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ORIGINAL ARTICLE

Vertebral fractures cascade: potential causes and risk factors

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Abstract

Summary We performed a study to identify potential causes and risk factors of vertebral fracture cascade. Vertebral fracture cascade is a severe clinical event in patients with bone fragility. Only half of patients have an identified cause of secondary osteoporosis.

Introduction Vertebral fracture (VF) is the most common osteoporotic fracture, and a strong risk factor of subsequent VFs leading to VF cascade (VFC). We prompted a study to identify potential causes and risk factors of VFC.

Methods VFC observations were collected retrospectively between January 2016 and April 2017. VFC was defined as an occurrence of at least three VFs within 1 year.

Results We included in 10 centers a total of 113 patients with VFC (79.6% of women, median age 73, median number of VFs in the cascade, 5). We observed 40.5% and 30.9% of patients with previous major fractures and a previous VF, respectively, and 68.6% with densitometric osteoporosis; 18.9% of patients were currently receiving oral glucocorticoids and 37.1% in the past.

VFC was attributed by the physician to postmenopausal osteoporosis in 54% of patients. A secondary osteoporosis associated with the VFC was diagnosed in 52 patients: glucocorticoid-induced osteoporosis (25.7%), non-malignant hemopathies (6.2%), alcoholism (4.4%), use of aromatase inhibitors (3.6%), primary hyperparathyroidism (2.7%), hypercorticism (2.7%), anorexia nervosa (2.7%), and pregnancy and lactation-associated osteoporosis (1.8%). A total of 11.8% of cases were reported following a vertebroplasty procedure. A total of 31.5% patients previously received an anti-osteoporotic treatment. In six patients, VFC occurred early after discontinuation of an anti-osteoporotic treatment, in the year after the last dose effect was depleted: five after denosumab and one after odanacatib.

Conclusion The results of this retrospective study showed that only half of VFC occurred in patients with a secondary cause of osteoporosis. Prospective studies are needed to further explore the determinants of this severe complication of osteoporosis.

Keywords Cascade · Osteoporosis · Risks factors · Vertebral fractures

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Introduction

Vertebral fractures (VFs) are the most common osteoporotic fractures [1]; they are a strong risk factor for future fractures, and recurrent fractures are associated with increase in mortality. This increase in mortality is associated with both the number and the severity of the VFs [2, 3]. The presence of a VF greatly increases the risk of sustaining subsequent VFs, a phenomenon often referred to as "vertebral fracture cascade" (VFC) [4, 5]. However, there is no clear definition of this "cascade" either in the number of fractures or the period of observation. VFC has been reported in secondary causes of osteoporosis such as initiation of systemic glucocorticoids [6], Cushing disease [7], systemic mastocytosis [8], and pregnancy and lactation-associated osteoporosis [9]. Although the relationship has been debated [10], some studies suggest that vertebroplasty procedure is associated with an increased risk of recurrent and adjacent VFs [11–14].

Special interest has been paid recently to VFC as cases of multiple VFs have been reported after discontinuation of denosumab (rebound VFs) in postmenopausal osteoporosis and in patients receiving aromatase inhibitors [15–24]. In clinical practice, VFC is observed in other contexts than the discontinuation of denosumab.

To better understand this phenomenon of VFC, we prompted a retrospective multicenter study to describe the profile of patients with VFC and identify potential causes and risk factors of VFC.

Patients and methods

We contacted by email 50 rheumatologists, experts in bone diseases, through the French National Society of Osteoporosis (GRIO: Groupe de Recherche et d'Informations sur les Ostéoporoses), to inform them that we were conducting a retrospective observational study around VFCs that occurred between January 2016 and April 2017. In France, GRIO is the organization of experts in bone diseases, and the majority of French bone specialists are affiliated with it. We defined a VFC as an occurrence of at least three VFs within 1 year, with the last one occurring between January 2016 and April 2017. We voluntarily chose a stringent definition of VFC to better identify potential causes and risk factors of VFC. The VFC could be diagnosed by either standard X-rays, vertebral fracture assessment (VFA), computerized tomography (CT) scan, or magnetic resonance imaging (MRI). We excluded pathological (multiple myeloma, bone metastasis) and high trauma VFs. For tertiary care centers, patient records were retrieved from coding. All the files were reviewed and validated by a single physician (HC). The following data were collected: gender, age, weight, height, height at age 20, drug-induced osteoporosis intake, median number of VFs at VFC diagnosis, circumstances of VFC occurrence, family past medical history of fracture and osteoporosis, prevalent osteoporotic fractures, age of menopause, current smoking, excessive alcohol consumption, current intake of glucocorticoids, presence of comorbidities, previous intake of anti-osteoporotic treatment, biological assays performed to explore the causes of VFC, and bone mineral density (BMD) measurements. For our study, we asked the physician to define, according to them, the cause of osteoporosis associated with the VFC, even if they are multifactorial.

Statistical analysis

We performed a descriptive analysis of the observations. Qualitative data were described with numbers and percentages and quantitative ones with their minimum, maximum, median, and quartiles (Q) (Q1; Q3). The cause of osteoporosis associated with VFC was the one retained by the physician at the time of diagnosis.

Results

A total of 113 patients (median age of 73, 90 female patients (79.6%)) were included retrospectively within a period of 16 months; the median number of patients per center was 8.5 (3; 20).

A total of 35 rheumatologists answered to the email; 25 were interested in the study and agreed to participate, but 13 of them answered later that they cannot participate in the study because of the difficulty of finding all the patients who could match the inclusion criteria. Finally, 12 rheumatologists (11 practicing in a tertiary care hospital and 1 in an outpatient clinic, distributed throughout the country), in 10 different centers, participated to the study, and allowed one of us (HC) to have access to the anonymized records and to compile the study's files. Among the 15 rheumatologists who did not answer, 3 worked in tertiary care centers that were involved in the study. While considering gender in our population, we did not find anything noteworthy about men in the different risk factors, except that a larger proportion (39.1%) had excessive alcohol consumption.

A total of 105 (92.9%) patients had BMD measurements with a median T-score at femoral neck, total femur, and lumbar spine of − 2.4 (− 3.1; − 2.0), − 2.3 (− 2.9; − 1.5) and − 2.5 (− 3.4; − 1.8), respectively. Seventy-two (68.6%) had a T-score ≤− 2.5 at at least one site. Patients' characteristics are shown in Table 1.

Table 1 Characteristics of patients

Variables		DA (*n*)
Number of patients (*n*)	113	
Age, median	73 (63; 82)	113
Gender, female *n* (%)	90 (79.6)	113
Age of menopause, median (years)	50 (45; 52)	68
Weight, median (kg)	61 (53; 71)	98
Height, median (cm)	157.0 (151.5; 163.7)	99
Height at age 20, median (cm)	164.0 (160; 169)	61
Current smoking, *n* (%)	14 (13.5)	104
Excessive alcohol consumption, *n* (%)	12 (11.7)	103
First degree-family past medical history of hip fracture, *n* (%)	18 (18.6)	97
Previous major osteoporotic fracture, *n* (%)	45 (40.5)	111
Previous vertebral fracture before diagnosis of vertebral fracture cascade, *n* (%)	35 (30.9)	113
Current use of anti-osteoporotic treatment, *n* (%)	19 (17.1)	111
Previous anti-osteoporotic treatment, *n* (%)	35 (31.5)	111
T-score median (Q1; Q3)		105
-Femoral neck	− 2.4 (− 3.1; − 2.0)	
-Total femur	− 2.3 (− 2.9; − 1.5)	
-Lumbar spine	− 2.5 (− 3.4; − 1.8)	
Prevalence of osteoporosis (T-score ≤ −2.5 at at least one site), *n* (%)	72 (68.6)	105

Median (Q1; Q3)

SD standard deviation, *n* number, *DA* data available

Number of incident vertebral fractures in VFC

The median number of incident VFs over 1 year was 5 (4; 6). Most of them were diagnosed with standard X-rays (67.6%), MRI (56.8%), and CT scan (45.0%). At the time of the first spine imaging during the VFC, 64 patients had already had 3 recent VFs (≤ 1 year).

Incident VFs of the VFC more frequently occurred at the thoraco-lumbar junction: L1 (67.3%) followed by T12 (63.7%) and L3 (60.2%) (Fig. 1). In the 35 patients with prevalent VF (before VFC), the predominant localization of VFs was the same.

The median height loss between height at age 20 (historical) and at VFC diagnosis (measured) was 7 (5; 10) centimeters.

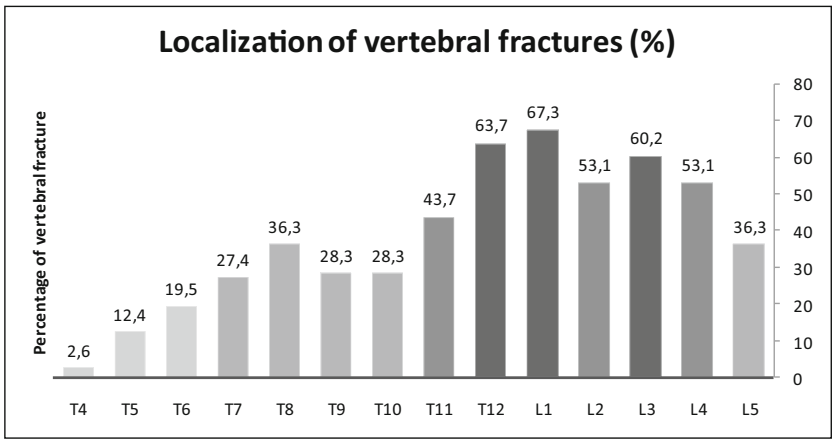

Fig. 1 Localization of vertebral fractures (both prevalent and incident VFs of the VFC). T = thoracic, L = lumbar, VFs = vertebral fractures, VFC = vertebral fracture cascade

Causes of the VFC

Assessment of the causes

Assessment of renal function, calcemia, phosphatemia, and 25-OH vitamin D were performed in all patients.

Other more frequent biological tests were serum electrophoresis protein ($n = 101$), parathyroid hormone ($n = 100$), and thyroid hormone ($n = 98$).

Other biological tests were performed to search rarer causes of secondary osteoporosis: serum or urinary cortisol ($n = 16$), testosterone (n = 10), serum tryptase ($n = 18$), celiac disease antibodies ($n = 16$), and serum ferritin ($n = 35$).

Additional imaging exams were bone scanning ($n = 32$), PET scanner ($n = 6$), bone marrow biopsy ($n = 7$), and bone biopsy of a VF ($n = 17$).

Causes according to the patients' physician

A secondary osteoporosis associated with the cascade was diagnosed in 52 patients (46.0%): glucocorticoid-induced osteoporosis ($n = 29$, 25.7%) and non-malignant hemopathies (mastocytosis, monoclonal gammopathy of skeletal significance) ($n = 7$, 6.2%). The other causes according to the physician were excessive alcohol consumption ($n = 5$, 4.4%), use of aromatase inhibitors ($n = 4$, 3.6%), primary hyperparathyroidism ($n = 3$, 2.7%), endogenous hypercorticism ($n = 3$, 2.7%), anorexia nervosa ($n = 3$, 2.7%), and pregnancy and lactation-associated osteoporosis ($n = 2$, 1.8%). In addition, 13 cases (11.8%) were associated with a recent vertebroplasty procedure. In two patients (1.8%), the physician considered withdrawal of denosumab as being the cause of the VFC. Twelve patients had several concomitant causes of secondary osteoporosis. Finally, either postmenopausal or idiopathic osteoporosis was diagnosed as the cause of the VFC in 61 patients (54.0%) by the physician.

Risk factors of fractures

Forty-five patients (40.5%) had a previous major fracture before the VFC including 35 prior VF (30.9%). Eighteen patients (18.6%) reported a family history of hip fracture.

Twenty (18.9%) patients were receiving oral glucocorticoids treatment at the time of the VFC, with a median daily dose of 10 mg of prednisone equivalent (5; 27.5) and a median time of treatment of 24 months (12.75; 61). Thirty-nine (37.1%) patients received systemic glucocorticoids in the past, with a median time of treatment of 24 months (12; 74). Information of period since discontinuation of glucocorticoids at the time of VFC was not available.

The main comorbidities were history of cancer ($n = 21$); chronic inflammatory diseases ($n = 33$) including rheumatoid arthritis ($n = 9$), asthma ($n = 8$), chronic obstructive pulmonary disease ($n = 8$), polymyalgia rheumatica ($n = 6$), and giant cell arteritis ($n = 2$); and diabetes mellitus ($n = 8$).

Finally, 14 patients (13.5%) were current smokers and 12 (11.7%) had an excessive alcohol consumption (> 2 units/day).

VFC was diagnosed in the context of a fall in 30 patients (28.8%), without being able to make a link between these falls and the occurrence of VF.

Use of an anti-osteoporotic treatment

A total of 35 (31.5%) patients previously received an anti-osteoporotic treatment before the occurrence of the VFC: 24 received oral bisphosphonates, 7 intravenous bisphosphonates (zoledronic acid), 10 denosumab, 5 teriparatide, 8 strontium ranelate, 6 hormonal replacement therapy, 4 raloxifene, and 1 odanacatib. Some patients had received several anti-osteoporotic treatments.

Nineteen patients (17.1%) were still receiving a treatment at the time of the VFC: 15 bisphosphonate, 2 teriparatide, and 2 denosumab.

In patients previously treated with anti-osteoporotic drugs, the incident VF occurred in a median time of 100 months (60; 120) and 45 months (33; 58.5) after discontinuation of oral bisphosphonates and strontium ranelate, respectively. VFC occurred, in three patients, a long time after teriparatide discontinuation (6 years, 4 years, and data not available for the three patients, respectively), with in-between other anti-osteoporotic treatment (bisphosphonates or strontium ranelate). No observations of VFC were made in patients who had just stopped teriparatide. In six patients (5.3%), VFC occurred early following discontinuation of an anti-osteoporotic treatment, in the year after the last dose effect was depleted: five after denosumab, and in one patient, 7 months after discontinuation of odanacatib. Among the five patients who had a VFC after denosumab discontinuation, three had prevalent VFs and one of them had not been treated with any anti-osteoporotic drug before denosumab (Table 2). In the patient who had a VFC after odanacatib discontinuation, no previous VF was detected; however, the patient had a celiac disease and a collagenous colitis that required glucocorticoid treatment. VFC occurred also later following discontinuation of an anti-osteoporotic treatment, in the second year after the last dose effect was depleted: three after denosumab and in one patient after 24 months of raloxifene withdrawal (Table 2).

Discussion

This is the first study which assesses the potential causes and risk factors of VFC, after the exclusion of pathological (multiple myeloma, bone metastasis) and high trauma VFs. Half of

Table 2 Patients with VFC early after anti-osteoporotic treatment discontinuation

	Age (years)	Location of VFs	Previous VF	Previous anti-OP TT	Previous TT by BP, name, duration, *period off-treatment*	TT with AI	Time between agent effect depletion and VFC*	T-scores FN TH LS
Early: in the first year after drug effect depletion								
Denosumab								
Patient 1	66	T10, T12, L1, L3, L4	Yes (T10, T12)	Yes	No	No	4 months	−3.1 −3.5 −4.1
Patient 2	64	T6, T7, T8, T9, T10, T11, T12, L1, L3	Yes (T8, T10)	Yes	Yes IBN, 5 years, *3 years*	No	6 months	−1.7 −0.65 −1.8
Patient 3	62	T11, T12, L1, L2, L3	No	Yes	Yes, ALN, 1 year, *NA*	No	6 months	−3.7 NA −2.2
Patient 4	58	T8, T10, T11, L1, L2, L3, L4, L5	No	No	No	Yes	4 months	−2.5 −0.9 −2.6
Patient 5	62	T7, T8, T10, T11, T12, L1, L2, L3, L5	Yes (L5)	Yes	Yes, ALN, 1 year, *7 years*	No	3 months	−1.0 −1.1 +1.0
Odanacatib								
Patient 1	79	T9, T12, L3	No	Yes	No	No	7 months	−2.4 −2.1 −3.1
Late: in the second year after drug effect depletion (supplementary analysis)								
Denosumab								
Patient 1	88	T12, L1, L3, L4, L5	Yes (T12, L4)	Yes	Yes, RIS, 12 years *1 year*	No	14 months	−4.0 −4.1 −1.3
Patient 2	80	L1, L2, L3, L4	Yes (L4)	Yes	Yes, IBN, 1 year ALN, 1 year *5 years*	No	14 months	−2.9 −3.0 −4.4
Patient 3	83	T5, T7, T8, L1	No	Yes	Yes ALN, 2 years RIS, 3 years ZOL, 1 year 5 years	No	18 months	−2.2 −3.5 −3.3
Raloxifene								
Patient 1	68	T9, T12, L1, L2, L3, L4, L5	Yes (T9)	Yes	Yes, HRT, *5 years*	No	24 months	−1.5 NA −2.8

BP bisphosphonates, *F* female, *OP* osteoporotic, *TT* treatment, *VFs* vertebral fractures, *VFC* vertebral fracture cascade, *AI* aromatase inhibitors, *T* thoracic, *L* lumbar, *NA* not available, *FN* femoral neck, *TH* total hip, *LS* lumbar spine, *IBN* ibandronate, *ALN* alendronate, *HRT* hormone replacement therapy

*Delay after a scheduled dose of treatment is omitted

the patients presenting with such a severe clinical event have no other cause other than underlying postmenopausal osteoporosis.

We observed these VFCs in a population of patients with underlying bone fragility, characterized by a high prevalence of low BMD and previous major osteoporotic fractures. The localization of the VFs, although numerous, was similar to the usual ones [25].

Our results confirm that the first cause of secondary osteoporosis in the context of VFC is the use of glucocorticoids. In our study, almost 20% of patients were receiving glucocorticoid treatments at the time of VFC with a median daily dose of

10 mg per day (5; 27.5), and more than one third had received glucocorticoids in the past.

The increase in fracture risk is immediate at the initiation of glucocorticoids, as early as 3 months, and reverses after discontinuation of glucocorticoids [26]. This can be related to the effects of glucocorticoids on bone remodeling previously uncoupled by the inflammation itself. The risk of fracture is mainly associated with recent glucocorticoid use [6]. Aromatase inhibitors used as drugs inhibiting sexual hormonal secretion or activity are also associated with an increased risk of fractures [27]. The profound suppression of biologically available estrogens has a deleterious effect on bone, and postmenopausal women receiving such treatments have increased bone resorption, decreased bone density, and increased risk of fractures. In our study, four patients received a treatment with aromatase inhibitors over 60–72 months: three did not have prior VF; two never had anti-osteoporotic treatment, one had treatment with denosumab (with VFC occurring 4 months after the last dose of denosumab was depleted), and one had an infusion of zoledronic acid (with VFC occurring 12 months after the infusion).

Non-malignant hemopathies are the second cause of VFC. Incidence of VFs is increased, 2.5-fold higher, in monoclonal gammopathies of skeletal significance (MGSS) or undetermined significance (MGUS) as compared to controls [28]. MGSS/MGUS represents a potentially pre-neoplastic condition that may progress to malignant B cell disorders. In MGSS/MGUS, a cytokine profile can lead to an uncoupling of bone remodeling with increased bone resorption contrasting with a reduction in bone formation [29].

In systemic mastocytosis, occurrence of nodular mast cell infiltrates in the bone marrow is associated with osteoporosis due to an increased osteoclastogenesis. The stimuli driving osteoclast activity are mostly to be the RANK-RANKL signaling although histamine and other cytokines may play a role. These patients present with spinal osteoporosis and VFs [30, 31]. In the absence of clinical signs, systemic mastocytosis should be suspected in young patients with osteoporosis or VFs without obvious cause and in patients with bone lesions of unknown origin [8, 32, 33]. Finally, few cases of VFC were reported in patients with endocrine diseases (endogenous hypercorticism, diabetes mellitus) [34, 35]. VFC was the circumstance of the diagnosis of a so far unknown primary hyperparathyroidism in one of our patients [36].

Some observations of VFC were reported after vertebroplasty [11–13, 37, 38]. However, the relationships between vertebroplasty and incident VFs remain debated as there are many confusing factors such as age, use of steroids, location at the thoraco-lumbar junction, osteoporosis, prior VFs, proximity to the initial fracture site, cement leakage into the discs, and vacuum clefts within the compression fracture [39]. We reported 13 patients with VFC after vertebroplasty; among them, 8 had VFs at proximity of procedure site, 6 had VFs at the thoraco-lumbar junction, 7 received corticosteroids, 8 had densitometric osteoporosis, and 5 had prior VFs.

In our study, patients with VFC had already bone fragility, as 40.5% and 30.9% of them had a history of major osteoporotic fracture and of prior VF, respectively; most of them did not receive any anti-osteoporotic treatment (68.5%). Diagnosis of VFC related to either primary postmenopausal or idiopathic osteoporosis was retained in 54% of patients. When considering population with primary postmenopausal or idiopathic osteoporosis, 38 in 61 (62.3%) had a history of major osteoporotic fracture and 23 in 61 (37.7%) had at least one previous VF. Previous VF is a marker of bone fragility and is associated with the onset of new VFs [5, 40–42]. The higher is the number of prevalent VFs, the higher is the risk of new VFs [5]. Indeed, in a study of patients with osteoporosis, receiving only calcium and vitamin D, 20% of patients sustained a new VF in the year following a VF [5].

In patients who received anti-osteoporotic treatment, VFC occurred more than 5 years after bisphosphonate discontinuation. This could be explained by the natural history of the disease. Likewise, after teriparatide discontinuation, VFC occurred more than 4 years later whereas patients were switched to another anti-osteoporotic treatment after teriparatide discontinuation. However, it seems difficult to impute occurrence of VFC to this bone anabolic therapy.

Nevertheless, a shorter time (less than 1 year) between the anti-osteoporotic treatment discontinuation and occurrence of VFC was observed in 5 patients treated with denosumab and in 1 patient treated with odanacatib.

Cases of patients with multiples VFs after denosumab withdrawal have been reported in postmenopausal osteoporosis and in patients receiving concomitant aromatase inhibitors [15–20]. Recent data in the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) trial and its extension showed cases of multiples VFs in the 6–12 months after denosumab discontinuation in 3.4% patients, and multiple VFs were also observed in 2.2% patients after placebo discontinuation. The risk of developing multiple VFs was 1.6 times higher with each additional year of off-treatment follow-up. The risk of sustaining a VF after discontinuation of denosumab was increased by prevalent VFs [19]. Rebound VFs have also been reported after 1 year [17]. We found three observations of VFC (two observations at 14 months and one at 18 months). However, the causality of drug discontinuation is decreased as time increases the proportion of VFs linked to the natural course of the disease with drugs without persistent effects. None of the eight patients who discontinued denosumab should have done so because BMD remained low or because of the history of fracture, reflecting either the patient's willingness to stop or the erroneous estimation of the need for a treatment by the caring physician.

VFC phenomenon could follow discontinuation of various potent osteoporosis therapies that produce major BMD increases but do not have persisting bone effects (i.e., non-bisphosphonates) [43]. One case report described a VFC (five new VFs in a patient with three prior VFs) in the 8 months following discontinuation of long-term odanacatib, a cathepsin K inhibitor. It has been reported rapid BMD loss following odanacatib discontinuation. These observations raise the question of effects of rebound fracture phenomenon after discontinuation of bone-active therapies [43].

We assessed potential causes which can act through a profound change in bone remodeling, mainly a huge increase in bone resorption. The paradigm of this mechanism is the discontinuation of some potent anti-resorptive drugs, suggesting that a rapid activation of osteoclast activity can precipitate the consequences of bone fragility [44]. However, we fully recognize that we did not assess another potential cause of the VFC phenomenon, the mechanical factors (such as changes in sagittal balance of the spine, increased thoracic kyphosis) that can play an important role in the occurrence of VFs [4, 45].

Our results should be interpreted with caution due to several limitations. We had a small sample size of participating rheumatologists and the restriction to one country (France), inducing a small sample size of patients, which could lead to potential selection bias. However, this was the first study designed to describe risk factors and potential causes of VFC and the number of cases of VFC was not that negligible. Although patients were mostly retrieved through medical record review, all the centers that participated had a software to find all patients, the research was exhaustive, and all the observations of VFC were controlled by a single investigator (HC) to check that the observations of VFC fulfilled the inclusion criteria.

The retrospective design of this study explains why some data were not collected or missing. We report only cases of VFC based on physicians' self-report. However, this was a descriptive study with difficulties to perform further statistical analyses as we just had at our disposal the data available on the medical records (no data on BMD determination conditions considering participating centers as experts in the field of osteoporosis, no data on quality of life, no data on circumstances of falls).

Finally, the definition of VFC was arbitrary as there was no consensual definition in the literature, especially no notion of number and delay of occurrence. We voluntarily chose a stringent definition in order to describe the most severe cases of VFC. Another important point is the notion of sequential fractures in VFC, with occurrence of separate fracture events within 1 year. However, this notion of sequence is sometimes difficult to highlight from the outset on the imaging at the same time.

Conclusion

VFC is a severe clinical event in patients with bone fragility. Only half of patients have an identified cause. Prospective studies are needed to further explore the determinants of such a severe complication of osteoporosis.

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Compliance with ethical standards

Conflicts of interest Dr. Breuil received grant support and lecture fees from Amgen, Novartis, Chugai, and Lilly. Dr. Briot has received research grants or honoraria from Amgen, Lilly, Medtronic, and MSD. Dr. Cortet has received research grants or honoraria from Amgen, Expanscience, Ferring, Lilly, Medtronic, MSD, Mylan, Novartis, Roche diagnostics, Théramex, and UCB. Dr. Thomas received grant support, lecture fees, and consulting fees from Amgen, Merck Sharp & Dohme, and UCB Pharma; grant support and lecture fees from Chugai and Pfizer; consulting fees from Expanscience, Gilead Sciences, LCA, Thuasne, and Medac; grant support and consulting fees from HAC Pharma; grant support from Novartis; lecture fees from AbbVie, Biogen, and Bristol-Myers Squibb; and lecture fees and consulting fees from Eli Lilly and Teva Pharmaceutical Industries. Dr. Roux has received grants and/or honoraria from Alexion, Amgen, MSD, UCB. Dr. Che, Dr. Paccou, Dr. Chapuis, Dr. Debiais, Dr. Mehsen-Cetre, Dr. Javier, and Dr. Loiseau Peres have no disclosure to declare.

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