


# Vertebral fracture risk in glucocorticoid-induced osteoporosis: the role of hypogonadism and corticosteroid boluses

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## ABSTRACT

**Objective** The aim of this study was to identify the risk factors associated with fragility fracture (FF) development in glucocorticoid (GC)-treated patients.

**Methods** 127 patients (aged 62±18 years, 63% women) on GC-treatment (mean dose 14.5±14.1 mg/day and duration 47.7±69 months) were included. The clinical data collected included bone metabolism study (including gonadal axis), GC-treatment, disease activity, dual-energy X-ray absorptiometry analysis (evaluating densitometric osteoporosis (OP) and trabecular bone score (TBS) degraded microarchitecture values (DMA)), X-ray (assessing vertebral fractures (VF)), FRAX risk (GC-adjusted) and previous FF.

**Results** 17% of the patients had VF, 28% FF (VF and/or non-VF), 29% OP and 52% DMA. Patients with VF received more GC boluses (57.1% vs 29.5%,  $p=0.03$ ), were older (68±13 vs 60±19 years,  $p=0.02$ ), postmenopausal (100% vs 67%,  $p=0.02$ ), had low testosterone levels (57% vs 11%,  $p=0.02$ ), lower TBS values (1.119±0.03 vs 1.237±0.013,  $p<0.001$ ) and higher FRAX risk (17.2±16 vs 9.3±7.6,  $p=0.003$ ). Patients with FF showed higher accumulated GC doses (16.6±18.4 vs 11.1±12.9 g,  $p=0.046$ ). On multivariate analysis, hypogonadism (OR 12.38; 95% CI 1.85 to >100,  $p=0.01$ ) and having received GC boluses (OR 3.45; 95% CI 1.04 to 12.15,  $p=0.01$ ) were the main factors related to VF. Hypogonadism (OR 7.03; 95% CI 1.47 to 38.37,  $p=0.01$ ) and FRAX >20 (OR 7.08; 95% CI 1.28 to 53.71,  $p=0.02$ ) were factors related to FF.

**Conclusion** Hypogonadism is the principal risk factor for developing fractures in GC-treated men and women, whereas receiving GC boluses is a major factor for VF. These results indicate the importance of evaluating the gonadal axis in these patients.

## INTRODUCTION

Glucocorticoids (GCs) constitute one of the principal treatments of chronic inflammatory disorders, including several rheumatic diseases, with more than 1% of the general adult population receiving chronic GC

## Key messages

### What is already known about this subject?

▶ Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis. Fractures in GIO frequently occur with higher bone mineral density (BMD) than expected and typically at the beginning of glucocorticoid (GC) treatment, complicating the identification of patients at risk for fracture.

### What does this study add?

▶ This study analyses the risk factors associated with the presence of fragility fractures in GC-treated patients. Hypogonadism (menopausal women or low testosterone levels in men) and having a FRAX score for a major osteoporotic fracture >20 were the main factors related to the presence of fragility fractures, whereas patients with only vertebral fractures (VF) more frequently were hypogonadal and had received GC boluses.

▶ Patients with degraded microarchitecture in trabecular bone score (TBS) (values <1.230) have a threefold increased risk of VF.

### How might this impact on clinical practice?

▶ As hypogonadism is the principal risk factor for developing fractures in GC-treated men and women, study of the gonadal axis in these patients should be taken into consideration in clinical practice. In addition, our results highlight the need to evaluate preventive antiosteoporotic treatment in these subjects, especially when receiving GC bolus(es).

▶ Evaluation of TBS and FRAX can improve the identification of high risk subjects, and thus, the therapeutic approach.

treatment.<sup>1–5</sup> Prolonged and/or high-dose treatment can be associated with several adverse effects, such as the development of osteoporosis (OP) and fractures. Indeed,



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glucocorticoid-induced osteoporosis (GIOP) is one of the most frequent causes of secondary OP and is present in up to 30–50% of the GC-treated patients. Age, GC doses and treatment duration are the main factors related to its development.<sup>1–6</sup> Nonetheless, despite the frequency of this complication, GIOP remains underdiagnosed and thereby under-treated, with <30% of the affected subjects receiving antiosteoporotic treatment.<sup>1–5</sup> This phenomenon may be partly explained by the special characteristics of GIOP. Thus, GC-treated patients have a high risk of fractures, particularly vertebral fractures (VF). Indeed, the development of VF is markedly increased in early periods of GC therapy, especially when high GC doses are used.<sup>1–7</sup> In addition, although low bone mineral density (BMD) is a well-known factor for developing fractures in GC-treated subjects, VF frequently occur with relatively normal BMD values, making identification of high-risk subjects difficult.<sup>1–6 8 9</sup> In this sense, our group recently reported the utility of including trabecular bone score (TBS) measurement to improve the evaluation of patients at risk of fracture in this cohort of patients.<sup>10 11</sup> The identification of patients at risk is also difficult using other assessment tools such as the FRAX algorithm, which must be adjusted for GC doses to improve its predictive yield.<sup>3</sup> Moreover, whereas menopausal status seems to be an additional risk factor for fracture development in these subjects, the role of hypogonadism in males with GIOP has been scarcely analysed.<sup>12</sup>

VF constitute the most common type of fracture in GIOP, affecting up to 50% of the GC-treated patients.<sup>1–5</sup> These fractures are frequently overlooked and thus, underdiagnosed, making identification of these patients even more difficult.<sup>13–15</sup> Thus, it is crucial to improve the identification of subjects treated with GC at high risk for fracture and in whom preventive antiosteoporotic therapy would be indicated.

Therefore, the aim of this study was to analyse the clinical characteristics and identify the risk factors associated with the development of fragility fractures (FFs), particularly VF, in GC-treated patients. We evaluated not only clinical factors but also dual-energy X-ray absorptiometry (DXA) measurements (BMD and TBS) and biochemical parameters of bone metabolism.

## METHODS

### Study design

We conducted a cross-sectional study from August 2017 to April 2018 including consecutive adult patients on chronic GC treatment ( $\geq 5$  mg/day of prednisone or equivalent, for  $>3$  months) for a rheumatological autoimmune disease.

All patients provided written informed consent to participate and the study was approved by the Ethics Committee of the Hospital Clínic (Reg. HCB/2017/0457).

## Assessments

Clinical assessment included medical history focusing on OP risk factors, the presence of menopause (defined as the cessation of menstruation for  $\geq 12$  months and considered as the presence of hypogonadism in women), self-reported history of low-impact trauma fractures (including location), falls in the previous year, autoimmune disease duration and activity, previous and/or present antiosteoporotic treatment, GC doses (daily current dose, duration, cumulative, maximum GC dose and bolus administration of prednisone or equivalent received) and the use of additional immunosuppressant agents. Anthropometric data (height, weight, body mass index (BMI,  $\text{kg}/\text{m}^2$ )) were also collected. Additionally, FRAX (GC-adjusted<sup>3</sup>) scores were calculated.

Blood samples were obtained between 08:00 and 10:00 after overnight fasting, and included acute phase reactants (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)), serum creatinine, glomerular filtration rate (GFR), total alkaline phosphatase, calcium, phosphate, thyroid function test, plasma parathyroid hormone (PTH) and serum 25-hydroxyvitamin D (25(OH)D) levels (determined by Atellica Solution (Siemens Healthineers, Tarrytown, NY, USA) and Liaison analyser (DiaSorin, Saluggia, Italy), respectively). Additionally, gonadotropins and total testosterone were measured in men (determined by Atellica Solution (Siemens Healthineers) and Roche Elecsys testosterone II assay with the Cobas e601 analyser (Roche Diagnostics, Mannheim, Germany), respectively). Hypogonadism was defined by testosterone levels  $<250$  ng/dL.<sup>16</sup> Biochemical bone turnover markers were also analysed, including serum procollagen type I amino-terminal propeptide, as a marker of bone formation, and the cross-linked C-terminal telopeptide of type I collagen, as a marker of bone resorption, both measured with the Cobas e601 analyser (Roche Diagnostics).

BMD ( $\text{g}/\text{cm}^2$ ) of the lumbar spine, femoral neck and total hip was assessed by DXA (Lunar Prodigy, General Electric Medical Systems, WI, USA). The coefficients of variation for total femur and lumbar spine in our centre are 0.6 and 0.8, respectively. Densitometric OP was defined according to the WHO criteria with T-score values  $\leq -2.5$  (in subjects  $\geq 50$  years) or Z-score values  $< -2$  (in subjects  $< 50$  years).<sup>17–19</sup>

The TBS was calculated using TBS iNsite software (version 3.0.2.0) (Medimaps group, Geneva, Switzerland) on the DXA lumbar spine images. A TBS value  $< 1.230$  was considered as degraded microarchitecture (DMA).<sup>10 20</sup>

Standard radiographs of the thoracic and lumbar spine were obtained to analyse the presence of VF. A VF was defined as a reduction of 20% or more in the anterior, middle or posterior height of the vertebral body compared with adjacent, undeformed vertebrae.<sup>21</sup>

## Statistical analysis

Statistical analyses were performed using R v3.5.3 (R Core Team, 2019).<sup>22</sup> Quantitative variables were described using mean and SD, whereas frequencies and percentages

were reported for qualitative variables. We analysed the factors for VF and also for all FFs, the latter including VF plus previous non-VF fractures (VF and/or non-VF). The association with qualitative covariates was assessed using the  $\chi^2$  test and Fisher's exact test when applicability conditions were not met. Adjusted ORs and p values were obtained by applying logistic regression models. The association with quantitative covariates was assessed by comparing the means using t-tests. Linear models were used when adjustment for confounding covariates was needed. Results were considered as significant if  $p < 0.05$  except for the case of multivariate model analysis where a  $p < 0.1$  was considered as sufficient to keep the covariates in the model.

## RESULTS

A total of 127 patients (63% women, 72.5% being postmenopausal) with a mean age of  $61.5 \pm 17.9$  years (range 18–89) on chronic treatment with GC were included. The mean GC dose at inclusion was  $14.5 \pm 14.1$  mg/day of prednisone, received during  $47.7 \pm 68.9$  months (range 3–348). The most frequent associated autoimmune diseases were systemic vasculitis (43%), polymyalgia rheumatica (19%), inflammatory myopathies (12%) and systemic lupus erythematosus (8%), with other miscellaneous disorders in the remaining patients (18%). Among the latter, there were very few patients with rheumatoid arthritis (RA) due to the low GC doses currently used. Twenty-one patients (17%) had VF, and 36 (28%) had any FF (VF and/or non-VF), being the radius, tibia, humerus and metatarsal stress fractures the most frequent non-VF. Thirty-seven patients (29.1%) had densitometric OP, 66 (52%) had DMA in the TBS measurement ( $TBS < 1.230$ ) and 53 (41.7%) had or were receiving antiosteoporotic treatment. **Table 1** shows the clinical characteristics of the patients. At inclusion, the mean FRAX risk scores (GC-adjusted<sup>3</sup>) were  $10.8 \pm 10.1\%$  and  $4.9 \pm 8.3\%$  for major osteoporotic fracture and hip fracture, respectively, in the patients over 40 years old.

When comparing patients with and without VF, those with VF were older ( $68.0 \pm 12.8$  vs  $60.1 \pm 18.6$  years,  $p = 0.02$ ), had more frequently received GC boluses (57.1% vs 29.5%,  $p = 0.03$ ), showed more deteriorated kidney function (higher creatinine serum levels and a lower GFR), lower BMD and T-score values at the lumbar spine and total hip, and a higher frequency of DMA values by TBS (**table 1**). Moreover, women with VF were all postmenopausal, and most males with VF had low testosterone levels (~60%). Subjects with VF also presented higher adjusted FRAX risk scores for major osteoporotic fracture (17.2% vs 9.3%,  $p = 0.003$ ) (**table 1**) and more frequently showed values  $> 20$  (OR 5.47; 95% CI 1.41 to 21.22,  $p = 0.019$ ), in addition to a trend towards more frequently having values  $> 10$  (OR 2.85; 95% CI 1.05 to 7.73,  $p = 0.064$ ). No differences in the frequency of previous or present antiosteoporotic treatment were observed. When patients with any FF (VF and/or non-VF) were compared with those without fractures, most findings were similar to

those in subjects with VF (hypogonadism, older age and lower BMD and TBS values) (**table 1**). Additionally, these subjects showed higher accumulated GC doses ( $16.6 \pm 18.4$  vs  $11.1 \pm 12.9$  g,  $p = 0.0461$ ), a trend towards more frequently having fallen during the previous year (OR 2.37; 95% CI 1.07 to 5.24,  $p = 0.051$ ), higher indices of disease activity (CRP values,  $1.2 \pm 1.8$  vs  $0.7 \pm 1.4$  mg/dL,  $p = 0.045$ ) and higher FRAX scores for hip fracture ( $7.7 \pm 12.9$  vs  $3.6 \pm 4.4$ ,  $p = 0.01$ ) (**table 1**). Conversely, BMI, bone turnover markers, PTH or 25(OH)D serum levels were not associated with the presence of VF or any FF. No differences in the indices of disease activity (ESR and CRP) were observed when we compared patients who did or did not receive GC boluses (ESR  $24.8 \pm 27.5$  vs  $19 \pm 19.8$  mm/hour,  $p = 0.304$ ; CRP  $0.98 \pm 1.74$  vs  $0.72 \pm 1.40$  mg/dL,  $p = 0.411$ , respectively).

On comparing males with normal and low serum testosterone values ( $< 250$  ng/dL), hypogonadal males showed higher BMI values ( $29.4 \pm 2.2$  vs  $26.3 \pm 2.7$ ,  $p = 0.005$ ) and indices of disease activity (ESR values,  $23.1 \pm 12.7$  vs  $12.3 \pm 14.1$  mm/hour,  $p = 0.0054$ ). Hypogonadal males also had lower lumbar TBS values ( $1.142 \pm 0.12$  vs  $1.265 \pm 0.12$ ,  $p = 0.014$ ) and more frequently had DMA (87.5% vs 42.9%,  $p = 0.046$ ) and a lower GFR ( $74.9 \pm 21.3$  vs  $83.0 \pm 11.9$  mL/min,  $p < 0.001$ ). No differences in age, doses and duration of GC treatment, falls during the previous year, bone turnover markers or BMD values were observed between the two groups of patients (**table 2**). Most patients with hypogonadism (7/8, 87.5%) presented increased gonadotropin values, indicative of hypergonadotrophic hypogonadism. Three subjects were previously treated (1) or under (2) immunosuppressive therapy (methotrexate, mycophenolate mofetil (none with cyclophosphamide (CYC))). Patients with low testosterone levels (eight subjects) more frequently presented VF (4/8 (50%) vs 3/34 (9%),  $p = 0.017$ ) and any type of FF (4/8 (50%) vs 5/35 (14%),  $p = 0.046$ ) than those with normal testosterone values.

In the multivariate analysis that included previous GC boluses, the presence of densitometric OP, DMA and hypogonadism, kidney function, CRP values and the FRAX index for major osteoporotic fractures, the principal risk factors related to the presence of VF were the presence of hypogonadism (OR 12.38; 95% CI 1.85 to  $> 100$ ,  $p = 0.01$ ) and having received GC boluses (OR 3.45; 95% CI 1.04 to 12.15,  $p = 0.01$ ); whereas having a degraded TBS was nearly significant (OR 2.36; 95% CI 0.51 to 12.97,  $p = 0.06$ ). The principal risk factors for any FF were again having hypogonadism (OR 7.03; 95% CI 1.47 to 38.37,  $p = 0.01$ ) and a FRAX index  $> 20$  for major osteoporotic fractures (OR 7.08; 95% CI 1.28 to 53.71,  $p = 0.02$ ). The analysis was adjusted for age ( $< 50$ , between 50–65 and  $\geq 66$  years), BMI, CRP and gender (**table 3**).

## DISCUSSION

This study shows several interesting and useful data related to risk factors for fracture in GC-treated patients.

**Table 1** Baseline characteristics of the patients according to the presence of vertebral and fragility fractures

	Overall (n=127)	VF (n=21)	Without VF (n=105)	P value	Any FF (n=36)	Without FF (n=91)	P value
Age (years, mean±SD)	61.5±17.9	<b>68.0±12.8</b>	<b>60.1±18.6</b>	<b>0.02</b>	<b>66.7±12.7</b>	<b>59.4±19.3</b>	<b>0.01</b>
Gender (F/M, n)	80/47	13/8	67/38	1	26/10	54/37	0.25
Menopause, n (%)	58 (72.5)	<b>13 (100)</b>	<b>45 (67.2)</b>	<b>0.02</b>	<b>24 (92.3)</b>	<b>34 (63.0)</b>	<b>0.01</b>
BMI (kg/m <sup>2</sup> , mean±SD)	26.7±4.6	27.4±3.9	26.6±4.8	0.45	27.9±3.9	26.3±4.9	0.07
Autoimmune disease duration (months, mean±SD)	61.9±98.8	63.4±84.1	62.0±102.1	0.95	65.7±87.8	60.4±103.2	0.5
<b>Osteoporosis risk factors</b>							
Current smoking, n (%)	14 (11)	4 (19.1)	10 (9.5)	0.17	4 (11.1)	10 (11)	0.985
Alcohol≥3 units/day, n (%)	1 (0.8)	0 (0)	1 (0.95)	1	0 (0)	1 (1.1)	0.735
Fractured hip in parents, n (%)	16 (12.8)	4 (20.0)	12 (11.5)	0.29	5 (14.3)	11 (12.2)	0.77
<b>Treatment</b>							
Current GC dose (mg/day, mean±SD)	14.5±14.1	14.9±16.3	14.4±13.8	0.89	12.8±13.7	15.1±14.3	0.4
GC treatment duration (months, mean ±SD)	47.7±68.9	55.4±81.8	46.4±66.5	0.60	62.2±86.3	41.9±60.2	0.29
Cumulative GC dose (g, mean±SD)	12.7±14.8	13.4±12.9	12.6±15.2	0.17	<b>16.6±18.4</b>	<b>11.1±12.9</b>	<b>0.046</b>
Intravenous GC boluses, n (%)	43 (33.9)	<b>12 (57.1)</b>	<b>31 (29.5)</b>	<b>0.03</b>	15 (41.6)	28 (30.8)	0.34
Immunosuppressant agents, n (%)	51 (40.2)	10 (47.6)	56 (53.3)	0.81	19 (53)	48 (53)	1
<b>BMD</b>							
Lumbar spine T-score (mean±SD)*	-0.84 ±1.73	<b>-1.62±0.37</b>	<b>-0.67±0.16</b>	<b>0.02</b>	<b>-1.45±1.34</b>	<b>-0.61±1.74</b>	<b>0.01</b>
Femoral neck T-score (mean±SD)*	-1.38 ±0.99	-1.75±0.21	-1.30±0.09	0.053	-1.50±0.83	-1.33±0.96	0.36
Total hip T-score (mean±SD)*	-1.10 ±1.05	<b>-1.51±0.22</b>	<b>-1.02±0.10</b>	<b>0.04</b>	-1.26±0.96	-1.05±0.99	0.3
Densitometric osteoporosis, n (%)	37 (29.1)	8 (38)	29 (28)	0.48	13 (36.1)	24 (26.4)	0.38
<b>TBS</b>							
TBS (mean±SD)*	1.22±0.18	<b>1.119 ±0.030</b>	<b>1.237 ±0.013</b>	<b>&lt;0.001</b>	<b>1.175 ±0.173</b>	<b>1.233 ±0.123</b>	<b>0.04</b>
Degraded microarchitecture, n (%)	66 (52)	<b>16 (76)</b>	<b>49 (47)</b>	<b>0.02</b>	<b>25 (69.4)</b>	<b>41 (45.1)</b>	<b>0.02</b>
<b>Fractures</b>							
Patients with VF, n (%)	21 (16.6)	–	–	–	–	–	–
Patients with any fragility fracture, n (%)	36 (28.3)	–	–	–	–	–	–
<b>FRAX risk</b>							
FRAX for major OP fracture (in patients ≥40 years old)	10.8 ±10.1%	<b>17.2±16.0</b>	<b>9.3±7.6</b>	<b>0.003</b>	<b>15.7±14.2</b>	<b>8.5±6.4</b>	<b>0.0002</b>
FRAX for hip fracture (in patients ≥40 years old)	4.9±8.3%	9.3±14.9	3.9±5.6	0.13	<b>7.7±12.9</b>	<b>3.6±4.4</b>	<b>0.01</b>
<b>Biochemical parameters</b>							
GFR (mL/min, mean±SD)†	77.6±17.8	<b>81.4±5.1</b>	<b>90.0±2.7</b>	<b>0.005</b>	86.1±4.1	89.8±2.9	0.73
ESR (mm/hour, mean±SD)	21.5±22.7	30.1±34.3	19.9±19.5	0.23	25.8±28.2	19.9±20.0	0.27
CRP (mg/dL, mean±SD)	0.8±1.5	1.2±2.0	0.7±1.4	0.09	<b>1.2±1.8</b>	<b>0.7±1.4</b>	<b>0.045</b>
PINP (ng/mL)	33.1±23.3	30.2±21.3	33.7±23.8	0.40	31.7±30.1	33.6±20.1	0.22
CTx (ng/mL)	0.34±0.2	0.39±0.3	0.34±0.2	0.38	0.34±0.3	0.35±0.2	0.30
25-hydroxyvitamin D (ng/mL)	27.6±15.4	26.4±15.4	28.0±15.5	0.60	28.8±13.5	27.1±16.1	0.34
Low testosterone values (<250 ng/dL; in men, %)	8 (18.6%)	<b>4 (57.1%)</b>	<b>4 (11.4%)</b>	<b>0.02</b>	<b>4 (44.4%)</b>	<b>4 (11.8%)</b>	<b>0.046</b>

\*Age- and BMI-adjusted values.

†Age-adjusted values.

BMD, bone mineral density; BMI, body mass index; CTx, C-terminal telopeptide of type I collagen; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FF, fragility fracture; F, female; GC, glucocorticoid; GFR, glomerular filtration rate; M, male; OP, osteoporotic; PINP, procollagen type I N-terminal propeptide; TBS, trabecular bone score; VF, vertebral fractures.

Bold values denote statistical significance at the p &lt; 0.05 level.

**Table 2** Clinical characteristics of men with hypogonadism

	Testosterone $\geq 250$ ng/dL n=35	Testosterone $< 250$ ng/dL n=8	P value
Age (years, mean $\pm$ SD)	64.5 $\pm$ 16.7	69.4 $\pm$ 13	0.38
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)	<b>26.3<math>\pm</math>2.7</b>	<b>29.4<math>\pm</math>2.3</b>	<b>0.005</b>
GC current dose (mg/day, mean $\pm$ SD)	17.7 $\pm$ 17	16.9 $\pm$ 14.7	0.89
GC cumulative dose (g, mean $\pm$ SD)	14.1 $\pm$ 15.8	10.4 $\pm$ 9	0.86
Intravenous GC boluses therapy, n (%)	11 (31.4)	2 (25)	1
Lumbar spine BMD (g/cm <sup>2</sup> )	1.161 $\pm$ 0.27	1.220 $\pm$ 0.31	0.59
Femoral neck BMD (g/cm <sup>2</sup> )	0.890 $\pm$ 0.11	0.898 $\pm$ 0.12	0.86
Total hip BMD (g/cm <sup>2</sup> )	0.942 $\pm$ 0.13	0.973 $\pm$ 0.13	0.53
Densitometric osteoporosis, n (%)	6 (17.1)	1 (12.5)	1
TBS (mean $\pm$ SD)	<b>1.265<math>\pm</math>0.12</b>	<b>1.142<math>\pm</math>0.12</b>	<b>0.01</b>
Degraded microarchitecture, n (%)	<b>15 (42.9)</b>	<b>7 (87.5)</b>	<b>0.046</b>
GFR (mL/min, mean $\pm$ SD)*	<b>83.0<math>\pm</math>11.9</b>	<b>74.9<math>\pm</math>21.3</b>	<b>&lt;0.001</b>
ESR (mm/hour, mean $\pm$ SD)	<b>12.3<math>\pm</math>14.2</b>	<b>23.1<math>\pm</math>12.7</b>	<b>0.005</b>
CRP (mg/dL, mean $\pm$ SD)	0.49 $\pm$ 1	0.88 $\pm$ 1.2	0.09
PINP (ng/mL)	32.1 $\pm$ 22.4	19.6 $\pm$ 8.9	0.09
CTx (ng/mL)	0.31 $\pm$ 0.19	0.25 $\pm$ 0.11	0.67
25-hydroxyvitamin D (ng/mL)	27.8 $\pm$ 113.3	22.1 $\pm$ 7.5	0.39

\*Age-adjusted values.

BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; CTx, C-terminal telopeptide of type I collagen; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; GFR, glomerular filtration rate; PINP, procollagen type I N-terminal propeptide; TBS, trabecular bone score

**Table 3** Multivariate analysis of the risk factors for fractures

	Vertebral fractures		Fragility fractures	
	OR (95% CI)	P value	OR (95% CI)	P value
Hypogonadism	<b>12.38 (1.85 to &gt;100)</b>	<b>0.01</b>	<b>7.03 (1.47 to 38.37)</b>	<b>0.01</b>
Intravenous GC boluses therapy	<b>3.45 (1.04 to 12.15)</b>	<b>0.01</b>	1.58 (0.55 to 4.50)	0.13
Densitometric osteoporosis	2.59 (0.49 to 16.27)	0.37	1.45 (0.45 to 4.55)	0.34
Degraded microarchitecture	2.36 (0.51 to 12.97)	0.06	1.65 (0.48 to 6.05)	0.12
FRAX for major OP fracture $\geq 20$	4.56 (0.82 to 27.34)	0.08	<b>7.08 (1.28 to 53.71)</b>	<b>0.02</b>
Creatinine values	3.12 (0.60 to 19.90)	0.17	–	–
Glomerular filtration rate	1.01 (0.94 to 1.08)	0.54	1.01 (0.98 to 1.05)	0.80
Age $\geq 65$ years	0.66 (0.08 to 6.75)	0.67	0.62 (0.13 to 3.39)	0.64
CRP	1.03 (0.71 to 1.39)	0.39	1.09 (0.83 to 1.43)	0.24

The analysis was adjusted for age (analysing the data according to age  $< 50$ , between 50–65 and  $\geq 66$  years), BMI, CRP and gender.

BMI, body mass index; CRP, C reactive protein; fragility fractures (VF+non-VF); GC, glucocorticoid; OP, osteoporosis; VF, vertebral fractures.

Our results confirm the determinant role of gonadal function in the development of either vertebral and/or any FF, being the presence of hypogonadism the principal risk factor. This finding was observed not only in women but also in men. Additionally, treatment with GC bolus(es) was associated with an increased risk of VF and the evaluation of TBS and FRAX improves the identification of high-risk subjects in whom preventive anti-osteoporotic treatment should be indicated.

In general, most risk factors related to the development of fractures in GC-treated patients coincide with those reported in the general population.<sup>4–6</sup> Advanced age is also an important and well-recognised risk factor for

fracture in GC-treated subjects, particularly when comparing subjects aged over 60 years with young individuals. Indeed, a previous study reported a relative risk for VF of 26 and a shorter interval between initiation of GC treatment and the occurrence of fracture(s) in the older population.<sup>23</sup> In our series, patients with fractures were older than non-fractured subjects. Nonetheless, although age is a determinant factor for fractures, hypogonadism was the principal risk factor for fracture. We observed that all women with VF were postmenopausal and, although the number of males was relatively small, most males with VF were hypogonadal. In fact, in the multivariate analysis, the presence of hypogonadism was the most important

risk factor for fracture, with an OR of 12.38 for VF, which remained significant after adjustment for different age groups. Although previous studies have also described the importance of menopausal status in the development of fractures in GC-treated subjects, the evaluation of hypogonadal status in GC-treated males has been scarcely analysed, and recent data suggest that it could be more frequent than expected.<sup>12</sup> Indeed, nearly 20% of the males in our study showed low testosterone levels, which were frequently associated with increased gonadotropin values indicative of primary hypogonadism in most cases. On comparing hypogonadal males with those with normal testosterone levels, the former presented higher indices of disease activity, with higher ESR values and a lower GFR, and a higher BMI. No differences were observed in either age or the mean GC exposure between the two groups of patients. In addition, hypogonadal males showed lower TBS values but similar BMD values at the lumbar spine and femur. In previous studies, male patients treated with GC and immunosuppressant agents, especially CYC, presented decreased testosterone levels.<sup>12</sup> This finding has also been attributed to the inflammatory disease<sup>12 24</sup> and may explain the inhibitory effects at more than one level of the hypothalamic–pituitary–testicular axis that can be observed in this type of patients.<sup>4 25–28</sup> Whatever the mechanism of hypogonadism in GC-treated males, the present data suggest the need to evaluate testosterone levels in these subjects. Moreover, the present data also confirm the protective role of estrogens in the development of GIOP in women. Thus, despite receiving long-term treatment with high GC doses, none of the premenopausal women included in this study developed VF. Previous reports have also described this finding.<sup>29 30</sup> It should be highlighted that in the placebo groups of several trials of antiosteoporotic therapy for GIOP, the fracture incidence was increased in postmenopausal women, but no fractures were observed in the nonmenopausal women, clearly suggesting a protective role of estrogens in this type of OP.<sup>29–31</sup> Considering this, young women who become long-term amenorrheic during GC treatment should be carefully assessed and likely treated.

We also observed that previous treatment with GC bolus(es) was associated with more than a threefold increased risk of VF, even when adjusted for CRP values. Indeed, patients with VF received GC boluses more frequently than non-fractured patients. In addition, subjects with any type of FF also received significantly higher cumulated GC doses, further confirming the importance of the magnitude and duration of GC therapy as determinant factors for fracture development. In this sense, several studies have reported a relationship between high cumulated GC doses and an increase in fracture risk, being particularly harmful, especially if maintained.<sup>1–6 32</sup> Nevertheless, the effect of GC boluses on GIOP development is controversial. Whereas some studies only reported a mild effect on bone<sup>33–35</sup> and even recommend its use to decrease accumulated GC doses,<sup>36</sup> other authors have

reported the harmful effects of GC boluses on bone metabolism.<sup>37</sup> The decrease in the inflammatory activity of the disease induced by GC boluses may possibly have played a role in these discordant results. Thus, systemic inflammation is a well-recognised factor related to bone loss and fractures, with several reports confirming the protective effect of decreased inflammatory activity on bone metabolism.<sup>4</sup> Nevertheless, although we observed higher indices of disease activity (with higher CRP values) in fractured patients, which suggests a contributory role of inflammation in this clinical condition, in the present study, CRP values were not related to the presence of fractures in the multivariate analysis. In addition, no differences were observed when we compared the ESR and CRP values between patients who did or did not receive GC boluses. Although the use of GC boluses could have interfered as a risk factor for inflammatory activity, our results suggest that GC boluses seem to contribute to the development of VF. Nevertheless, this point needs to be better analysed in longitudinal studies addressed to this subject.

Low BMD constitutes a well-established risk factor for fracture. In GIOP, however, patients present skeletal fractures at higher BMD values than expected. This finding has been attributed to the additional effect of GC on bone quality,<sup>1–6</sup> with recent studies recommending TBS evaluation in this process.<sup>10 11 38–44</sup> This does not mean that measuring BMD is not recommended, but rather that additional analysis are needed to identify subjects at risk. In fact, although we observed significantly lower T-score values in the BMD of fractured patients, the presence of OP was low, with only 38% of the fractured patients having OP. Conversely, as previously reported by our group, fractured patients not only showed significantly lower TBS values but also frequently presented DMA, which was observed in 76% of the subjects with VF. Indeed, patients with DMA had a greater than threefold increased risk of VF (OR 3.55; 95% CI 1 to 14.85,  $p=0.049$ ). These results confirm the usefulness of adding TBS analysis to BMD measurement to better identify patients at increased risk for fracture.<sup>10</sup>

In relation to the identification of patients at risk of fracture, we also analysed the value of the FRAX algorithm adjusted for GC treatment in patients >40 years of age. As expected, patients with either VF or any type of fracture showed significantly higher FRAX scores than non-fractured subjects. Additionally, fractured patients more frequently presented FRAX scores for a major osteoporotic fracture >20, being indicative of high risk for fracture. Indeed, in the multivariate analysis, this value (>20) significantly increased the risk of any FF by nearly sevenfold, further confirming the utility of FRAX in this population, especially when scores are high. Nonetheless, lower FRAX scores (>10) could also likely indicate increased risk. According to the American College of Rheumatology guidelines, preventive antiosteoporotic treatment is recommended in GC-treated patients >40 years old with adjusted FRAX values >10<sup>3</sup>. Thus, we observed a trend

towards subjects with VF more frequently having values >10 (OR 2.85; 95% CI 1.05 to 7.73,  $p=0.064$ ).

Our study has some limitations, such as those related to the cross-sectional nature of the study and the absence of a control group. In addition, most patients included in the study had vasculitis or polymyalgia rheumatica, with isolated cases of RA, thereby limiting the results in patients with similar clinical characteristics. The low number of males with hypogonadism could also constitute a partial limitation in the analysis of this particular subgroup of patients. Nonetheless, the strengths of this study include the homogeneity of the patients (all on chronic GC treatment with doses  $\geq 5$  mg/day for autoimmune disorders), together with in-depth clinical evaluation, extensive bone metabolism analysis and radiological and DXA studies related to the development of fractures.

In conclusion, hypogonadism constitutes the principal risk factor for developing fractures in GC-treated men and women, highlighting the importance of evaluating gonadal status in these patients. Additionally, GC bolus(es) can be associated with an increased risk of VF, indicating the need to evaluate this particular risk factor in further prospective studies with concomitant analysis of the inflammatory activity as a confounding risk factor. Evaluation of TBS and FRAX can improve the identification of high-risk subjects, and thus, the therapeutic approach.

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