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ORIGINAL ARTICLE

Increased risk of hip and major osteoporotic fractures in 8463 patients who have undergone stem cell transplantation, a Swedish population-based study

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Abstract

Summary In this retrospective cohort study of adult stem cell transplanted patients ($n = 8463$), a significant increased risk of both MOF and hip fractures was seen compared with the Swedish population and occurred in mean more than 2 years after stem cell transplantation.

Purpose To explore the risk for osteoporotic fracture in patients who have undergone hematopoietic stem cell transplantation (HSCT) compared with the Swedish population.

Methods The risk of osteoporotic fractures was determined in a retrospective population cohort study of adult (≥ 18 years) Swedish patients ($n = 8463$), who were transplanted with HSCT 1997–2016 and compared with all adults living in Sweden during the same period.

Results In the *total* study group ($n = 8463$), 90 hip fractures (1.1% both in males and females) and 361 major osteoporotic fractures (MOF) (3.2% in men and 6.0% in women) were identified. In the total study population, the ratio of observed and expected number of hip fracture for women was 1.99 (95% CI 1.39–2.75) and for men 2.54 (95% CI 1.91–3.31). The corresponding ratio for MOF in women was 1.36 (CI 1.18–1.56) and for men 1.61 (CI 1.37–1.88). From 2005 onwards, when differentiation in the registry between allo- and auto-HSCT was possible, the observed number of hip fracture and MOF in allo-HSCT ($n = 1865$) were significantly increased (observed/expected hip fracture 5.24 (95% CI 3.28–7.93) and observed/expected MOF 2.08 (95% CI 1.63–2.62)). Fractures occurred in mean 2.7 (hip) and 2.5 (MOF) years after allo-HSCT. Graft-versus-host disease (GVHD) was not associated with an increased risk of fracture.

Conclusion Patients who underwent HSCT had an increased risk of both hip and major osteoporotic fracture compared with the Swedish population and occurred in 4.3% of patients. GVHD was not statistically significantly associated with fracture risk.

Keywords Hip fracture · HSCT · MOF · Osteoporosis

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Introduction

Osteoporosis is a disease characterized by loss of bone mineral density (BMD), resulting in an increased risk of fracture. Osteoporosis does not display any symptoms prior to fracture. Consequently, the manifestation of osteoporosis is osteoporotic fractures, which are defined as low-energy fractures and classical osteoporotic fractures most often occur in the spine, hip, proximal humerus, and wrist. Osteoporotic fractures are the most devastating outcome of bone loss/osteoporosis. It is well known that Swedish men and women in general have among the highest risk in the world of fractures in the hip and vertebrae [1]. Every year, roughly 70,000 osteoporotic-related fractures occur in Sweden. Fractures have a great impact on both mortality and morbidity [1]. Hematopoietic stem cell transplantation (HSCT) is an option for cure and gives a longer remission of various diseases (https://www.ebmt.org/education/ebmt-handbook). The most prevalent underlying disease is blood cancer; however, both immunological and other malignancies can additionally be treated. The two main types of HSCT are autologous (auto) HSCT and allogenic (allo) HSCT. Bone loss is a potential and well-known complication after HSCT and occurs within the first 6–12 months after HSCT [2]; however, long-term follow-up has also demonstrated a high prevalence of osteopenia/osteoporosis in survivors many years after allo-HSCT [3, 4]. The consequences of osteoporosis, namely osteoporotic fractures after HSCT, are insufficiently described [4, 5]. In a prospective study of 258 patients who underwent allo-HSCT between 2005 and 2016 in a single-center in France, researchers found decreased bone mineral density [6]. Incident fractures were found in 5.7% during 3-year follow-up after HSCT. Baumgartner et al. studied risk factors for fractures and impaired bone health in 652 patients undergoing allo-HSCT during the years 2003–2014 [7]. Out of these, 32 (5%) developed a new fracture, a yearly incidence of 1.6%. Chronic graft-versus-host disease (GVHD) has the potential to increase the risk of osteoporotic fractures partly through the inflammation status and partly since these patients are frequently exposed to prolonged and high-dose corticosteroid therapy.

The aim of our study was, for the first time, to investigate the risk for osteoporotic fractures in patients who have undergone HSCT compared with the Swedish population. In addition, we wanted to investigate if there was a difference between allo- and auto-HSCT regarding risk of fractures.

Populations and methods

Data were retrieved from various national registers at Statistics Sweden (SCB) including the Swedish Total Population Register (RTB). The Swedish Tax Agency collects comprehensive data on residence, marital status, migration, and deaths forwarding this information directly to Statistics Sweden. From the National Board of Health and Welfare, registry information such as the Cancer Registry, the Swedish Patient Registry, and the Cause of Death Registry was obtained. The patient registry includes the outpatient and inpatient registry with information about diagnosis and operational procedures including stem cell transplantation (ICD codes). From these registers, we collected all adult (≥ 18–80 years) patients who underwent HSCT from January 1, 1997, until December 31, 2016. We identified 8463 patients. Subjects were followed until the first fracture, death, or end of study.

Patients were observed until December 31, 2016, for ascertainment of osteoporotic fracture occurrence (hip fracture and major osteoporotic fracture (MOF)). The International Classification of Diseases (ICD-9) was used.

To compare the risk of fractures in transplanted patients with the entire Swedish population, we included all adults (≥ 18 years) living in Sweden during the same period and examined the incidence of osteoporotic fractures in this population. From the National Board of Health and Welfare, all hospital admissions are documented. A unique personal identifier permits tracking the individual for multiple admissions. The vast majority of patients with hip fractures undergo surgical treatment, and this procedure is registered. Hip fractures were identified by the ICD-9 code 820× and ICD-10 code S72.0–2. Surgical procedure for proximal femur fracture was registered by operation code ICD-9 841,82× or NFJ 09–99 or NFB. MOF fractures were defined as fracture of the hip, pelvis, proximal humerus, and forearm as well as clinical vertebral fractures corresponding to ICD 10 codes S22.0, S22.1, S32.0, S32.1, S32.4, S32.5, S42.2, S52.5, S56.6, S72.0, S72.1, and S72.2. Information about HSCT patients were retrieved from the patient registry. After 2001, the outpatient registry was started, and after 2005, the classification of HSCT was expanded, and it was thus possible to differentiate more accurately between various sources of HSCT. For allo-HSCT, the following codes were used: DR008, DR041, DR042, DR043, DE044, DR045, DR046, DR 047, V9120, V9534, and V9536. For auto-HSCT, the following codes were used: V9120, V9535, V9537, DR010, DR043, and DR048.

Graft-versus-host disease (GVHD) was registered according to ICD 10 code T860B.

Each patient's date of birth and gender at the time of transplantation was obtained from Statistics Sweden. The study was conducted according to the principles of the Declaration of Helsinki and approved by the Regional Ethical Review Board in Gothenburg (Dnr: 202–16).

Entire Swedish population

We collected information from RTB on all adults (≥ 18 years) living in Sweden during the period 1997–2016. In this population, which thus consisted of the entire Swedish population residing in Sweden during these years (hereafter named total population), we examined the incidence of fractures between 1997 and 2016. Data for admissions to hospital, demographic variables, the ICD code of hip fractures and MOF, and surgical operation codes were collected in the same manner described above for transplanted patients.

Statistical analysis

Entire Swedish population When calculating the expected number of fractures in the study population with HSCT, a hazard function (HF) of fracture from the entire Swedish population was used. To estimate the HF, an extension of the Poisson regression model [8, 9] was used to study the relationship between the risk of fracture on the one hand and age, latitude, calendar year, population density, and seasonal variation on the other. For all fractures, the exact date of fracture was included in the calculations. Separate HFs for the entire Swedish population were developed for each gender. Further details of the HFs of fracture were that they were piecewise linear in age and calendar year with breakpoints at ages 40, 60, and 75 years. The breakpoint in calendar year was 2002 and 2009 for hip fracture and 2001 and 2006 for MOF. Population density, an index of urban/rural status, was given the value 1 if the number of inhabitants of the home community per km^2 of land area exceeded exp(7), that is, 1097 per km^2. This population density is comparable to the larger cities of Sweden. Latitude was considered a continuous variable and was determined for each county of Sweden.

HSCT patients group Patients who underwent HSCT between January 1, 1997, and December 31, 2016, were included in the study and monitored for fractures until December 31, 2016. This means that some patients have had a limited duration for fracture follow-up. However, this was accounted for in the analysis. The Poisson regression model was used to study the relationship between the risk of fracture on the one hand and the time since the HSCT diagnosis, age, and calendar year, on the other, with separate models for each gender. The observation period for each participant was divided into intervals of 1 month. One fracture per person and time to the first fracture were counted, and time at risk was censored at the time of first fracture, migration, death, or end of follow-up. The breakpoints in age were at 40, 60, and 75 years for the outcome of MOF and for hip fracture. The breakpoint in calendar year was 2001 and 2006 for the outcome of MOF and 2002 and 2009 for hip fracture.

For the total study population, the expected number of fractures was calculated using the HFs of fracture from the total population. The ratio between the observed and expected number of fractures and a 95% confidence interval (CI) were calculated.

The hazard ratio (HR) for the type of HSCT and diagnosis of HSCT was determined for each sex from the Poisson regression model, adjusted for current age, time since HSCT, and current calendar year.

To study the overall effect of GVHD on the risk of fracture within the study population, we used the variable T860B as a time-dependent covariate in the Poisson regression model, adjusted for current age, time since HSCT, sex, and current calendar year.

Two-sided p-values were used for all analyses, and $p < 0.05$ was considered to be statistically significant.

Results

Study population

The total number of patients who had undergone a HSCT in Sweden between January 1, 1997, and December 31, 2016, was 8463. Adult patients between 18 and 80 years of age were studied. The patients were followed regarding fracture until December 31, 2016. The mean age at HSCT was 52.4 years (range 18–79 years). A total of 39.3% were women ($n = 3322$). According to patient registry, it was not possible to properly differentiate between auto- and allo-HSCT until 2005. During the period 2005–2016, 1865 patients underwent allo-HSCT and 3982 underwent auto-HSCT.

The main underlying diagnoses which led to allo-HSCT were acute leukemia (both myeloid and lymphatic) (53%), myelodysplastic syndrome (12%), lymphoma (6%), chronic lymphocytic leukemia (6%), chronic myeloid leukemia (6%), myeloproliferative disorders (6%), myeloma/plasma cell disease (2%), and others (9%). The main underlying diagnoses for auto-HSCT were myeloma/plasma cell disease (52%), lymphoma (37%), multiple sclerosis/inflammatory neuropathy (4%), testicular cancer (1.6%), and others (5.4%). The diagnoses were retrieved from the patient registry.

Demographic data and number (%) of fractures of the study population are presented in Table 1. In the total study group ($n = 8463$), we identified 90 hip fractures (1.1% both in males and females), and 361 MOF (3.2% in men and 6.0% in women) were identified. Hip fractures occurred in mean 4.3 years (range 0.1–17.7 years) and MOF 4.5 years (range 0.1–18.5 years) after HSCT. The

Table 1 **A**: patients who underwent HSCT (both auto and allo) between 1997 and 2016; **B**: patients who underwent allo-HSCT between 2005 and 2016; **C**: patients who underwent auto-HSCT between 2005 and 2016. Selected demographic data, number of hip, and major osteoporotic fractures (MOF) (%). The data are shown as mean (standard deviation (SD) or %)

	A (1997–2016) Allo- and auto-HSCT ($n=8463$)	*B (2005–2016)* Allo-HSCT ($n=1865$)	*C* (2005–2016) Auto-HSCT ($n=3982$)
Mean age at HSCT	52.4 (12.9); range 18–79	49.8 (14.4); range 18–79	55.4 (11.8); range 18–77
Gender (female)	39.3%	42.6%	37.2%
Days from diagnosis to HSCT	539 (829)	601 (938)	581 (898)
Death	46.0%	39.9%	34.9%
Hip fracture	1.1%	1.2%	0.8%
MOF	4.3%	3.9%	3.5%
Time (years) to fracture (hip)	4.29 (3.96); $n=90$	2.69 (2.47); $n=22$	3.59 (2.93); $n=31$
Time (years) to fracture (MOF)	4.47 (4.08); $n=361$	2.49 (2.16); $n=72$	3.0 (2.46); $n=139$

Table 2 Observed and expected number of hip fractures and major osteoporotic fractures (MOF) in patients who underwent HSCT ($n=8463$) during 1997–2016. Models are adjusted for age, calendar year, latitude, density of residence, and time of follow-up

	Observed	Expected	Observed/expected (95% CI)
Hip fracture			
Men	54	21.3	2.54 (1.91–3.31)
Women	36	18.1	1.99 (1.39–2.75)
MOF			
Men	163	101.2	1.61 (1.37–1.88)
Women	198	145.5	1.36 (1.18–1.56)

incidence of hip fracture was not statistically significantly different between women and men ($p>0.30$), increased by age in general ($p<0.001$), and did not decrease statistically significantly by calendar year ($p>0.30$) (data not shown). Most hip fractures occurred in patients aged 60–69 years (50% for men and 44.4% for women).

The mean follow-up time after HSCT (time to hip fracture, death, or end of study) was 5.0 years (SD 4.7, range 0.0–20.0 years), and the mean follow-up time to MOF, death, or end of study was 4.9 years (SD 4.7, range 0.0–20.0 years).

Risk of osteoporotic fracture in the total study population ($n=8463$) in relation to the total Swedish population (1997–2016)

In the total study group, there was an increased risk for both hip fracture and MOF compared with the Swedish total population, as demonstrated in Table 2. Transplanted men had a 2.5 times increased risk and women almost doubled risk for hip fracture compared with the Swedish total population. There was also a significant increase in MOF in these patients.

Risk of osteoporotic fracture in allo-HSCT ($n=1865$) and auto-HSCT ($n=3982$) patients in relation to the Swedish total population (2005–2016)

In the total group of allo-HSCT patients, there was an increased risk for fracture compared with the total population (observed/expected hip fracture 5.24 (95% CI 3.28–7.93) and observed/expected MOF 2.08 (95% CI 1.63–2.62)). This was also true when further division according to gender (Table 3(a)).

In auto-HSCT patients, the observed number of hip fracture and MOF was significantly increased in men (Table 3(b)).

Risk of fracture according to the type of HSCT (allo- vs auto-HSCT)

In women, the risk of both hip fracture and MOF was significantly increased in allo-HSCT patients compared with auto patients (HR 4.39 (95% CI 1.70–11.38); $p<0.01$ and HR 1.90 (95% CI 1.27–2.85); $p<0.01$) respectively. For men, the difference was not significant (HR 2.00 (95% CI 0.98–4.09); $p=0.056$ and HR 1.31 (95% CI 0.85–2.02); $p=0.22$).

As expected, the mortality was increased in allo- compared with auto-HSCT patients ($p<0.001$) both in men (HR 1.56 (95% CI 1.39–1.77)) and women (HR 1.56 (95% CI 1.35–1.81)). Models were adjusted for time since HSCT, age, and calendar year.

Risk of fracture according to GVHD

The diagnosis of GVHD was retrieved from the patient registry according to the code T860B and was observed in 959 of the total 1865 (51.4%) of allo patients. In patients with GVHD, 1.1% of hip fracture and 4.5% of MOF were diagnosed. In Poisson regression analysis with T860 as

Table 3 (**a** and **b**) Observed and expected number of hip fractures and MOF in men and women who underwent allo-HSCT ($n=1865$) or auto-HSCT ($n=3982$) during 2005 to 2016. Models are adjusted for age, calendar year, latitude, density of residence, and time of follow-up

Allo-HSCT		Observed	Expected	Observed/expected (95% CI)
a				
Hip	Men	12	2.2	5.41 (2.80–9.46)
	Women	10	2.0	4.95 (2.37–9.11)
MOF	Men	30	14.2	2.11 (1.43–3.02)
	Women	42	20.4	2.05 (1.48–2.78)
Auto-HSCT		Observed	Expected	Observed/expected (95% CI)
b				
Hip	Men	23	9.8	2.34 (1.48–3.52)
	Women	8	7.5	1.07 (0.46–2.10)
MOF	Men	75	42.4	1.77 (1.39–2.22)
	Women	64	61.5	1.04 (0.80–1.33)

time-dependent variable, GVHD was not associated with an increased risk of fracture; models were adjusted for time since diagnosis, age, gender, and calendar year.

Risk of fracture after HSCT ($n=8463$) according to diagnosis

There was no increased risk for hip fracture or MOF in patients with myeloma compared with other diagnoses of transplanted patients (data not shown).

Discussion

In this large population-based retrospective cohort of Swedish patients who underwent HSCT between 1997 and 2016, the risk of both hip fractures and MOF were significantly increased both in men and women compared with the Swedish total population and occurred just over 4 years in mean after HSCT. For hip fracture, the risk was at least doubled. The strength of our study is the investigation of a significant clinical endpoint, i.e., fractures. Additionally, it is performed in a large population-based study encompassing nearly 20 years. Not many studies have investigated the risk of fracture in HSCT patients in comparison with the general population. Osteoporosis is a surrogate marker for osteoporotic fracture, and hip fracture is the most devastating outcome of osteoporosis; it increases the mortality rate and accounts for more than one-half of all direct healthcare costs related to fractures. Thus, it is important to be aware of long-term outcome effects such as osteoporotic fractures after HSCT [10]. Recommendations to prevent osteoporosis in patients undergoing HSCT have recently been published [11]. Studies have shown an increased risk for osteoporosis in patients with hematological diseases undergoing allo-HSCT with a loss of bone density following the first 4 to 6 months after transplantation. This process continues but at a slower rate between 6 and 12 months and begins to recover after 12 months from transplantation [6, 12, 13]. There are not many studies of long-term survivors of allo-HSCT (> 3 years from transplantation) regarding bone loss, but there are reports that show a stabilization of BMD after 3–5 years post allo-HSCT and an improvement occurring between 5 and 15 years [14]. However, other studies have shown a high incidence of osteopenia/osteoporosis even many years after allo-HSCT [3]. In the present study, fractures occurred in mean more than 2 years after allo-HSCT and almost 3 years after auto-HSCT. The prevalence of osteoporosis and thereby the risk for osteoporotic fractures may also decrease over time, maybe according to awareness of this disease [15]; however, a decrease was not shown in the present study.

In the present study of patients who underwent either auto- or allo-HSCT, osteoporotic fractures were seen in 4.3% followed up to 19 years and fractures occurred in mean slightly over 4 years after HSCT. The corresponding figure after allo-HSCT was 3.9%. The number of fractures is in accordance with earlier studies [6, 7]. From Taiwan, a retrospective study comprising 1040 cancer patients who underwent HSCT from 2000 to 2008 was performed, and they found a risk of fractures which was 1.40 times higher than in a matched non-HSCT population [16]. In a large cohort of 1087 patients who have undergone HSCT, 493 auto and 594 allo, the prevalence of osteoporosis increased after HSCT. In auto, the prevalence increased from 2.4 to 9.7%, and in allo, from 1.4 to 23% [17]. From a single-center in Singapore, a small cohort of 31 patients was studied; 6.5% had preexisting bone loss, and after allo-HSCT, this proportion increased to 71% [18]. Of note, in the above studies, osteoporosis and not fracture was studied. In our study, we found

an increased risk for fractures after allo-HSCT; after auto-HSCT, this was noted only in men compared with the Swedish background population. In a study from MD Andersson, 5170 patients were identified who underwent HSCT between 2001 and 2010 [19]. Approximately 50% was auto- and 50% allo-HSCT. Ten percent developed an osteoporotic fracture during a median follow-up of 3.2 years. In another study from MD Andersson, they investigated the risk of fractures in a retrospective cohort of 7620 patients with HSCT (51% auto) during the years 1997–2011 [20]. Not only osteoporotic fractures were included but also fractures of the ribs, clavicle, hand, and foot. Eight percent developed a fracture with a higher risk in auto-HSCT (11%) compared with allo-HSCT (5%), explained by a high incidence of multiple myeloma patients. In comparison with a matched population, they found for the cohort aged 45–64 years an eight times greater risk in females and approximately seven to nine times greater risk in men. In accordance, we found the highest incidence of hip fracture in patients aged 60–69 years, that is, hip fractures occurred at a younger age than in the general population where these fractures are more common at older age [21].

We did find a higher risk for both hip fracture and MOF in women who underwent allo-HSCT compared with auto-HSCT; however, this difference was not seen in men. The higher risk of fracture post allo- compared with post auto-HSCT could possibly be explained by different risk factors between these procedures.

Classical risk factors for osteoporosis are well known, such as age, gender, smoking, low BMD, previous fracture, falls, BMI, and concomitant disease (rheumatoid arthritis) [22]. Further risk factors that could be associated with HSCT and/or its underlying disease are treatment-related factors (high-dose chemotherapy, radiation, and corticosteroid- and immunosuppressive therapy), endocrine abnormalities (e.g., diabetes mellitus, adrenal insufficiency, and thyroid dysfunction), lack of physical activity, and malnutrition [23]. Thus, many factors might contribute to bone loss post HSCT, and the exact mechanism is not known. In a prospective study of 104 patients who had undergone allo-HSCT, nontraumatic fractures occurred in 10.6% of patients within 3 years post transplantation [2]. Glucocorticoid therapy and immunosuppressive therapy (cyclosporine or tacrolimus) showed significant associations with loss of BMD, age, and total body irradiation, while diagnosis and donor type did not. A limitation in our retrospective registry study is the lack of information on potential risk factors for osteoporosis and fracture such as concomitant diseases, BMI, smoking, and therapy given including corticosteroids. We cannot, therefore, definitively state that the SCT itself is solely responsible for the increased risk of fractures. It is possible that patients undergoing SCT have other risk factors for fractures including high and chronic steroid use. Our study might have underestimated the incidence of some osteoporotic fractures since fractures were only reported by the physicians in the medical records and these were used as the basis for diagnoses. However, the vast majority of patients with hip fractures undergo surgical treatment, and this procedure is registered by an operation code. The different incidence of fractures of various studies may reflect differences in time periods, study design (including manner of fracture diagnosis), the definition of fractures, i.e., we only used osteoporotic fractures rather than all fractures, and further populations studied.

The underlying disease including treatment leading to HSCT might also play a role.

Multiple myeloma is a blood cancer with an increased risk of fracture both at diagnosis and under follow-up [24]. Nearly 30% were affected by a fracture either at diagnosis or at follow-up. The risk of death was significantly increased in patients with a fracture. Our group has published papers regarding the risk for hip fracture in a large cohort of lymphoma and myeloproliferative patients, and in these patient groups, we identified an increased risk for fracture [15, 25]. However, in the present study, myeloma patients did not have an increased risk of fracture compared with other diagnoses of transplanted patients, suggesting that there may be other reasons for fracture risk than the disease itself.

In a retrospective analysis of 453 acute myeloid leukemia (AML) patients treated with chemotherapy only or chemotherapy and allo-HSCT, and in remission for more than 3 years, an analysis of osteopenia/osteoporosis was performed. At the diagnosis of AML, only 1% had osteopenia/osteoporosis in contrast to 15% after at least 3 years in complete remission. There was a huge difference in 38% of HSCT patients and in 3% of chemotherapy patients [26]. Confounding by indication is a prevalent issue in observational studies when comparing treatments. However, it was not applicable in this analysis, as our primary aim was to study fracture risk, independent of treatment comparison, particularly with HSCT.

GVHD could potentially contribute to osteoporosis/fracture, partly through the inflammation status and partly since GVHD is typically treated with oral corticosteroids, often for several months. There is sparingly with data regarding GVHD and risk of osteoporosis/fractures. In the study by Wolff et al. [27], osteopenia/osteoporosis was present in 18.4% in the patients with chronic GVHD versus 2.8% in patients without GVHD. From a heterogenous pediatric population single-center study ($n=237$), the incidence of fractures was significantly increased in patients with chronic GVHD versus in patients without (15% vs 6%, $p=0.02$) [28]. The authors explained it to be likely to have higher glucocorticoid exposure for the GVHD patients. However, we did not find an increased risk for fractures in the group

of GVHD vs non-GVHD. In the present study, the diagnosis of GVHD was retrieved from the patient registry according to the code T860B and was observed in 51.9%. The reason for this discrepancy between studies is partly unclear and may be due to differences in methodology and population studied.

Conclusions

In conclusion, in this large Swedish population-based study, we found an increased risk of both hip and major osteoporotic fractures after HSCT compared with the Swedish population in both men and women and an incidence of 4.3% osteoporotic fractures in patients followed up to 19 years post HSCT. The expected risk was higher in patients undergoing allo-HSCT compared with auto-HSCT. GVHD was not associated with fracture risk. It is important to be aware of the increased risk of fracture and take preventive measures whenever possible, as well as to examine risk patients adequately with BMD measurement.

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Declarations

Conflict of interest None.

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