Prevalence of silent nontraumatic vertebral fracture in rheumatoid arthritis: relation with disease duration, disease activity, corticosteroid, and hip buckling ratio

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Objectives

To detect the prevalence of silent nontraumatic vertebral fractures (VFs) in patients with rheumatoid arthritis (RA) and its relation with disease duration, disease activity, corticosteroid (CS), and hip buckling ratio (BR).

Patients and methods

This cross-sectional study included a total of 150 RA patients. Disease activity was assessed using Disease Activity Score-28 (DAS-28). Dual-energy x-ray absorptiometry (DXA) was used to detect bone mineral density (BMD), VFs by vertebral fracture assessment (VFA), and hip BR by hip structural analysis program.

Results

A total of 17 (11.33%) RA patients had 27 silent VFs. Of the 17 VFs patients, 11 and six patients had single and multiple VFs, respectively. Of the 27 VFs, nine and 18 VFs had mild and moderate degree of VF. VF cases were significantly older in age ($P = 0.001$), had longer disease duration ($P < 0.001$), more active DAS-28 ($P < 0.001$), more cumulative CS dose, decreased spinal BMD ($P = 0.02$), and increased BR ($P = 0.001$). There were statistically significant relation between VFs and disease duration, DAS-28 and BR ($P < 0.001$ for all). VFs were independently associated with increased cumulative CS dose, high disease duration, and increased DAS-28 score ($P < 0.001$).

Conclusion

VFA-DXA should be performed on all RA patients. VF cases were significantly older in age, had long-standing disease duration, increased disease activity, reduced spinal BMD, increased cumulative CS dose, and increased BR. VFs were significantly related to increased disease duration, increased disease activity score, and increased BR of more than 10.

Keywords:
disease activity, osteoporosis, rheumatoid arthritis, vertebral fracture assessment

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic polyarticular inflammatory disease that not only involves joints but also affects several organs, and is associated with excessive disability, mortality, and morbidity [1]. RA has an increased risk of osteopenia and osteoporosis (OP) [2], which are usually complicated by fragility fractures [3] found in the areas characterized by large amounts of trabecular bone, such as the vertebrae [4]. Vertebral fractures (VFs) usually occur without a definite trauma [5], and about one-third is clinically obvious [6]. Several studies have shown that the risk of VFs or hip fractures is higher in RA patients than in those with primary OP [7–10].

The cause of OP in RA is multifactorial, with inflammation, inactivation, and the use of corticosteroids (CS) contributing to decreased bone mineral density (BMD) [11]. The inflammatory process of RA, with the release of interleukins 1 and 6, tumor necrosis factor α, and interferon γ, probably increases bone loss [12]. CS is usually prescribed for those with severe disease activity. CS is known to uncouple bone formation and resorption leading to OP [13]. It decreases the intestinal absorption and increases the renal excretion of calcium. In addition, it inhibits osteoblast proliferation. The effects of CS depend on the duration and dose of therapy [10].

Vertebral fracture assessment (VFA) is a relatively new utility for diagnosing VF by using dual-energy x-ray absorptiometry (DXA) imaging of the lateral dorsal and lumbar spine [14]. Hip structural analysis, mostly applied on images created by DXA, is used to assess the hip strength indices, based on hip geometric measures in the proximal femur [15], and would enhance fracture prediction for the hip [16]. This method extracts data on cross-sectional geometry from certain regions of interest, one of them being the narrow neck (NN). One of these hip strength measures is the buckling ratio (BR), which is an index of cortical instability

under compression. Moreover, it is thought that with BR of more than 10 a precipitous loss of strength may occur with local buckling [17].

The primary purpose of this study was to detect the prevalence of silent nontraumatic VFs in RA and its relation with disease duration, disease activity, CS, and hip BR.

Patients and methods

Patients

A cross-sectional study included a total of 150 premenopausal RA patients who fulfilled the 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA [18]. The inclusion criteria included patients with adult-onset RA, with at least 1 year of disease duration, without back pain or history of back trauma. Patients with other comorbidities, including endocrine diseases, lung, heart, kidney or liver failure, malignancy, severe osteoarthritis of the spine, or unable to keep the correct DXA scanning position, were excluded from the study. All patients provided written informed consent before their inclusion, and the study was approved by the local ethical committees and in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Taking detailed history and clinical examination, including general and articular examination, were conducted on all patients. Demographic data including patients' age and disease duration were reported. Body weight, height, and BMI (kg/m^2) were measured and calculated in all participants. At the time of the study, all patients were administered methotrexate at a dose ranging between 12.5 and 15 mg/week, leflunomide 20 mg/day, hydroxychloroquine 400 mg/day, calcium carbonate 500 mg/day, and vitamin D 400 IU/day. The cumulative prednisone dose (or its equivalent) during the last year was calculated in all patients in g/year. None of our patients underwent biologics or OP therapy that includes bisphosphonates, calcitonin, hormone replacement, selective estrogen receptor modulator, parathormone, and strontium ranelate. Routine laboratory investigations including complete blood picture, liver and kidney functions, complete urine analysis, erythrocyte sedimentation rate (ESR), determined by the Westergren method, rheumatoid factor (considered positive if it is > 20 IU/ml), determined by the nephelometric method and anticyclic citrullinated polypeptide (anti-CCP, considered positive if it is ^{3}5 U/ml), determined by microparticle enzyme immunoassay, were measured in all patients.

Disease activity assessment: Modified 28-joint Disease Activity Score (DAS-28) was calculated using three variables: the 28 tender and swollen joints count (TJC-28and SJC-28) and ESR (mm/first hour) according to formula by Prevoo *et al.* [19]: DAS-28 = (0.56 × √TJC-28 + 0.28 × √SJC-28 + 0.70 × Ln ESR) × 1.08 + 0.16. Patients were considered for remission if DAS-28 less than 2.6, low disease activity if DAS-28 less than 3.2, moderate disease activity if DAS-28 between 3.2 and 5.1, and high disease activity if DAS-28 more than 5.1 [19].

DXA

Lunar Prodigy DXA (GE Lunar Corp., Madison, Wisconsin, USA) was used in the present study. The patient's examination and the quality assurance scans were conducted according to the manufacturer's recommended guidelines. The reports were reviewed by two expert radiologists to ensure accurate report analysis.

BMD, femoral NN geometry, and BR measures: EnCore software version 11.40.004 (GE-Healthcare, Madison, WI, USA) enables the DXA machine to measure BMD at the hip, lumbar spine, and distal forearm, as well as to measure the femoral NN geometry, using the HAS program. This program helps to measure the total, trabecular, and cross-sectional areas (CSA), the subperiosteal and trabecular radii, and to measure the cortical thickness. These measurements are crucial to calculate hip strength indices, one of them being BR. BR is calculated as *Y*/cortical thickness, where *Y* (cm) is the maximum distance between the centroid and the superior outer cortical neck margin [17].

VFA is a utility used by DXA for lateral spinal imaging, performed at the time of BMD measurements, to diagnose VFs from T4 to L4, according to Genant's semiquantitative method [20]. Vertical height of a vertebral body was measured at its anterior, middle, and posterior margins. If any of these measurements differ from each other or differ from the same measurements in the supra-adjacent or subadjacent vertebrae by 20% or more, the vertebra is considered to have a fracture deformity provided that congenital, developmental, or degenerative causes are excluded. The severity of VF is graded as follows: mild in 20–25%, moderate in 26–40%, and severe in more than 40% loss of heights. VFs detected by VFA were confirmed by plain dorsolumbar radiograph.

Statistical analysis

Data were analyzed using statistical package for the social sciences version 19 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were summarized as mean ± SD and categorical variables as frequency (%). Independent student *t*-test was used to determine

the significance of differences between VF-RA cases and other RA patients without VF at *P*-value of less than 0.05. Associations between categorical groups were tested using the χ^2-test, with Yates correction or Fisher's exact test as appropriate. Pearson correlation test was used as a measure of association of quantitative variables. Two-tailed *P*-values of 0.05 or less were considered to be statistically significant. Stepwise regression analysis was used to study the risk factor independently associated with VFs.

Results

Patients

The present study included 150 premenopausal adult-onset RA patients with at least 1 year of disease duration. Their mean BMI (30.05 ± 6.93 kg/m^2) classified them in the obese category. Their mean DAS-28 (3.56 ± 0.99) showed moderate disease activity. They had high titer of both rheumatoid factor (88.16 ± 130.74) and anti-CCP (118.5 ± 116.62). Detailed demographic, clinical, and laboratory data, as well as the cumulative CS dose of patients, were shown in Table 1.

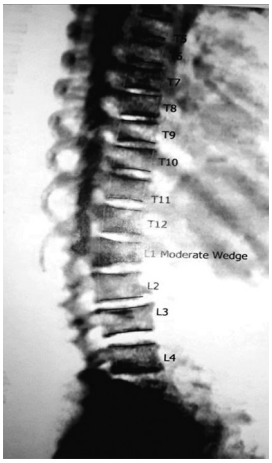
BMD, femoral NN geometry, and BR measures

The mean T-scores of the three examined sites, the hips, spine, and distal radius, were in the osteopenic range, as shown in Table 2.

VFA

Of the 150 RA patients, 17 (11.33%) had 27 VFs. Eleven (64.7%) patients had single VF, and six (35.3%) patients had multiple VFs. Of the 27 VFs, nine (33.3%) had mild VF, and 18 (66.7%) had moderate VF (Figs. 1 and 2).

Figure 1



Lateral morphometry using DXA, showed RA patient with moderate wedge fracture of L1.

According to the presence or absence of VFs, patients were subdivided into two groups. VF cases were significantly older in age (*P* = 0.001), had longer disease duration (*P* < 0.001), more active DAS-28,

Table 1 Demographic, clinical and laboratory data, and cumulative CS dose of RA patients

Variables	Range	Mean ± SD
Age (years)	25–52	43.11 ± 6.84
Body weight (kg)	37–130	75.37 ± 17.76
Height (m)	1.43–1.79	1.58 ± 0.068
BMI (kg/m^2)	16.41–50.8	30.05 ± 6.93
Disease duration (years)	1–31	9.01 ± 6.73
TJC-28	0–7	1.72 ± 1.78
SJC-28	0–4	0.77 ± 1.16
DAS-28	1.73–5.47	3.56 ± 0.99
ESR (mm/first hour)	8–80	35.63 ± 16.99
RF (IU/ml)	0–648	88.16 ± 130.74
Anti-CCP (U/ml)	0–416.3	118.5 ± 116.62
Cumulative CS dose in last year (g)	0.35–7.5	1.88 ± 1.28)

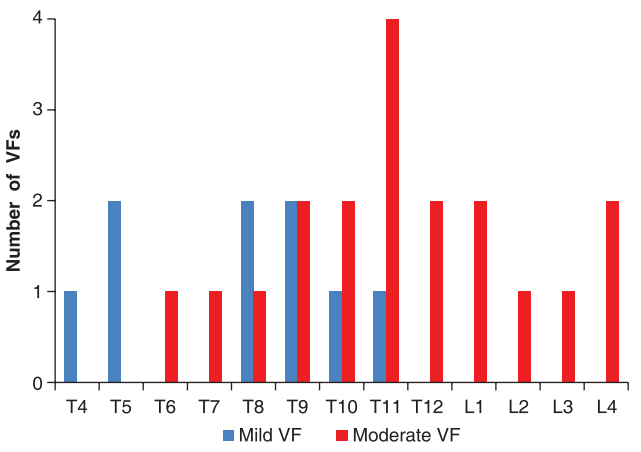
Anti-CCP, anticitrullinated polypeptide; CS, corticosteroid; DAS-28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC-28, 28 swollen joint count; TJC-28, 28 tender joint count.

Table 2 BMD, geometric hip measurement, and BR of RA patients

Variables	Mean ± SD
BMD	
T-femur	−1.36 ± 1.23
T-spine – AP	−1.82 ± 1.44
T-spine – Lat	−1.30 ± 1.58
T-radius	−2.14 ± 1.97
Geometric hipmeasurements	
CSA (cm^2)	1.2 ± 0.25
CT (cm)	0.17 ± 0.03
BR	10.15 ± 2.78

AP, anteroposterior view; BMD, bone mineral density; BR, buckling ratio; CSA, cross-sectional area; CT, cortical thickness; Lat, lateral view; RA, rheumatoid arthritis.

Figure 2



Severity and distribution of vertebral fractures (VFs) from T4 to L4.

and its three components (P < 0.001 for all), more cumulative CS dose (P < 0.001), and reduced spinal T-scores, either the anteroposteriorly or laterally (P = 0.02 and 0.04, respectively). Moreover, VF cases had significantly reduced CSA and CT (P < 0.001) and increased BR (P = 0.001). Detailed comparison is shown in Table 3.

The increased VFs' prevalence was significantly related to increased disease duration, increased disease activity, and increased BR. In our cohort study, there was a significant relation between the VFs' prevalence and disease duration using the χ^2-test (P < 0.001). It was found that 4.65% (two patients), 19% (four patients), and 42.3% (11 patients) with more than 5, 10, and 15 years of disease duration had VFs, respectively. On the contrary, of those with VFs, 11.7% (two patients), 23.5% (four patients), and 64.7% (11 patients) had disease duration more than 5, 10, and 15 years, respectively. None of our patients with less than 5 years of disease duration had VF, as shown in Table 4 and Fig. 3.

In addition, in our cohort study, there was a significant relation between the VFs' prevalence and DAS-28 using the χ^2-test (P < 0.001). About 56.25% (nine patients) of our RA patients with high DAS-28 score had VFs. On the contrary, of the VF cases, 53 and 47% had high and moderate disease activity state, and none of the VF cases had either remission or mild disease activity as shown in Table 4 and Fig. 4.

There was a statistically significant relation between VFs prevalence and increased BR (BR > 10) using χ^2-test (P < 0.001). Of the total number of VFs, 94% cases had BR more than 10 versus 24.6% of the non-VF cases (Table 4).

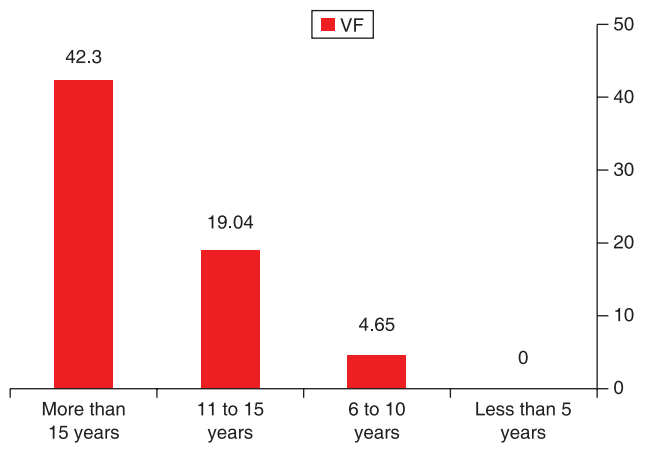
According to the WHO classification of the BMD, 16.7 and 10.3% of the cohort with OP and osteopenia had VFs, respectively. However, it was not statistically significant by using χ^2 (P = 0.073). In contrast, of the VFs, OP and osteopenia were found in 11 (64.7%) and

Table 3 Comparison of means of different variables between the VF and non-VF RA cases

Variables	VF (n = 17)	Non-VF (n = 133)	P
Age (years)	48.25 ± 5.55	42.45 ± 6.73	0.001
Body weight (kg)	73.47 ± 20.04	75.61 ± 17.52	0.68
Height (m)	1.58 ± 0.07	1.58 ± 0.07	0.74
BMI (kg/m^2)	29.38 ± 7.28	30.14 ± 6.9	0.69
Disease duration (years)	18.65 ± 6.74	7.78 ± 5.67	<0.001
TJC-28	3.65 ± 1.5	1.47 ± 1.67	<0.001
SJC-28	2.23 ± 1.2	0.59 ± 1.01	<0.001
DAS-28	4.66 ± 0.62	3.42 ± 0.93	<0.001
ESR	52.41 ± 16.52	33.49 ± 15.86	<0.001
RF (IU/ml)	173.54 ± 151.03	66.81 ± 117.3	0.031
Anti-CCP (U/ml)	225.46 ± 101.27	82.82 ± 98.97	<0.001
Cumulative CS dose in last year (g)	4.63 ± 1.41	1.52 ± 0.7	<0.001
BMD			
T-femur	−1.74 ± 1.16	−1.27 ± 1.25	0.13
Z-femur	−0.95 ± 0.88	−0.8 ± 0.99	0.52
T-spine – AP	−2.66 ± 1.41	−1.71 ± 1.42	0.02
Z-spine – AP	−1.62 ± 1.02	−1.13 ± 1.21	0.09
T-spine – Lat	−2.01 ± 1.33	−1.2 ± 1.6	0.04
Z-spine – Lat	−0.74 ± 1.1	−0.38 ± 1.4	0.24
T-radius	−1.91 ± 2.63	−2.16 ± 1.87	0.72
Z-radius	−0.92 ± 2.57	−1.56 ± 1.75	0.35
Hip geometry			
CSA (cm^2)	1 ± 0.17	1.24 ± 0.25	<0.000
CT (cm)	0.13 ± 0.02	0.17 ± 0.03	<0.000
BR	12.34 ± 2.4	9.8 ± 2.66	0.001

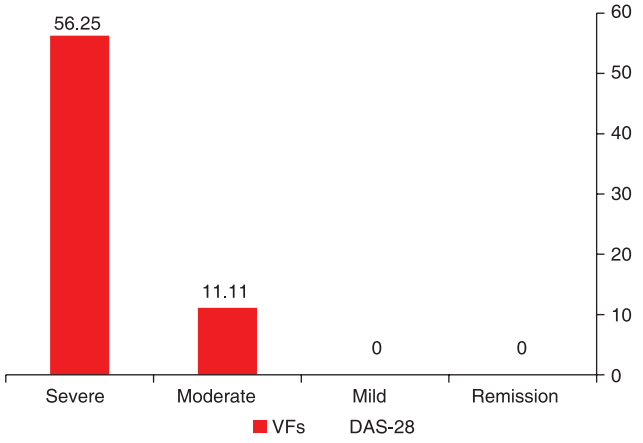
Anti-CCP, anticitrullinated polypeptide; AP, anteroposterior view; BMD, bone mineral density; BR, buckling ratio; CS, corticosteroid; CSA, cross-sectional area; CT, cortical thickness; DAS-28, 28 joints disease activity score; ESR, erythrocyte sedimentation rate; Lat, lateral view; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC-28, 28 swollen joint count; TJC-28, 28 tender joint count; VF, vertebral fracture.

Figure 3



Vertebral fractures (VFs) prevalence and disease duration.

Figure 4



Vertebral fractures (VFs) prevalence and 28-joint Disease Activity Score (DAS-28).

Table 4 Relation between VFs and disease duration, DAS-28, and BMD

Variables	VF [*n* (%)]	Non-VF [*n* (%)]	*P*
Disease duration (years)			
0–5	0	60 (100)	<0.001
6–10	2 (4.65)	41 (95.35)	
11–15	4 (19)	17 (81)	
>16	11 (42.3)	15 (57.7)	
DAS-28			
Remission	0	29 (100)	<0.001
Mild	0	33 (100)	
Moderate	8 (11.11)	64 (88.89)	
High	9 (56.25)	7 (43.75)	
BMD			
Normal	0	26 (100)	0.073
Osteopenia	6 (10.35)	52 (89.65)	
OP	11 (16.7)	55 (83.3)	
BR			
BR>10	16 (94)	32 (24.6)	<0.001

BMD, bone mineral density; DAS-28, 28 joints' disease activity score; VF, vertebral fracture; BR, buckling ratio.

six (35.3%) patients, respectively, and none had normal BMD as shown in Table 4.

Stepwise regression analysis showed that the presence of VFs was independently associated with increased cumulative CS dose, high disease duration and increased DAS-28 score.

Discussion

VFs are the most common but least recognized type of fragility fracture [5]. Although the spinal radiograph is the gold standard diagnostic tool for VF, VFA-DXA offers more advantage over radiograph being carried out at the time of BMD assessment, with a lower cost and radiation dose and with more patients' convenience. In our study, all VFs detected by spinal radiograph are also detected by VFA. This came in accordance with the previous studies [11,21].

In our study, the prevalence of silent VFs was 11.33% (17 of the 150 patients) in RA patients. Our result was less than detected by de Nijs *et al*. [10], who found VFs in 25% of the 205 RA patients on CS, and in 13% of another 205 RA patients, not on CS. In addition, El Maghraoui *et al*. [11], detected 36% VF prevalence among their RA cohort. This difference in the prevalence between ours and others might be because of the younger age group of our patients being premenopausal. The mean age of our patients was 43.11 years old, whereas in a study by de Nijs *et al*. [10] the mean age was 65 years, and in a study by El Maghraoui *et al*. [11] it was 49.4 years old.

VF cases were significantly older in age ($P = 0.001$), had longer disease duration ($P < 0.001$), more active disease ($P < 0.001$), and hence had more cumulative CS dose ($P < 0.001$), with reduced spinal T-scores, either the anteroposteriorly or laterally ($P = 0.02$ and 0.04, respectively). This came in accordance with a previous study by El Maghraoui *et al.* [11] who showed same significant older age ($P = 0.004$), longer disease duration ($P < 0.001$), more active disease ($P < 0.001$), and hence had more cumulative CS dose, with reduced spinal T-scores ($P < 0.001$) in RA patients with VFs. In addition, our finding met with previous studies that confirmed significant older age among RA patients with VFs [9,23].

In our cohort study, there was a significant relation between the VF prevalence and disease duration ($P < 0.001$). It was found that more than 31% who had more than 10 years' disease duration had VFs and more than 88% of VFs had disease duration more than 10 years. This came in accordance with previous studies [11].

There was a significant relation between the VFs' prevalence and DAS-28 state ($P < 0.001$). About 56.25% of our RA patients with high DAS-28 had VFs. On the contrary, of the total number of VF cases, 53 and 47% had high and moderate disease activity state, and none of the cases had either remission or mild disease activity. Haugeberg *et al.* [2] found a significant relationship between disease activity and the presence of VFs, which met our finding [2].

BR is an index of susceptibility to local cortical buckling under compressive loads and has been shown to be elevated in hip fracture cases [23,24]. Our VF cases had significantly reduced femoral NN CSA and CT ($P < 0.001$) and increased BR ($P = 0.001$). This came in accordance with Wright *et al.* [25] who found a significant reduction in femoral NN CSA and CT in their large cohort study in RA. In addition, this came in accordance with Elwakd *et al*. [26], who found a significant reduction in femoral NN CSA and CT and increased BR in post-menopausal with VFs in comparison with non-VF cases. At the same time, there was a statistically significant relation between the elevated BR (BR > 10) and VFs ($P < 0.001$). Of the number of VF cases, 94% had BR more than 10. On the contrary, 32.65% of those with BR less than 10 had VFs. These finding might give an insight into exposing the hips to the fragility fractures in VF cases and highlighting the importance of calculating BR.

About -13.7% of the RA cohort with OP and osteopenia had VFs. However, it was not statistically significant ($P = 0.073$). In contrast, none of the VF cases had normal BMD. All VF cases had either OP or osteopenia and this came in accordance with previous studies [25,26].

Our regression analysis showed that VFs were independently associated with increased cumulative CS dose, high disease duration, and increased DAS-28 score. However, El Maghraoui *et al.* [11] stated that VFs were independently associated with increased low weight and total hip T-score, and long disease duration.

There were no statistically significant differences between the mean height and BMI between those with and without VFs. This might be because of the presence of one-third of patients had single VF and also one-third had mild VF, and none had severe VFs that help in the height and BMI reduction.

In conclusion, silent VFs were detected in 11.33% of premenopausal RA female patients by using VFA-DXA. VF cases were significantly older in age with long-standing disease duration, increased disease activity, reduced spinal BMD, and associated with increased cumulative CS dose. VFs were significantly related to increased disease duration, increased disease activity score, and increased BR of more than 10.

Recommendations

VFA-DXA should be performed on all RA patients at the same time for measurement of BMD to diagnose the silent VFs. Early control of the disease is important to control the disease activity, and to minimize the steroid dose to reduce the prevalence of VFs. Assessment of the hip BR might be important to discover the possibility of hip fragility.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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