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ORIGINAL ARTICLE

Osteoporosis and Fractures After Solid Organ Transplantation: A Nationwide Population-Based Cohort Study

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Abstract

Objective: To investigate the incidence of bone disorders after solid organ transplantation (SOT).

Participants and Methods: We used Taiwan's National Health Insurance Research Database to identify 9428 recipients of SOT and 38,140 sex- and age- matched control subjects between January 1, 1997, and December 31, 2010, to compare the incidence and risk of bone disorders between groups.

Results: Recipients of SOT had a significantly higher incidence of osteoporosis and related fractures compared with the non-SOT group. The overall hazard ratio (HR) of osteoporosis after SOT was 5.14 (95% CI, 3.13-8.43), and the HR of related fractures was 5.76 (95% CI, 3.80-8.74). The highest HRs were observed in male patients (HR, 7.09; 95% CI, 3.09-16.3) and in those aged 50 years or younger (HR, 7.38; 95% CI, 2.46-22.1). In addition, SOT patients without any comorbidities had a 9.03-fold higher risk of osteoporosis than non-SOT participants (HR, 9.03; 95% CI, 5.29-15.4). To compare the risk of osteoporosis and related fractures in different recipients of SOT, the highest risk of osteoporosis and fractures was noted in patients receiving lung transplantation, followed by other types of SOT.

Conclusion: We report high rates of metabolic bone disorders after SOT in chronic transplant patients over a long follow-up. Both underlying bone disorders before transplantation and use of immunosuppressant agents may contribute to bone disorders after transplantation.

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Solid organ transplantation (SOT) is the only lifesaving treatment for patients with major organ failure, including heart, lung, and liver, and it is considered the treatment of choice for end-stage kidney failure. Because of the progress made in surgical techniques, perioperative care, and immunosuppressive regimens, long-term outcomes of SOT are better than ever before. Despite improvements in patient and graft survival in SOT, an increasing number of complications after transplantation have become a major concern in caring for recipients of SOT that may have been caused by either the recipient's diseases or treatment with immunosuppressant agents. Compared with lethal complications, such as cancer, cardiovascular diseases, and infection, and some metabolic disorders, such as diabetic mellitus, after transplantation, the importance of metabolic bone diseases seems to be ignored in patients after SOT.

It is reasonable to anticipate that recipients of SOT are at high risk for bone disorders owing to several unfavorable situations. First, in these candidates with chronic, catastrophic illnesses before transplantation, multiple comorbidities such as the underlying disease itself, poor nutrition, immobility, cachexia, and unhealthy lifestyle factors (heavy tobacco and alcohol consumption) eventually result in metabolic bone disorders.[1] For example, in patients with hepatic osteodystrophy, multiple factors have been considered as contributing to reduced bone formation, including excessive alcohol consumption,[2] decreased insulinlike growth factor 1 levels,[3] and hyperbilirubinemia.[4] Substantial bone absorption caused by hypogonadism is a frequent finding in patients with liver cirrhosis.[5] Renal osteodystrophy prevails in most patients with chronic renal disease who unavoidably acquired excessive derangement of bone mineralization in a uremic state. Studies have reported an approximately 4.4-fold risk of hip fracture and a risk of vertebral fracture as high as 21% in patients with end-stage renal disease compared with the general population.[6-8]

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Recipients of SOT inevitably take immunosuppressive medications, such as glucocorticoids (GCs) and calcineurin inhibitors, for the rest of their lives. Glucocorticoids have been demonstrated to play a dominant role in bone loss and to profoundly affect bone absorption in patients after organ transplantation.[9,10] The mechanisms are complex, including decreasing osteoblast replication and differentiation, wasting renal calcium, attenuating intestinal absorption of calcium, and hypogonadism.[11] The deleterious effects of GCs on osteoblast activity and life span are considered to be crucial in contributing to bone disorders after transplantation. Consequently, these unfavorable conditions synergistically compel the transplant cohort to be at high risk for bone fracture. Although every SOT has different underlying bone diseases depending on disease progress and the individual immunosuppressant drug regimen, it is generally believed that the occurrence of bone disorders after organ transplantation is similar irrespective of organ type.[12]

The impact of osteoporosis in the general population has been clearly addressed and is characterized by low bone mass and vulnerability to bone fractures, leading to excess mortality of 10% to 20% and up to 25% of the general population requiring long-term nursing home care; nevertheless, a large gap still exists in clinical practice.[13,14] To date, data regarding the risk of bone diseases after SOT are limited owing to either small group sizes or restrictions regarding individual SOT or lack of long-term follow-up. The aim of this study was to compare the risk of osteoporosis and fracture among different types of SOT in a nationwide population-based cohort over a long-term period and to look for potential risk factors associated with patients receiving SOT.

PARTICIPANTS AND METHODS

Data Sources

Data analyzed in this study were retrieved from the Taiwan National Health Insurance Research Database (NHIRD), which is managed by the Taiwan National Health Research Institute. In 1995, Taiwan commenced its state-run National Health Insurance program, which registers all medical claims and provides affordable health care for all residents. The National Health Insurance program covers more than 99% of the population and has contracted with 97% of the hospitals in Taiwan.

Sets of information available for the NHIRD include all medical services by each insurant from 1996 to 2010 and characteristics of the patients, hospitals, and physicians. In this study, we used the hospitalization claims data of all enrollees (23 million) in Taiwan, which contained information on sex, date of birth, dates of hospital admission and discharge, diagnoses, surgical procedures, discharge status, and expenditures by admission. Diagnoses were coded using the *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*). Several Taiwan studies demonstrated the high accuracy and validity of *ICD-9* code diagnoses in the NHIRD.[15,16]

Study Participants

The study participants were identified in the database between January 1, 1997, and December 31, 2010, as having newly diagnosed SOT, including kidney transplantation (*ICD-9-CM* code V42.0 or operation code 55.69), liver transplantation (*ICD-9-CM* code V42.7 or operation codes 50.51-50.59), heart transplantation (*ICD-9-CM* code V42.1 or operation code 37.5), and lung transplantation (*ICD-9-CM* code V42.6 or operation codes 33.50-33.52). The date of the first hospital admission for transplant was used as the index date. We excluded patients with osteoporosis (*ICD-9-CM* codes 733.00-733.09) or pathologic fracture (*ICD-9-CM* codes 733.10-733.19) before the index date. Patients with multiple SOTs or retransplantation were excluded. In Taiwan, the diagnosis of osteoporosis and fracture through *ICD-9* codes is derived from the evidence strictly based on the clinic data of bone mineral density (BMD) measurement by dual X-ray absorptiometry (for the hip and spine) and ultrasound densitometry (for the heel). In this study, patients who acquired fractures by trauma or tumor metastasis were also excluded. The diagnosis of pathologic fracture was defined as related fracture when it did not result from trauma or metastasis. Finally, we extracted 9428 transplant recipients to be used as study patients, defined as the SOT cohort.

For each SOT patient, we randomly selected 4 non-SOT patients from the same study period and used the same exclusion criteria and frequency matched them with the SOT cohort for age and sex to form the non-SOT cohort with 38,140 individuals.

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