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ORIGINAL ARTICLE

Risk of osteoporosis and fracture in victims with burn injury

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Abstract

Summary Osteoporosis is a well-known bone disorder affecting people worldwide. Patients with osteoporosis have an increased risk of bone fracture. This study provides new information on the risk of developing osteoporosis post burn injury and the risk of fracture among those with osteoporosis developed.

Introduction The relationship between burn injury and hip fracture risk is unclear. Population-based evaluation on relationships between burn injury and osteoporosis development and subsequent fractures is limited. We conducted a retrospective cohort study as the investigation.

Methods From the insurance data of Taiwan, we established a cohort of 43,532 patients with a burn injury in 2000–2012 and a comparison cohort of 174,124 individuals without such an injury, frequency matched by sex, age, and diagnosis date. Both cohorts were followed up to the end of 2013 to evaluate the occurrence of osteoporosis and hip fracture.

Results The incidence of osteoporosis was greater in the burn cohort than in the comparison cohort (6.40 vs. 4.75 per 1,000 person-years) with an adjusted IRR of 1.35 (95% confidence interval = 1.32–1.39). The incidence rates in both cohorts were greater in women than in men, increased with age, income, and Charlson comorbidity index. Patients with burns involving 20%–49% of total body surface area and with burns confined to the lower/upper limbs had the greatest incidence rates, 8.32 and 8.58 per 1,000 person-years, respectively. Osteoporosis incidence increased further to 22.7 per 1,000 person-years for burn victims with comorbid diabetes. The risk of fracture was over five-fold greater for burn victims with osteoporosis developed than for comparisons without osteoporosis.

Conclusion Patients who have a burn injury deserve prevention intervention to reduce the risk of osteoporosis and fracture.

Keywords Burn injury · Diabetes · Insurance claims data · Osteoporosis · Retrospective cohort study

Introduction

Osteoporosis is a well-known and well-defined bone disorder with high prevalence affecting hundreds of millions of people of all races worldwide [1]. Patients with osteoporosis are at an increased risk of fractures because of low bone mass and deterioration of bone tissue [1, 2]. Costs for osteoporosis prevention and for the consequence of fractures are a huge burden for families and societies, particularly for the western societies. Osteoporosis and fracture-related annual costs in the USA may reach 23.5 billion US dollar by 2025, approaching 50 billion US dollar by 2040 [3, 4]. In Taiwan, the incidence of osteoporosis-related hip fracture or spine fracture of the middle-aged and aged patients is higher than the world's average, especially for men, whose adjusted incidence rate is among the highest in the world [5]. Dempster has reported that medical costs for caring osteoporosis, related fractures, and related complications are a greater burden than the costs of stroke, breast cancer, diabetes, or chronic lung disease. Therefore, it is extremely important to prevent and control the development of osteoporosis [4].

Postmenopausal status and aging are the well-known major factors associated with the development of osteoporosis. The osteoporosis development has also been associated with

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behavioral, nutritional, and genetic status and clinical and medical conditions, including endocrine disorders [6–10]. These risk factors can compromise bone quality that can lead to a decrease in bone strength and fragility fractures. Among the medical conditions, limited studies have evaluated subsequent bone loss or skeletal disorders for burn victims [11–16].

Studies have reported that patients with burn injury are at the risk of metabolic and hormonal changes, leading to histomorphometric and musculoskeletal abnormalities, including catabolism-associated bone loss and muscle breakdown [12–15]. Longitudinal population study on the musculoskeletal abnormalities for burn victims is limited. Randall et al. evaluated medical records of 17,753 patients with the first burn injury in Western Australia and found that 14.5% of disorders of bone density and structure were attributable to the burn injury [16]. Our recent study using insurance claims data of Taiwan found that patients with burn injury were at an increased risk of bone fracture and the risk increased further for victims with baseline comorbid osteoporosis [17]. However, the previous study did not measure the subsequent development of osteoporosis in those who survived the burn injury. The present study used the claims data to estimate the development of osteoporosis for patients with burn injury and the subsequent fracture for those who had osteoporosis developed.

Methods and materials

Study design

The insurance system is a government-run single-payer system covering more than 99% of 23 million population in Taiwan. We used a subset of claims data of the National Health Insurance Research Database (NHIRD), including medical records in the period 1996–2013 for one million people randomly selected from all insured population. The data set, obtained from the National Health Research Institutes of Taiwan, consisted of information on insured demographic status, healthcares and medications patients received, and costs for cares. Data files could be linked using surrogate identification numbers defined by the Institutes.

In the database, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to define diseases. We identified from the database 43,532 patients with burn injury (ICD 940–948) newly diagnosed from January 1, 2000 to December 31, 2012 as the burn cohort. Patients with the history of osteoporosis and/or fracture at the baseline were excluded. The comparison cohort, consisting of 174,124 insured people without burn injury, osteoporosis, and fracture at baseline, was randomly selected from the claims data, frequency matched by sex, age, and diagnosis year. Individuals in both cohorts were followed up, and person-years of follow-up time were estimated until the incidence of osteoporosis was diagnosed, or censored for death or withdrawal from the insurance or censored by the end of 2013. The incident osteoporosis and subsequent incident fractures were measured for and compared between the two cohorts. We also defined osteoporosis (ICD 733) and subsequent fracture (ICD-9-CM 820–829) based on ICD-9-CM.

Statistical analysis

We used four weight scores to estimate the Charlson's comorbidity index for each person. Distributions of demographic characteristics and Charlson's comorbidity index were compared between the burn cohort and the comparison cohort. Categorical variables were examined using chi-squared test, and the difference between two means was examined using *t* test. We used Kaplan-Meier method to estimate cumulative incidence of osteoporosis for both cohorts and used log-rank test to examine the difference between the two curves. The incidence densities of osteoporosis were calculated for both cohorts in per 1000 person-years. Poisson regression analysis was used to assess incidence rate ratio (IRR) of osteoporosis with 95% confidence interval (CI) for the burn cohort compared with the comparison cohort. The adjusted incidence rate ratio (aIRR) was measured by including sex, age, income, and Charlson's comorbidity index in the multivariate model. The osteoporosis incidence rates were also estimated by the burn size (percent of total body surface area: < 20%, 20–49%, and 50% and greater) and by the burned site (eyes/face and head, trunk, limbs, wrist and hand, and others). We also evaluated the osteoporosis incidence for patients of burn with comorbid diabetes, for patients with only burn, and for patients with only diabetes, comparing with individuals with neither burn nor diabetes as the reference. Further data analysis evaluated the incidence of fracture among subgroups with and without burn injury by osteoporosis status; adjusted odds ratio (aOR) with 95% CI was calculated for each subgroup. A p value < 0.05 is considered as statistical significance in this study.

Results

Patients with burn showed consistently higher incidence rates of osteoporosis

Table 1 shows that slightly over half of burn victims were females (51.6%). About two thirds of the subjects were less than 50 years of age with the mean age slightly higher in the burn cohort than in the comparison cohort. Patients with burn injury had lower income, but higher Charlson's comorbidity index.

Table 1 Demographic characteristics and Charlson's comorbidity index in patients with and without burn injury

Variable	Burn		*P* value
	No *N* = 174,124 *n* (%)	Yes *N* = 43,532 *n* (%)	
Sex			0.96
Female	89,784 (51.6)	22,446 (51.6)	
Male	84,340 (48.4)	21,086 (48.4)	
Age, mean (SD)	41.8 (16.5)	42.0 (16.3)	0.03[a]
Age, year			0.94
< 35	68,156 (39.1)	17,039 (39.1)	
35–49	53,092 (30.5)	13,273 (30.5)	
50+	52,876 (30.4)	13,220 (30.4)	
Income, NTD			< 0.001
< 15,000	79,449 (45.6)	19,522 (44.9)	
15,000–19,999	43,631 (25.1)	12,036 (27.7)	
≥ 20,000	51,044 (29.3)	11,974 (27.5)	
Charlson's comorbidity index			< 0.001
0	161,939 (93.0)	39,340 (90.4)	
1	8032 (4.61)	2675 (6.14)	
2	2075 (1.19)	756 (1.74)	
3+	2078 (1.19)	761 (1.75)	

All used chi-squared test. Case group mean follow-up years 7.00 (3.86), control group follow-up years 7.09 (3.84)

NTD New Taiwan dollar

[a] Two samples where *t* test is used for mean

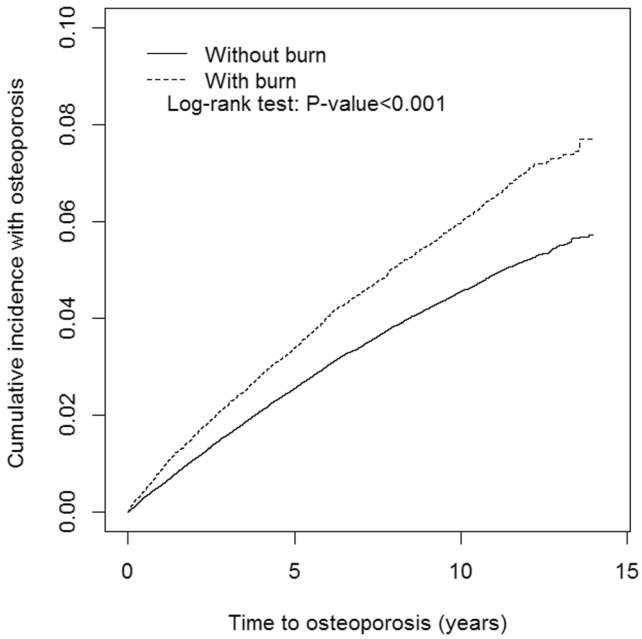

Fig. 1 Cumulative incidence of osteoporosis compared between patients with and without burn using the Kaplan-Meier method

The cumulative incidence of osteoporosis was 2.1% more in the burn cohort than in the comparison cohort ($p < 0.001$) by the end of 2013 (Fig. 1). Table 2 shows that the incidence rate of osteoporosis was 1.35 times greater in patients with burn than in patients without burn (6.40 vs. 4.75 per 1000 person-years) with an aIRR of 1.35 (95% CI = 1.32–1.39). Patients with burn injury showed consistently higher incidence rates of osteoporosis than did controls by the status of sex, age, and Charlson's comorbidity index. The incidence increment was greater in the burn cohort than in the comparison cohort.

Patients with burn injury of 20–49% of body area and burn confined to lower/upper limbs were more likely to have a higher incidence of osteoporosis: 8.32 and 8.58 per 1000 person-years, respectively (Table 3).

Table 4 shows that the person with diabetes had an elevated incidence of osteoporosis in both burn injury cohort and comparison cohort (22.7 vs. 18.1 per 1000 person-years) with an aIRRs of 1.86 (95% CI 1.58–2.18) and 1.19 (95% CI 1.03–1.37), respectively, compared with controls without diabetes.

Patients with burn injury and osteoporosis had increased fracture

The incidence of fracture was the highest in burn victims with osteoporosis developed, followed by comparisons with osteoporosis, burn victims without osteoporosis, and the least in comparisons without osteoporosis (35.4, 28.9, 11.3, and 7.61 per 100) (Table 5). The aOR was 5.68 (95% CI = 5.15–6.26) for burn victims with osteoporosis developed compared with comparisons without osteoporosis.

Discussion

Incident fracture for burn victims with osteoporosis developed increases greatly

To the best of our knowledge, this study is the first to evaluate specifically for the development of osteoporosis associated with burn injury for Asian population. Results demonstrated that the incident osteoporosis was 35% greater for patients with burn injury than for comparison cohort without burn. Once osteoporosis develops, the occurrence of fracture for burn victims increases greatly and is near 5-fold greater than it is for individuals without burn and osteoporosis.

A Western Australia study has evaluated a broad post burn subsequent musculoskeletal disorder, including arthropathies, systemic connective tissue disorders, dorsopathies, soft tissue disorders, and osteopathies and chrondropathies, instead of specifically about osteoporosis. Some disorders in osteopathies and chrondropathies are disorders of bone density and structure, which is 83% higher in burn patients than it is in

Table 2 Incidence rates of osteoporosis and burn cohort to comparison cohort incidence rate ratio of osteoporosis by sex, age, and Charlson's comorbidity index

Variables	Burn						Crude IRR (95% CI)	Adjusted IRR[b] (95% CI)
	No			Yes				
	Event	PY	Rate[a]	Event	PY	Rate[a]		
All	5863	1,234,981	4.75	1950	304,640	6.40	1.35 (1.31–1.39)***	1.35 (1.32–1.39)***
Sex								
Female	4081	632,488	6.45	1305	156,607	8.33	1.29 (1.24–1.34)***	1.31 (1.26–1.35)***
Male	1782	602,493	2.96	645	148,033	4.36	1.47 (1.41–1.54)***	1.45 (1.39–1.51)***
Age, year								
≤ 34	384	511,170	0.75	153	127,417	1.20	1.60 (1.52–1.68)***	1.55 (1.48–1.63)***
35–49	1263	401,557	3.15	445	99,089	4.49	1.43 (1.36–1.50)***	1.38 (1.31–1.46)***
50+	4216	322,253	13.1	1352	78,134	17.3	1.32 (1.26–1.39)***	1.30 (1.24–1.36)***
Income, NTD								
< 15,000	1748	537,926	3.25	584	131,024	4.46	1.37 (1.31–1.43)***	1.38 (1.33–1.44)***
15,000–19,-999	1820	317,584	5.73	667	86,128	7.74	1.35 (1.28–1.43)***	1.43 (1.36–1.50)***
≥ 20,000	2295	379,471	6.05	699	87,489	7.99	1.32 (1.25–1.39)***	1.25 (1.19–1.32)***
Charlson's comorbidity index								
0	4850	1,167,649	4.15	1520	281,615	5.40	1.30 (1.26–1.34)***	1.34 (1.30–1.37)***
1	659	47,815	13.8	284	15,842	17.9	1.30 (1.17–1.45)***	1.44 (1.30–1.60)***
2	189	10,672	17.7	78	3942	19.8	1.12 (0.91–1.37)	1.18 (0.96–1.44)
3+	165	8845	18.7	68	3242	21.0	1.12 (0.91–1.38)	1.24 (1.01–1.52)*

PY follow-up person-years, *crude IRR* crude incidence rate ratio, *CI* confidence interval

[a] Rate, incidence rate, per 1000 person-years

[b] Adjusted IRR, multivariable analysis including age, sex, income, and Charlson's comorbidity index

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

people without burn (3.3% vs. 1.8%) [16]. The follow-up time is longer in the Western Australia study than it is in ours.

Our data showed that the osteoporosis incidence was consistently elevated at all age groups in post burn patients, but with a greater impact for younger patients. Women had higher incidence rate of osteoporosis than men, although the adjusted IRR was greater in men than in women.

Our study also showed that the incidence of osteoporosis varied by the proportion of body burn and the site of burn. Patients with burn injury < 50% of total body area had a much higher incidence of osteoporosis than those with the injury > 50% of total body area. The IRR of osteoporosis for patients with burn area more than 50% was not significant; it may be due to the small number of patients with such a severe injury in this cohort. Similarly, the Western Australia study also found that patients with minor burns are associated with much greater hospitalization rates for osteopathies and chrondropathies than are patients with severe burns [16]. There were a larger number patients with burn of lower and upper limbs, wrist, and hand and were more likely had minor burns and somewhat at an increased incident osteoporosis.

Hypermetabolism leads to protein catabolism, which increases incident osteoporosis and fracture

Burn injury affects multiple body functions [11–15]. The adaptive process of burn injury induces inflammatory and hypermetabolic responses which may decrease bone mineral density [18, 19] and suppress bone formation [14, 15]. Edelman et al. found in a prospective study no changes in muscle and fat mass but a great change in bone mineral density approximately 131 days after burn injury [18]. In addition, burn patients experience vitamin D insufficiency and inability of bone to take up calcium, leading to bone loss [20, 21]. However, studies also reported that hypermetabolism leads to protein catabolism, to lose body weight and lean body mass, and subsequently to lose bone mineral density [18, 19, 22, 23], which increase the occurrence of osteoporosis and fracture. Our further data analysis among those developed osteoporosis revealed a near 5-fold greater incident fractures in the burn cohort than in the comparison cohort with an aOR of 5.68. The fracture incidence might increase further for a longer follow-up time.

Table 3 Incidence rates of osteoporosis by subtypes of burn and incidence rate ratios compared to comparison cohort

Variables	Number	No. of event	Rate[a]	Crude IRR (95% CI)	Adjusted IRR[b] (95% CI)
Comparison cohort	174,124	5863	4.75	1.00 (Reference)	1.00 (Reference)
Burn cohort					
Area					
Unspecified	38,260	1734	6.47	1.36 (1.32–1.40)***	1.36 (1.33–1.40)***
< 20%	4944	198	5.78	1.22 (1.13–1.32)***	1.26 (1.17–1.36)***
20–49%	260	17	8.32	1.75 (1.34–2.28)***	1.68 (1.31–2.14)***
> 50%	68	1	2.51	0.53 (0.18–1.57)	0.46 (0.17–1.26)
Eye, face/head	2661	105	5.96	1.26 (1.13–1.40)***	1.21 (1.09–1.33)***
Trunk	6593	225	4.84	1.02 (0.95–1.10)	1.18 (1.11–1.27)***
Lower/upper limbs	2052	120	8.58	1.81 (1.63–2.00)***	1.49 (1.36–1.64)***
Wrist/hand	22,220	1026	6.65	1.40 (1.35–1.45)***	1.35 (1.30–1.39)***
Others	10,006	474	6.56	1.38 (1.31–1.46)***	1.47 (1.40–1.54)***

Crude IRR crude incidence rate ratio, *CI* confidence interval

[a] Rate, incidence rate, per 1000 person-years

[b] Adjusted IRR, multivariable analysis including age, sex, and Charlson's comorbidity index

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Charlson's comorbidity index was assessed as a means to evaluate whether the development of osteoporosis increases with the level of comorbidity. Incidence rates of osteoporosis increasing with the index were identified in both cohorts, suggesting that various disorders could be associated with the osteoporosis development. Studies have found that individuals with diabetes are at an increased risk of developing osteoporosis and fracture [24–27]. Our study also showed that the incidence of osteoporosis increased further for diabetic individuals who experienced burn injury. The osteoporosis incidence was 3.6-fold greater in burn patients with comorbid diabetes than those without (22.7 vs. 6.29 per 1000 person-years) in the burn cohort. This evidence suggests that osteoporosis for burn injury patients may increase through its interaction with other disorders. Diabetes has a much greater impact on the development of osteoporosis than burn injury alone has.

Patients with diabetes are at increased bone loss

Diabetes has long been associated with low bone density and fracture [28–30]. The bone metabolism is affected by the insulin-like growth factors and other types of cytokine [30]. The initial onset of type 1 diabetes occurs often at a young age, when bone mineral, bone mass, and bone density are still being accrued. Thus, type 1 diabetes patients are thus likely complicated by low bone mass, whereas

Table 4 Joint effects for osteoporosis between burn and diabetes

Variables	Number	No. of events	Rate[a]	Crude IRR (95% CI)	Adjusted IRR[b] (95% CI)
Comparison cohort					
Diabetes					
No	173,341	5802	4.71	1.00 (Reference)	1.00 (Reference)
Yes	783	61	18.1	3.85 (3.34–4.43)***	1.19 (1.03–1.37)*
Burn cohort					
Diabetes					
No	43,080	1905	6.29	1.34 (1.30–1.38)***	1.35 (1.31–1.38)***
Yes	452	45	22.7	4.82 (4.10–5.67)***	1.86 (1.58–2.18)***

Crude IRR crude incidence rate ratio, *CI* confidence interval

[a] Rate, incidence rate, per 1000 person-years

[b] Adjusted IRR, multivariable analysis including age, sex, and Charlson's comorbidity index

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Table 5 Incidence and odds ratio of fracture in burn cohort and comparison cohort by osteoporosis status

	Comparison cohort		Burn cohort	
	Osteoporosis		Osteoporosis	
Fracture	No	Yes	No	Yes
	$N = 168,261$	$N = 5863$	$N = 41,582$	$N = 1950$
N	12,801	1694	4696	691
Rate/100	7.61	28.9	11.3	35.4
aOR (95% CI)	1.00	4.20 (3.94–4.47)	1.00	3.93 (3.54–4.36)
aOR (95% CI)	1.00	4.26 (4.00–4.53)	1.51 (1.45–1.56)	5.68 (5.15–6.26)

aOR (95% CI), adjusted odds ratio (95% confidence interval), controlling for age, sex, and Charlson's comorbidity index; all odds ratios with $p < 0.001$

type 2 diabetes patients are characterized by the reduced bone strength but with normal or high bone mineral density [28, 31]. The Iowa Women's Health Study found that the hip fracture risk is much greater for women with type 1 diabetes (12.25 times) than for women with type 2 diabetes (1.7 times), compared to women without diabetes [29]. Schwartz et al. found in the Study of Osteoporotic Fractures that women with type 2 diabetes are at a higher fracture rates than women without diabetes [32]. Patients with well-controlled diabetes are at reduced bone loss [33]. Burn patients with comorbid diabetes need to take an action for osteoporosis prevention and control to reduce bone loss.

Strength and study limitation

The insurance claims data provided us with a sufficient large size of representative study population enabling us to perform stratified quantitative data analyses with reliable findings. This administrative data reduced issues of selection and reporting bias. We were able to determine the osteoporosis risk by Charlson's comorbidity index to observe the interaction between burn injury and other disorders. We assumed that individuals with severe burn injury and/or with high Charlson's comorbidity index could increase bone loss. However, few study limitations were inherited from using the health insurance claims data. Information on dual-energy X-ray absorptiometry (DEXA) scan and bone mineral density was not available in the claims data, preventing us from estimating the relationship between burn severity and osteoporosis status. We were thus unable to use the data on lean body mass to evaluate if there was a concomitant decline in muscle mass, which would lead to increased falling and contributing to a greater incidence of fractures. There were only 68 persons with their burn areas > 50% of the body surface. The relatively small sample size of severe burn injury limited the evaluation of the impact. A lower incidence of osteoporosis in patients with severe burn injury could be a type 2 error. Therefore, our findings may be confined to patients with moderate burn injury involving burns of 25–49% of total body surface area.

Conclusion

Previous studies have reported that patients with burns are at an increased incidence of osteoporosis and consequent fracture. Our study confirmed these associations. The osteoporosis incidence increases further for those with increasing Charlson's comorbidity index. This reflects that comorbidities may interact with burn in the development of osteoporosis. The incidence increases much more for victims with comorbid diabetes. We also found that victims with post burn osteoporosis have their bones more fragile and susceptible to fractures. It is necessary for those who have sustained a burn to take osteoporosis and fracture prevention and treatment measures, particularly for victims with a higher Charlson's comorbidity index. More population studies are needed to confirm our findings.

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Compliance with ethical standards

Because the surrogate identifications could protect privacy, no consents were required from persons selected in this retrospective cohort study. This study was approved by the Research Ethics Committee, China Medical University and Hospital.

Conflicts of interest None.

Human and animal rights and informed consent This study used secondary data of insurance with surrogate identifications, requiring no consent.

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