 2. Cumulative incidence of osteoporosis among ED (solid line) and non-ED (dashed line) cohorts. ED = erectile dysfunction.

increased with age. However, younger patients were at a significantly higher risk than were older patients (HR = 3.59, 95% CI = 2.65–4.88, $P < 0.001$).

The follow-up duration analysis revealed a significant relationship between the ED and non-ED groups. The incidence of osteoporosis in the ED groups remained increased compared to the non-ED groups in all the follow-up durations.

The Kaplan–Meier curve of the cumulative incidence of osteoporosis in patients with and without ED after a 15-year follow-up is shown in Fig. 2. The 1-, 5-, 10-, and 15-year actual osteoporosis rates were 0.915%, 4.670%, 8.170%, 12.030% and 0.006%, 0.768%, 2.210%, 3.650% in the ED and non-ED groups, respectively.

The relationships between the types of ED and the associated relative risks and HRs of osteoporosis are presented in Table 3. Compared with patients without ED, patients with psychogenic and organic ED were 3.19- and 3.03-fold more likely to develop osteoporosis (95% CI: 1.98–5.13 and 2.56–3.58, respectively); however, no significant differences were observed between the 2 groups.

The multivariate Cox regression analysis presented in Table 4 revealed age, chronic pulmonary disease, and stroke as the 3 risk factors for osteoporosis in the ED group.

4. Discussion

In this study, we found a relationship between ED and osteoporosis which persisted even after adjustment for comorbidities. To the best of our understanding, this is the first nationwide population-based study investigating the relationship between ED and subsequent osteoporosis in an Asian population. During the follow-up period, we observed that 264 (5.92%)

Table 3

Incidence and hazard ratios of osteoporosis in patients with different types of erectile dysfunction.

Variables	**Osteoporosis**	**PY**	**Rate***	**IRR (95% CI)**	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**
Without ED	651	263519.26	2.47	1.00 (reference)	1.00 (reference)	
ED						
Psychogenic ED	18	1733.73	10.38	4.20 (2.63–6.71)†	3.19 (1.98–5.13)†	1.00 (reference)
Organic ED	246	25365.79	9.70	3.93 (3.39–4.55)†	3.03 (2.56–3.58)†	0.95 (0.59–1.53)‡

95% CI = 95% confidence interval, HR = relative hazard ratio, IRR = incidence rate ratio, PY = person-years.

* Rate, incidence rate in per 1000 person-years.

† $P < 0.001$.

‡ $P = 0.831$.

Table 4

Cox regression model of significant predictors of osteoporosis in erectile dysfunction.

Variables	Adjusted HR	(95% CI)	P
Age (in 10-year interval)	1.76	(1.56–1.98)	<0.001
Chronic pulmonary disease	2.15	(1.54–3.00)	<0.001
Stroke	1.83	(1.41–2.38)	<0.001

95% CI = 95% confidence interval, HR = relative hazard ratio.

patients with ED and 651 (3.65%) patients without ED developed osteoporosis. After controlling for potential confounding factors, the risk of osteoporosis was 3.04-fold higher in the ED group than in the non-ED group. Psychogenic and organic ED were associated with osteoporosis when the relative risks and HRs were estimated. Patients with ED, particularly those in the age group of 40 to 59 years, exhibited a high risk of osteoporosis.

The mechanisms underlying the relationship between ED and osteoporosis are likely to be complex; some possible explanations are as follows. First, patients with ED have lower naturally available free testosterone than those without ED.[26] Androgens may play a critical role in the regulation of bone formation in men.[27] Reports have highlighted a marked increase in the risk of fragility fractures among patients with low testosterone levels.[28,29] In addition, androgen deprivation therapy and orchiectomy has been associated with an increased risk of osteoporosis and fractures.[30] Therefore, testosterone depletion might increase the risk of osteoporosis. ED has been highly associated with inflammation. Inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha, can substantially damage the endothelium in the systemic vascular circulation and in the peripheral vascular bed of organs, such as the penis, thus contributing to endothelial dysfunction, which subsequently leads to ED.[31] Furthermore, these cytokines may inhibit osteoblast growth, thus causing osteoporosis.[32,33]

Nitric oxide bioactivity is crucial to penile engorgement and is a major pathogenic mechanism underlying ED; therefore, nitric oxide is a possible explanation for the relationship between ED and osteoporosis. In addition, nitric oxide may affect bone metabolism through osteoblastic activity.[34,35] High concentrations of nitric oxide can directly inhibit osteoclast proliferation and bone resorption, suggesting its role in bone remodeling.[36,37]

The role of endothelial function in erectile physiology is well established. Any factor that contributes to endothelial dysfunction certainly contributes significantly to ED. Furthermore, penile vascular hemodynamics depend on the integrity of the vascular bed.[31] Moreover, endothelial dysfunction is indicative of early-stage atherosclerosis; however, this condition is also considered an essential regulator of vascular and bone health.[38] Patients with osteoporosis are more likely to have CVD and coronary microvascular endothelial dysfunction.[39–42] Endothelial dysfunction may be a common precursor for osteoporosis and ED, potentially explaining the relationship between the 2 conditions. Furthermore, ED has been highly associated with vitamin D deficiency. Low vitamin D levels might increase ED risk by promoting endothelial dysfunction. Endothelial dysfunction is critical in ED pathogenesis, and vitamin D deficiency is considered to promote endothelial dysfunctions.[43] Furthermore, vitamin D plays a major role in maintaining the bone health in people of all age groups. Lower vitamin D levels lead to substantial losses in the bone mass, eventually causing osteoporosis.[44] Another report with 267 patients with hip fractures (mean age, 80.3 years) reported that the serum vitamin D levels at admission of 67% of these patients were <25 ng/mL. These results assert the high frequency of vitamin D deficiency in men with osteoporosis.[45]

Traditional ED risk factors, such as DM, hypertension, and dyslipidemia, are known predictors of osteoporosis. ED and osteoporosis share similar risk factors; hence, unsurprisingly, an ED diagnosis increases the risk for osteoporosis, according to our results. The relationship between ED and osteoporosis may in part be caused by these comorbidities; however, these comorbidities do not account for the complete relationship between ED and osteoporosis.

The strength of our study lies in the use of a large population-based dataset, and our results confirm that ED is associated with an increased risk of osteoporosis. However, several limitations must be considered when interpreting these findings. The diagnoses were based on the ICD-9-CM codes, the accuracy of which depends on the performance of the clinical physicians; hence, verifying data could not be easily achieved. However, diagnostic accuracy was enhanced by limiting the study population to patients who had received medical care on ≥2 separate visits. Besides, medical experts of the BNHI conduct regular scrutinization to ensure the accuracy of diagnostic codes used in the dataset. Physicians are motivated to enter diagnostic codes accurately for that they are subject to large fines for incorrect entries. Furthermore, the NHIRD data have been used for various studies for several years.[14,15,20–25] Second, the NHIRD does not contain detailed information regarding such risk factors as body mass index, exercise capacity, dietary habits, alcohol consumption, and smoking, which potentially compromises our findings.[3,4] Discussion regarding impotence remains a sensitive issue in Taiwan. Patients with ED may not visit a specialist but may seek alternative medicine or receive treatment privately, possibly underestimating the real incidence of ED. In addition, imaging results, environmental exposure, and laboratory data are not documented in the database. Moreover, most inhabitants of Taiwan are of Chinese ethnicity; it is uncertain whether our results can be generalized to other ethnic populations. Finally, statistical significance does not always represent clinical significance. Without knowing detailed individual records of the aforementioned data, population-based studies cannot directly clarify the exact relationship between ED and osteoporosis. Additional clinical trials are necessary to confirm the underlying mechanisms of this relationship.

In conclusion, an increased risk of osteoporosis was observed among patients with ED, particularly among younger males. ED can be considered an early predictor of osteoporosis. Additional studies are required to gather in-depth information and explore the mechanisms underlying these relationships. Physicians should be aware of this relationship for early identifying such groups of patients. Because of the easy and noninvasive evaluation of osteoporosis, patients with ED should be examined for bone mineral density, and men with osteoporosis should be evaluated for ED.

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