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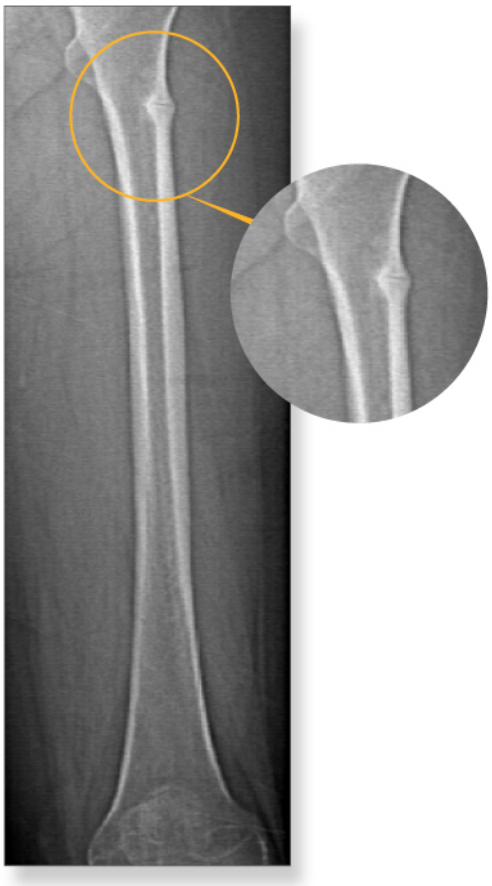

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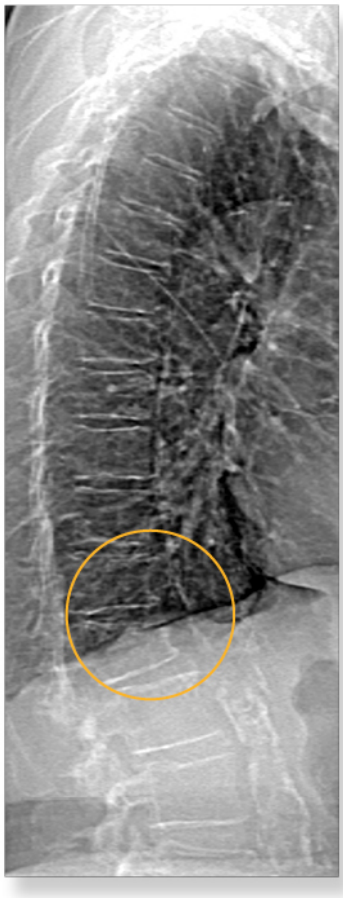

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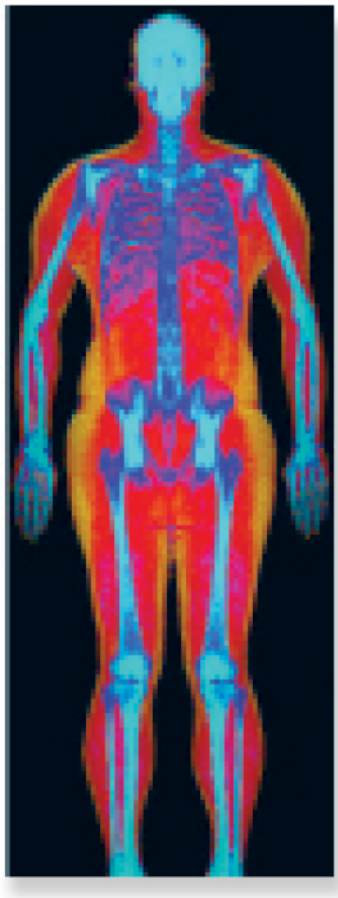

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ORIGINAL ARTICLE

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Bone-Specific Drugs and Osteonecrosis of Sites Other Than the Jaw: A Nationwide Cohort Study

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ABSTRACT

Bone-specific drugs (BSDs) increase the risk of osteonecrosis of the jaw (ONJ), but whether they increase the risk of osteonecrosis at other sites is not known. Two studies, a cohort study and a case–control study, were conducted using registry data on everyone who was residing in Sweden on December 31, 2005, and who was 50 years of age or older at the time (n = 3,523,912). In the cohort study, individuals prescribed a BSD during the period 2006–2017 (n = 217,387) were 1:1 matched with nonusers on birth year, sex, hip fracture status, and Swedish or foreign origin. In the case–control study, individuals diagnosed with osteonecrosis during 2006–2017 (n = 12,614) were 1:1 matched with individuals without a diagnosis of osteonecrosis on birth year, sex, and Swedish or foreign background. In the cohort study, osteonecrosis was diagnosed in 983 BSD users and 214 nonusers (adjusted hazard ratio [aHR] 4.02; 95% CI, 3.32–4.87), during a mean treatment time of 2.8 years. A similar association was observed in a subcohort where all individuals diagnosed with cancer (HR 4.82; 95% CI, 2.52–9.22). The greatest difference in incidence between BSD users and nonusers was observed in patients with a femoral neck fracture that was not treated with total hip arthroplasty or hemiarthroplasty (incidence rate difference, 77.8 cases per 10,000 person-years, $p < .05$). The risk of osteonecrosis was higher in users of denosumab (HR 1.93; 95% CI, 1.33–2.79) and users of zoledronic acid (HR 1.95; 95% CI, 1.31–2.91) than in users of other BSDs. The increased risk of osteonecrosis decreased after the end of therapy ($p < .001$ for time trend). The results were confirmed in the case–control study. In summary, use of BSDs, especially more potent BSDs, is associated with increased risk of osteonecrosis of sites other than the jaw. This increased risk decreases after the final dose of BSD. © 2020 American Society for Bone and Mineral Research.

KEY WORDS: BISPHOSPHONATES; HIP FRACTURE; OSTEONECROSIS

Introduction

Bone-specific drugs (BSDs) play an important role in the treatment of patients with low bone mineral density, fractures, or bone complications due to metastatic cancer.[1–3] BSDs are usually categorized as either antiresorptive (eg, bisphosphonates, estrogens, estrogen agonist/antagonists, and denosumab) or anabolic (eg, teriparatide). The potent antiresorptives known as bisphosphonates are the most widely used BSDs,[4] and they are first-line therapy for osteoporosis and fracture prevention in many countries.[5,6] The use of bisphosphonates increased in Europe and the United States in the early 2000s but decreased around 2010.[7,8] This decline may be explained by a fear of serious adverse effects, primarily atypical femoral fractures and osteonecrosis of the jaw (ONJ).[7,8]

ONJ was first linked to bisphosphonate treatment in 2003,[9] and it is now widely recognized as an adverse effect of bisphosphonate and other BSD treatment.[10–12] The incidence of ONJ is much greater in patients treated with high-dose intravenous bisphosphonates for cancer than in patients treated with oral or low-dose intravenous bisphosphonates for osteoporosis.[10] Poor dental health has been identified as a risk factor for ONJ, so an interaction effect between bacterial infection and BSDs could explain why the jaw is affected.[13] However, few studies have investigated whether BSDs also are associated with osteonecrosis of other sites (also known as avascular necrosis), and these studies showed conflicting results.[14,15] Given the widespread use of BSDs and the fact that osteonecrosis of other skeletal sites is much more common,[16–18] this possible association would be of importance to study further. In the present study, we examined whether use of BSDs is associated with an increased risk of osteonecrosis of sites other than the jaw in a Swedish nationwide cohort.

Received in original form October 7, 2019; revised form April 1, 2020; accepted April 27, 2020. Accepted manuscript online May 7, 2020.
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Additional Supporting Information may be found in the online version of this article.
The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4040.

Journal of Bone and Mineral Research, Vol. 35, No. 9, September 2020, pp 1703–1710.
DOI: 10.1002/jbmr.4040

Subjects and Methods

Study cohort

The cohort considered for inclusion consisted of all residents of Sweden who were at least 50 years of age on December 31, 2005 (n = 3,523,912). This cohort was identified through the Register of the Total Population, which is managed by Statistics Sweden (https://www.scb.se/). We used this cohort to conduct both a matched cohort study and a matched case–control study.

Cohort matching

In the cohort study, we excluded 74,049 individuals who were prescribed a BSD or diagnosed with osteonecrosis before 2006. Of the resulting eligible cohort, 233,626 individuals were dispensed a BSD at least once during the period 2006–2017. These BSD users were 1:1 matched to randomly selected nonusers on birth year, sex, Swedish or foreign background (foreign background refers to being born outside Sweden or born in Sweden but both parents were born outside of Sweden), history of hip fracture (no history, femoral neck fracture, or other hip fracture), and type of hip fracture operation (none, hip replacement with total hip arthroplasty or hemiarthroplasty, or other). The baseline date for a user and the corresponding nonuser was the date of the first dispensed dose of BSD. Nonusers were excluded if they died prior to the corresponding user's last dispensed dose of BSD or if they were diagnosed with osteonecrosis before the baseline date. In this case, a new nonuser was searched for. This procedure resulted in a cohort study of 434,774 individuals, who were followed for the outcome of diagnosis of osteonecrosis. In an additional analysis, BSD users and nonusers were followed for osteonecrosis from the time of cessation of BSD treatment. The cohort study was the main analysis of this study.

Case–control matching

In the case–control study, 12,746 individuals who were diagnosed with osteonecrosis during the period 2006–2017 were 1:1 matched to randomly selected controls who had not been diagnosed by the end of this period. Controls were also required to have been alive on the date the case was diagnosed with osteonecrosis (the baseline date). The matching variables were birth year, sex, and Swedish or foreign background. This procedure resulted in a case–control study of 25,228 individuals. Use of BSDs and other potential risk factors for osteonecrosis were then searched for in the period before baseline.

Variables

Supporting Table 1 provides a summary of the variables used in this study. Data about diagnoses were collected from the National Patient Register (NPR) and the Swedish Cancer Registry, both managed by the National Board of Health and Welfare (NBHW, https://www.socialstyrelsen.se/). In the present study, we did not consider very rare risk factors for osteonecrosis; eg, organ transplantation. The NPR records all diagnoses made in inpatient care in Sweden since 1987 and all secondary outpatient care since 2001. The Swedish Cancer Registry records all new cases of cancer diagnosed in Sweden since 1958. In both databases, diagnoses are coded according the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). The study outcome was diagnosis of primary (idiopathic) or secondary osteonecrosis (ICD 10th Revision code M87), or avascular necrosis, made either during hospitalization or at a visit to a specialist physician. A recent validation study of the NPR concluded that 27 of 30 osteonecrosis diagnoses were correct, two likely correct, and only one incorrect.[18]

Data about prescription medication use were collected from the Prescribed Drug Registry, also managed by the NBHW. This database records every prescription drug dispensed at a pharmacy in Sweden since July 2005. Drugs are coded according to Anatomical Therapeutic Chemical codes (Supporting Table 1).

Mortality data were collected from the Cause of Death Registry. Socioeconomic data (civil status, annual disposable income, education, Swedish or foreign background, and receipt of municipal homemaker service) were collected from Statistics Sweden.

Statistical analysis

The matched groups were compared using t tests for paired samples and standardized mean differences. Standardized mean differences of <0.1 were considered negligible.[19]

In the cohort study, hazard ratios (HRs) were estimated using Cox regression. These models were stratified by matched pairs and adjusted for the variables listed in Table 1 (except for the matching variables). These variables include drugs and diagnoses that have been previously associated with osteonecrosis. Follow-up time ended at the date of last prescription for BSD + 90 days, date of osteonecrosis diagnosis, date of death, or study end (December 31, 2017), whichever came first. To test whether the association between BSDs and osteonecrosis was time-dependent, tests for correlation between Schoenfeld residuals and time were used. Because this test was significant for the analysis of the period after BSD treatment, these associations were investigated in three time frames: <2 years after end of treatment; 2 to 5 years after end of treatment; and >5 years after end of treatment. In this analysis, baseline was the date of last prescription of BSD + 90 days for both individuals prescribed BSD and the corresponding controls. Follow-up ended at date of osteonecrosis diagnosis, date of death, or study end (December 31, 2017), whichever came first. Furthermore, the time-dependent effect was visualized using a flexible parametric model with knots in default positions and three degrees of freedom.[20]

Subgroup analyses were conducted according to age, sex, type of BSD, use of glucocorticoids, type of hip fracture, type of hip fracture operation, and history of nonhip fracture. The reason for not also analyzing other subgroups relates to the fact that there would have been too few outcomes of osteonecrosis. To test for interaction between time from hip fracture to start of BSD treatment, we included a product term in the Cox model. To test whether the more potent BSDs of denosumab and zoledronic acid were associated with higher risks of osteonecrosis than were other BSDs, Cox regression was run using the data of the entire eligible cohort. A similar approach was used to test whether the higher dose of denosumab was associated with a higher risk than were lower doses.

In the case–control study, odds ratios (ORs) were estimated using conditional logistic regression. These models were adjusted for the same variables as were adjusted for in the cohort study. All statistical analyses were performed in Stata version 13.1 (Stata Corporation, Inc., College Station, TX, USA) or in SPSS version 25 (IBM Corp., Armonk, NY, USA) for Mac. A p value of <.05 was considered significant.

Table 1. Baseline Characteristics in the Cohort Study

Baseline characteristics	Users of BSDs (n = 217,387)	Nonusers of BSDs (n = 217,387)	SMD	p
Age (years), mean ± SD	73.2 ± 8.8	73.2 ± 8.8	0.00	.73
Female sex, n (%)	171,812 (79.0)	171,812 (79.0)	0	
Socioeconomic factors, n (%)				
Nursing home resident	3263 (1.5)	4977 (2.3)	0.06	<.001
Homemaker service recipient	32,159 (14.8)	22,966 (10.6)	0.13	<.001
Civil status				
Married	110,023 (50.6)	110,958 (51.0)	0.01	
Never married	18,759 (8.6)	18,844 (8.7)	0.00	
Divorced	38,678 (17.8)	36,764 (16.9)	0.02	
Widow(er)	49,811 (22.9)	49,635 (22.8)		
Education				
Primary and lower secondary, <9 years	64,134 (29.5)	65,717 (30.2)	0.02	
Primary and lower secondary, 9 years	18,394 (8.5)	18,656 (8.6)	0.00	
Upper secondary, 2 years	66,390 (30.5)	63,016 (29.0)	0.03	
Upper secondary, >2 years	17,377 (8.0)	17,436 (8.0)	0.00	
Postsecondary	48,868 (22.5)	47,810 (22.0)	0.01	
Disposable income (SEK/year), mean ± SD	180,547 ± 288,578	182,410 ± 256,013	0.01	.02
Missing data for any socioeconomic factor	65 (0.03)	1,150 (0.5)		
Medications and radiation therapy, n (%)				
Glucocorticoids	111,730 (51.4)	36,128 (16.6)	0.79	<.001
Immunosuppressants	17,755 (8.2)	3256 (1.5)	0.32	<.001
Chemotherapy	2069 (1.0)	592 (0.3)	0.09	<.001
Radiation therapy	8885 (4.1)	3864 (1.8)	0.14	<.001
Diagnoses, n (%)				
Hip fracture	12,178 (5.6)	12,178 (5.6)	0	
Femoral neck, operated with prosthesis	2131 (1.0)	2131 (1.0)	0	
Femoral neck, not operated with prosthesis	3427 (1.6)	3427 (1.6)	0	
Other	6620 (3.0)	6620 (3.0)	0	
Non-hip fracture	59,015 (27.1)	23,500 (10.8)	0.43	<.001
Osteoporosis	27,412 (12.6)	2294 (1.1)	0.47	<.001
Osteomyelitis	815 (0.4)	481 (0.2)	0.03	<.001
Cancer	56,020 (25.8)	40,824 (18.8)	0.17	<.001
Dialysis	634 (0.3)	209 (0.1)	0.04	<.001
Kidney failure	3829 (1.8)	2256 (1.0)	0.06	<.001
Diabetes	21,828 (10.0)	23,888 (11.0)	0.03	<.001
Stroke	11,242 (5.2)	10,379 (4.8)	0.02	<.001
Myocardial infarction	10,614 (4.9)	9438 (4.3)	0.03	<.001
Chronic obstructive pulmonary disease	13,576 (6.2)	4739 (2.2)	0.20	<.001
Rheumatoid arthritis	13,459 (6.2)	2795 (1.3)	0.26	<.001
Crohn's disease	2689 (1.2)	1152 (0.5)	0.08	<.001
Ulcerative colitis	2485 (1.1)	1305 (0.6)	0.06	<.001
Alcohol intoxication	3403 (1.6)	2549 (1.2)	0.03	<.001

BSD = bone-specific drug; SEK = Swedish Krona; SMD = standardized mean difference.

Results

Cohort study: baseline characteristics

Table 1 presents baseline characteristics of BSD users and nonusers in the cohort study. Compared to nonusers, BSD users had more often received glucocorticoids and other immunosuppressants, and they had more often been diagnosed with a fracture (Table 1). Among BSD users, the most common first dispensed BSD was alendronate (83.2%), followed by risedronate (7.5%), denosumab (2.9%), and zoledronic acid (2.4%). Among BSD users, 83.1% were dispensed at least two doses. During follow-up, 1970 individuals were diagnosed with osteonecrosis. The most common sites of osteonecrosis were the hip (n = 992, 50.3% of the total cases), knee/lower leg (n = 288, 14.6%), and shoulder/upper arm (n = 130, 6.6%) (Table 2).

Cohort study: osteonecrosis during BSD treatment

The mean duration of BSD treatment was 2.8 years (range, 0–12.0 years). During this time, osteonecrosis was diagnosed in 983 BSD users (incidence rate, 16.1 cases per 10,000 person-years) and 214 nonusers (incidence rate, 3.5). Cumulative incidence curves are provided in Fig. 1. When users were compared to nonusers, the unadjusted HR for osteonecrosis was 4.72 (95% confidence interval [CI], 4.06–5.48). This association weakened slightly upon adjustment for confounders (HR 4.02; 95% CI,

Table 2. Characteristics of Osteonecrosis Diagnoses in the Cohort Study

Osteonecrosis diagnosis	Total (*n* = 434,744)	Users of BSDs (*n* = 217,387)	Nonusers of BSDs (*n* = 217,387)
Total, *n*	1970	1516	454
Hip, *n*	992	754	238
No previous hip fracture	645	477	168
Previous hip fracture	347	277	70
Knee/lower leg, *n*	288	211	77
No previous fracture of the lower leg	270	202	68
Previous fracture of the lower leg	18	9	9
Shoulder/upper arm, *n*	130	108	22
No previous fracture of the humerus	52	41	11
Previous fracture of the humerus	78	67	11
Foot joint/foot, *n*	65	44	21
No previous fracture of the lower leg	55	37	18
Previous fracture of the lower leg	10	7	3
Elbow/forearm, *n*	2	1	1
No previous fracture of the forearm	1	1	0
Previous fracture of the forearm	1	0	1
Other location than above or unspecified, *n*	356	263	93
Diagnosed as due to medication, *n*	137	135	2
No previous fracture of any type	79	77	2
Any previous fracture	58	58	0

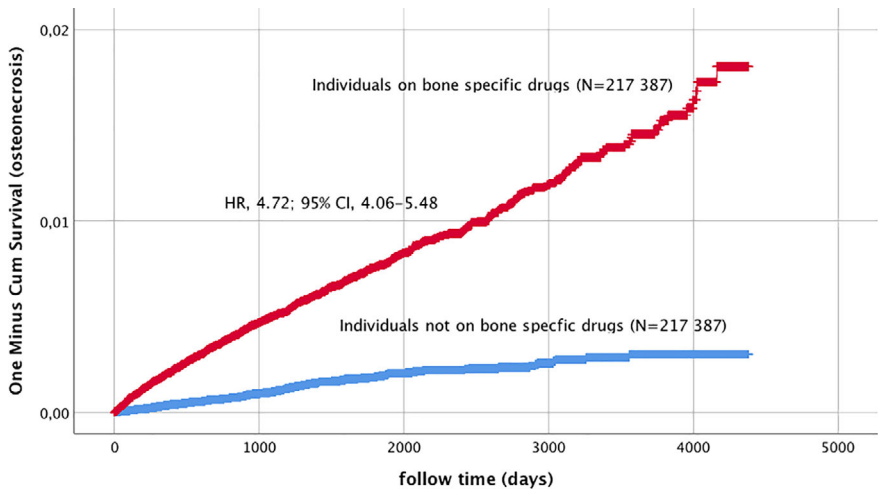

Fig. 1. Cumulative incidence of osteonecrosis for users of BSDs and nonusers in the cohort study. HRs and 95% CIs are also presented, along with the number of individuals at risk (number of outcomes) at different time points. BSD = bone-specific drug; HR = hazard ratio.

3.32–4.87). There was no significant evidence of a time trend in the HR over the course of treatment ($p = .82$).

Figure 2 presents the association between BSDs and osteonecrosis in subgroups. Among patients with a history of hip fracture, BSD use was associated with increased risk of osteonecrosis in patients with a femoral neck fracture that was not treated with total hip arthroplasty or hemiarthroplasty (HR 2.53; 95% CI, 1.72–3.72), and in patients with nonfemoral neck fractures (HR 3.23; 95% CI, 1.73–6.02), but not in patients with a femoral neck fracture treated with total hip arthroplasty or hemiarthroplasty (HR 0.75; 95% CI, 0.17–3.35), among whom only seven individuals were diagnosed with osteonecrosis. The greatest difference in incidence rates been BSD users and nonusers was observed among patients with a femoral neck fracture that was not operated with prosthesis (incidence rate difference, 77.8 per 10,000 person-years, $p < .05$).

In the total subgroup of hip fracture patients, the time between hip fracture and initiation of therapy with BSDs significantly influenced the risk of osteonecrosis ($p = .006$ for interaction). Thus, use of BSD was associated with a greater increase of osteonecrosis among the 10,490 patients who had less than a year between hip fracture and initiation of BSD (HR 3.62; 95% CI, 2.31–5.70) than it was among the 9604 patients with at least 1 year until initiation of therapy (HR 1.84; 95% CI, 1.13–2.99).

Denosumab and zoledronic acid were associated with a greater risk of osteonecrosis than were alendronate and risedronate (Fig. 2). When users of denosumab and zoledronic acid were compared to users of other BSDs, instead of to nonusers, the risk

	Bone specific agent					
	Yes	No	HR	95% CI	aHR	95% CI
	No. (rate /10000 person-yrs)					
Overall (N=434 774)	983 (16.1)	214 (3.5)	4.72	4.06-5.48	4.02	3.33-4.85
Age						
<65 years (N=84 772)	278 (18.5)	39 (2.6)	7.51	5.33-10.59	7.63	4.70-12-39
65-80 years (N=238 620)	542 (15.9)	117 (3.4)	4.80	3.92-5.87	3.72	3.00-4.62
>80 years (N=102 168)	148 (14.2)	51 (4.8)	2.88	2.10-3.96		
Sex						
Women (N=343 624)	784 (15.2)	168 (3.2)	4.80	4.06-5.69	3.97	3.23-4.88
Men (N=91 250)	199 (20.7)	46 (4.8)	4.38	3.18-6.04	7.46	4.07-13.67
Bone specific drug						
Alendronate (N=361 732)	779 (15.5)	180 (3.6)	4.47	3.79-5.27	3.72	3.05-4.55
Risedronate (N=32 660)	98 (15.1)	18 (2.8)	5.44	3.29-9.00		
Zoledronic acid (N=10 510)	25 (32.6)	2 (2.5)	12.8	3.04-54.21*		
Denosumab (N=12 436)	29 (33.2)	1 (1.1)	29.0	3.95-212.89*		
Use of glucocorticoids at baseline						
Yes (N=38 832)	75 (19.6)	19 (4.9)	3.95	2.39-6.53		
No (N=177 890)	371 (12.6)	92 (3.1)	4.25	3.37-5.37	4.29	3.24-5.68
Cancer at baseline						
Yes (N=22 130)	53 (22.5)	11 (4.6)	4.82	2.52-9.22		
No (N=263 2169)	605 (15.2)	134 (3.3)	4.65	3.85-5.62	4.14	3.26-5.24
Subcohort matched on hip fracture						
Collum fracture, op. with prosthesis (N=4 262)	3 (8.1)	4 (10.7)	0.75	0.17-3.35		
Collum fracture, no prosthesis (N=6 854)	92 (135)	40 (57.2)	2.53	1.72-3.72		
Other hip fracture (N=13 240)	42 (35.0)	13 (10.6)	3.29	1.76-6.12		
No fracture at baseline (N=260 142)	547 (14.4)	99 (2.6)	5.58	4.50-6.92	4.69	3.54-6.22

*No data presented in the diagram because of out of range

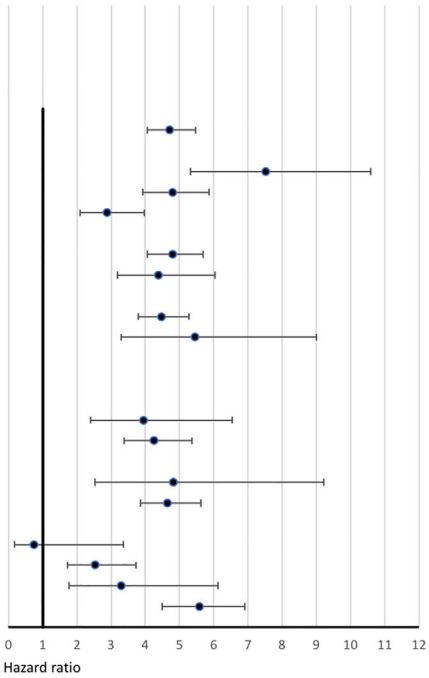

Fig. 2. Incidence rates and unadjusted HRs for osteonecrosis according to subgroups in the cohort study. For subgroups with more than 210 outcomes of osteonecrosis, HRs are shown after adjustment for the 21 covariates listed in Table 1. HR = hazard ratio.

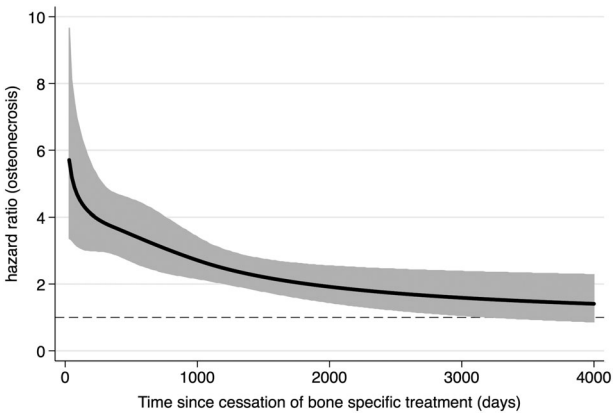

Fig. 3. Hazard ratio for osteonecrosis after the end of treatment with bone specific drugs. The shaded areas indicate 95% confidence interval.

of osteonecrosis was still higher among both denosumab users (HR 1.93; 95% CI, 1.33–2.79) and zoledronic acid users (HR 1.95; 95% CI, 1.31–2.91). Furthermore, the risk was significantly greater for individuals on the higher dose (120 mg versus 60 mg) of denosumab (HR 2.95; 95% CI, 1.70–5.14). The increased risk associated with BSD use was similar irrespective of use of glucocorticoids at baseline (Fig. 2).

Cohort study: osteonecrosis after BSD treatment

A total of 146,001 individuals on BSDs and the same number of nonusers could be followed from cessation of treatment. The mean follow-up after cessation was 3.5 years (range, 0–11.7 years). The HR for osteonecrosis decreased with increasing time since cessation of treatment ($p < .001$ for trend; Fig. 3). In the first 2 years after cessation, the risk for osteonecrosis was increased by about four times (HR 4.31; 95% CI, 3.33–5.59), which was reduced but still increased 2 to 5 years after cessation of treatment (HR 2.71; 95% CI, 1.97–3.73), and further reduced more than 5 years after cessation of treatment (HR 1.75; 95% CI, 1.06–2.89).

Case–control study

As Table 3 shows, 2405 (19.1%) osteonecrosis cases had previously been dispensed a BSD, compared to 997 (7.9%) controls (OR 2.93; 95% CI, 2.69–3.18). Adjustment for confounding attenuated the association (OR 1.83; 95% CI, 1.63–2.05). Among the covariates, a particularly strong association with osteonecrosis was seen for femoral neck fractures that were not operated with prosthesis (OR 22.9; 95% CI, 18.8–27.8; Table 3).

Discussion

In this nationwide cohort, we found that use of BSDs was associated with an increased risk of osteonecrosis of other sites than the jaw. This association was independent of several previously known risk factors for osteonecrosis. Zoledronic acid and denosumab were associated with a higher risk of osteonecrosis than were less potent BSDs, primarily alendronate. The increased risk of osteonecrosis gradually decreased after the end of therapy, although it was still increased >5 years later. These associations might be influenced by residual confounding or bias, because BSD users likely are monitored more carefully for adverse events.

Table 3. Baseline Characteristics and ORs With 95% CIs in the Case–Control Study

Baseline characteristics	Cases (n = 12,614)	Controls (n = 12,614)	SMD	p	OR[1]	95% CI
Age (years), mean ± SD	73.3 ± 9.7	73.3 ± 9.7	0.00	.94	0.86	0.77–0.96
Female sex, n (%)	8353 (66.2)	8353 (66.2)	0			
Socioeconomic factors, n (%)						
Nursing home resident	554 (4.4)	426 (3.4)	0.05	<.001	0.56	0.45–0.68
Homemaker service recipient	3257 (25.8)	1877 (14.9)	0.27	<.001	1.76	1.58–1.96
Civil status						
Married	5739 (45.5)	6018 (47.7)	0.04	<.001	1 (ref)	
Never married	1343 (10.6)	1336 (10.6)	0.00	.87	0.87	0.78–0.97
Divorced	2471 (19.6)	2569 (20.4)	0.02	.12	0.85	0.78–0.93
Widow(er)	3051 (24.2)	2561 (20.3)	0.09	<.001	1.09	0.99–1.20
Education						
Primary and lower secondary, <9 years	3624 (28.7)	2017 (16.0)	0.31	<.001	1 (ref)	
Primary and lower secondary, 9 years	1187 (9.4)	1285 (10.2)	0.03	.04	0.48	0.43–0.54
Upper secondary, 2 years	3755 (29.8)	3363 (26.7)	0.07	<.001	0.57	0.52–0.63
Upper secondary, >2 years	1141 (9.0)	1588 (12.6)	0.11	<.001	0.36	0.32–0.41
Postsecondary	2748 (21.8)	3846 (30.5)	0.20	<.001	0.38	0.35–0.42
Disposable income (SEK/year), mean ± SD	195,297 ± 232,093	222,684 ± 305,859	0.10	<.001	0.99	0.99–0.99
Missing data for any socioeconomic factor	159 (1.3)	515 (4.1)				
Medications and radiation therapy, n (%)						
Bone specific drugs	2405 (19.1)	997 (7.9)	0.33	<.001	1.83	1.63–2.05
Glucocorticoids	4463 (35.4)	2713 (21.5)	0.31	<.001	1.86	1.72–2.00
Immunosuppressants	819 (6.5)	289 (2.3)	0.21	<.001	1.50	1.23–1.85
Chemotherapy	151 (1.2)	31 (0.2)	0.11	<.001	1.96	1.25–3.05
Radiation therapy	762 (6.0)	316 (2.5)	0.18	<.001	1.95	1.64–2.31
Diagnoses, n (%)						
Hip fracture	3378 (26.8)	563 (4.5)	0.64	<.001		
Femoral neck, operated with prosthesis	153 (1.2)	139 (1.1)	0.01	.41	1.39	1.03–1.88
Femoral neck, not operated with prosthesis	2385 (18.9)	158 (1.3)	0.61	<.001	22.9	18.8–27.8
Other hip fracture	840 (6.7)	266 (2.1)	0.22	<.001	4.55	3.77–5.49
Non-hip fracture	3715 (29.5)	2737 (21.7)	0.18	<.001	1.61	1.49–1.73
Osteoporosis	981 (7.8)	396 (3.1)	0.21	<.001	1.18	0.99–1.40
Osteomyelitis	221 (1.8)	44 (0.3)	0.14	<.001	3.85	2.59–5.72
Cancer	3545 (28.1)	2637 (20.9)	0.14	<.001	1.31	1.21–1.42
Dialysis	133 (1.1)	19 (0.2)	0.12	<.001	3.42	1.85–6.32
Kidney failure	493 (3.9)	226 (1.8)	0.13	<.001	1.26	1.01–1.57
Diabetes	1683 (13.3)	1452 (11.5)	0.06	<.001	1.03	0.93–1.14
Stroke	892 (7.1)	698 (5.5)	0.04	<.001	0.95	0.83–1.10
Myocardial infarction	777 (6.2)	562 (4.5)	0.08	<.001	1.24	1.07–1.43
Chronic obstructive pulmonary disease	690 (5.5)	426 (3.4)	0.10	<.001	0.89	0.76–1.06
Rheumatoid arthritis	543 (4.3)	218 (1.7)	0.15	<.001	1.24	0.98–1.57
Crohn's disease	145 (1.1)	113 (0.9)	0.03	.04	0.63	0.43–0.91
Ulcerative colitis	140 (1.1)	96 (0.8)	0.04	.004	1.48	0.99–2.20
Alcohol intoxication	503 (4.0)	264 (2.1)	0.11	<.001	1.27	1.05–1.53

The p values presented refer to the SMD.

CI = confidence interval; OR = odds ratio; SMD = standardized mean difference.

[1] Adjusted for all variables in the table.

The clinical relevance of osteonecrosis is related to the severity and the incidence of the disease. Patients with osteonecrosis often need surgery and often suffer from pain, reduced mobility, and increased dependency.[16] Recently,[18] we reported that the incidence of osteonecrosis is about 10 times more common than previous studies have suggested,[15,21] a finding that increases the clinical relevance of osteonecrosis. In the present study, the incidence of osteonecrosis of any site was 0.16% per year of exposure to BSD, although it was more than twice as high for patients taking zoledronic acid or denosumab. In contrast, the incidence of ONJ is estimated to be only 0.001% to 0.15% per year in patients treated with BSDs for osteoporosis, although it is estimated to be 0% to 12.2% per year in patients taking zoledronic acid or denosumab for cancer.[22,23]

Although many potential risk factors for osteonecrosis have been previously identified,[24–28] the present study suggests that it is the frail older individual, often suffering from fractures or cancer and taking glucocorticoids or immunosuppressants, that

is most prone to osteonecrosis. Consistent with previous research,[16] the highest incidence of osteonecrosis was observed in hip fracture patients. Because hip fracture is also a strong indication for prescribing BSDs,[29,30] the clinical relevance of osteonecrosis is greatest in this patient group. Our study showed that patients with a femoral neck fracture who were not treated with total hip arthroplasty or hemiarthroplasty developed osteonecrosis of a rate of 1.4% per year if treated with a BSD, compared to 0.6% if they were not treated with a BSD. The excess rate of 0.8% corresponds to one additional case of osteonecrosis for every 125 patients exposed for 1 year. Notably, BSD use was not associated with osteonecrosis in patients with a femoral neck fracture that was not treated with total hip arthroplasty or hemiarthroplasty. It is also interesting that, among all hip fracture patients, the increased risk of osteonecrosis was 70% lower if BSD therapy started at least 1 year after the hip fracture compared to if it was started earlier. Together these findings suggest that one mechanism linking BSD to osteonecrosis of the femoral head could be through reduced blood supply during fracture healing. This mechanism would also explain the pattern at the shoulder, where the majority of patients diagnosed with osteonecrosis had a history of fracture and use of BSD. In support of this theory, studies have shown that bisphosphonates have anti-angiogenic effects both in vitro and in vivo,[31,32] properties that are used in the treatment of malignant bone disease, such as multiple myeloma and breast cancer.[33] In malignant bone disease, higher doses and more potent BSDs are used, a practice that has been previously linked to a higher risk of ONJ.[22,23] Given this knowledge and the results of the present study, it is of interest that bisphosphonates are used in clinical practice to treat osteonecrosis. Randomized controlled studies do not show effects from bisphosphonates on disease progression, although observational studies may suggest pain relief.[34] Yet, it should be noted that the use of BSDs has been shown to reduce the total risk of skeletal complications in patients with cancer, although higher doses are not always more effective.[2,35]

The main limitation of the present study is the observational design. It would therefore be of interest if the associations could be evaluated in previous randomized controlled trials. In our study, the highest incidence of osteonecrosis (1.1%) was found in patients prescribed BSD after hip fractures. Therefore, the risk of osteonecrosis would be of interest in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture Trial (HORIZON RFT),[3] where one-half of the about 2000 included individuals with hip fracture were given zoledronic acid. Osteonecrosis at any site was a prespecified safety outcome adjudicated by an independent expert committee. Although data was not presented in the published paper, the clinical study report described six adjudicated cases of osteonecrosis at sites other than the jaw in the zoledronate group compared to four cases in the placebo group (D Black (Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA), written communication; January 18, 2020). Cases of osteonecrosis of the hip or knee were also evaluated in the HORIZON PFT, where four cases were found in the zoledronate group compared to three cases in the placebo group.[36] Clearly, the number of cases is too small to evaluate the associations found in the present study for causality, although the incidence in those receiving zoledronate was similar to what we found. Another limitation of the present study is that drugs given to patients during inpatient and outpatient care, instead of those collected at pharmacies, are not registered in the Prescribed Drug Registry. Thus, the use more potent drugs given intravenously was likely underestimated, which is likely to result in attenuated associations. Another potential limitation is that it was not possible to verify the accuracy of diagnoses or dates of diagnoses for all cases of osteonecrosis in the present study. Because bisphosphonates are sometimes used to treat osteonecrosis, in the hope that increased bone mass will prevent progression of the disease,[37] we cannot rule out the possibility that BSD treatment was initiated and that the diagnosis of osteonecrosis was for some reason set later on. This possibility would produce a false association between BSD and osteonecrosis. However, it should be noted that this was not the case in a recent validation study, where 30 cases of osteonecrosis were validated for accuracy.[18] Finally, given the observational study design, the associations found are most likely influenced by different forms of bias and confounding. Thus, although a recent study in a similar cohort suggested that only hip fracture contribute substantially to the risk of osteonecrosis,[18] there may be unknown confounders that could influence the associations found in the present study. With respect to previous fractures as a risk factor, it should also be noted that from registers it is not possible to determine if a previous fracture occurred at the same side as later osteonecrosis. In addition, those prescribed BSD may in general be more closely monitored by health care for complications. However, this is likely not the case with respect to osteonecrosis caused by hip fracture, where symptoms such as pain during movement of the hip and walking are likely to be the cause for evaluation. The strengths of the present study included the nationwide coverage, the high power due to the large number of patients diagnosed with osteonecrosis, the inclusion of many potential confounders, a validated outcome, and virtually no loss to follow up. Altogether, these strengths increase the internal and external validity of the study.

In summary, the present study showed that use of BSDs was associated with an increased risk of osteonecrosis of sites other than the jaw. More potent drugs and higher doses of more potent drugs were associated with higher risks. The highest absolute additional risk associated with use of BSD was observed in patients with a hip fracture that was not operated with prosthesis. The risk of osteonecrosis decreased with longer time between the hip fracture and start of BSD treatment. Given the few cases reported from clinical trials, our results could not be evaluated for causality.

Disclosures

None of the authors declare any conflicts of interest.

Acknowledgments

Authors' roles: Study design: PN. Study conduct: PN. Data collection: PN. Data analysis: PN. Data interpretation: PN, JB, MB, SB, and AN. Drafting manuscript: PN and JB. Revising manuscript content: PN, JB, MB, SB, and AN. Approving final version of manuscript: PN, JB, MB, SB, and AN. PN takes responsibility for the integrity of the data analysis.

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