Prevalence and incidence of osteoporotic fractures in patients on long-term glucocorticoid treatment for rheumatic diseases: the Glucocorticoid Induced OsTeoporosis TOol (GIOTTO) study

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SUMMARY

Osteoporosis and fractures are common and invalidating consequences of chronic glucorticoid (GC) treatment. Reliable information regarding the epidemiology of GC induced osteoporosis (GIOP) comes exclusively from the placebo group of randomized clinical trials while observational studies are generally lacking data on the real prevalence of vertebral fractures, GC dosage and primary diagnosis. The objective of this study was to evaluate the prevalence and incidence of osteoporotic fractures and to identify their major determinants (primary disease, GC dosage, bone mineral density, risk factors, specific treatment for GIOP) in a large cohort of consecutive patients aged >21 years, on chronic treatment with GC (≥5 mg prednisone - PN - equivalent) and attending rheumatology centers located all over Italy. Glucocorticoid Induced OsTeoporosis TOol (GIOTTO) is a national multicenter cross-sectional and longitudinal observational study. 553 patients suffering from Rheumatoid Arthritis (RA), Polymyalgia Rheumatica (PMR) and Connective Tissue Diseases (CTDs) and in chronic treatment with GCs were enrolled.

Osteoporotic BMD values (T score <-2.5) were observed in 28%, 38% and 35% of patients with CTDs, PMR or RA at the lumbar spine, and in 18%, 29% and 26% at the femoral neck, respectively. Before GC treatment, prevalent clinical fractures were reported by 12%, 37% and 17% of patients with CTDs, PMR, or RA, respectively. New clinical fragility fractures during GC treatment were reported by 12%, 10% and 23% of CTDs, PMR and RA patients, respectively. Vertebral fractures were the prevailing type of fragility fracture. More than 30% of patients had recurrence of fracture. An average of 80% of patients were in supplementation with calcium and/or vitamin D during treatment with GCs. Respectively, 64%, 80%, and 72% of the CTDs, PMR and RA patients were on pharmacological treatment for GIOP, almost exclusively with bisphosphonates. The GIOTTO study might provide relevant contributions to clinical practice, in particular by highlighting and quantifying in real life the prevalence of GIOP and relative fractures, the frequency of the main risk factors, and the currently sub-optimal prevention. Moreover, these results emphasize the importance of the underlying rheumatic disease on the risk of GIOP associated fractures.

Key words: Glucocorticoids; rheumatic diseases; osteoporosis; fractures.

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■ INTRODUCTION

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Glucocorticoid therapy (GCs) is a frequently used treatment for rheumatic diseases, such as Rheumatoid Arthritis (RA), Polymyalgia Rheumatica (PMR), and Connective Tissue Diseases (CTDs) such as Systemic Lupus Erythematosus (SLE) (1-3).

In RA the use of low-dose GCs has a well-defined effect on disease activity (4). Different studies about early RA have demonstrat-

ed that the treatment with disease-modifying anti-rheumatic drugs (DMARDs) in association with GCs may induce high and persistent remission rates (5).

This disease-modifying effect of GCs is supported by different studies (5-12). In addition, the results also showed that GCs have an action in retarding the progression of erosive joint damage in early RA (prior to any joint damage) and a control of disease activity (5-12). The CAMERA II study, in which patients with RA were treated with 10 mg/day of prednisone, has demonstrated that the co-treatment with GCs has a role in the *treat-to-target* and *tight control* strategy (13). Many reviews concluded that a low dose of GCs (<7.5 mg/day) can represent a *bridging-therapy* while waiting for DMARDs to begin to have effect (8, 13). This conclusion was recommended by EULAR in 2010 and then in a 2014 update (14-16). The 2012 ACR recommendations update concerned only the use of conventional DMARDs and biological therapies, while it did not recommend the use of GCs (17). In RA the combination therapy with GCs (at a stable low dose of 7.5 mg/day) and traditional DMARDs frequently leads to a suppression of inflammation, and allows a lasting clinical remission (5).

GCs represent the gold standard treatment in PMR, reducing symptoms and suppressing inflammation within a few weeks. GCs act as inhibitors of the circadian release of pro-inflammatory cytokines (such as IL-6), reducing the duration of morning stiffness (2). Although a universal regimen of daily doses of GCs in PMR is not accepted, the EULAR/ACR 2015 recommendations for the management of PMR suggest an initial GCs administration dose within a range of 12.5-25 mg prednisone (PN), and then of 10 mg for 4-8 weeks before being tapered by 1 mg every 4-8 weeks (18). In addition, the experts panel discourages conditionally the use of initial doses of ≤7.5 mg/day or >30 mg/day. At the same time, the panel recommends considering the early introduction of methotrexate (MTX) in addition to GCs, particularly in patients at a high risk of relapse. MTX may also be considered during follow-up of patients with a re-

lapse, without significant response to GCs or experiencing GC-related adverse events (18). GCs are extensively used also for the treatment of CTDs and their complications or flares.

The use of GCs is associated with the occurrence of side effects, including hypertension, diabetes mellitus, and cataract (19, 20). One of the main complications of long-term GCs use is an important alteration of bone metabolism. Bone loss associated with GCs generally involves trabecular and cortical bone, with increased bone resorption but mainly decreased bone formation (21). Bone loss is likely to proceed more rapidly and involves firstly the trabecular compartment because trabecular bone has more available surface upon which the cycle of resorption and formation occurs. Rapid bone loss is marked mostly on endo-cortical surfaces (22). Doses of GCs >5 mg PN equivalent per day are associated with bone loss due to reduced bone formation. Doses of <5 mg per day may be skeletal sparing, but it is uncertain whether doses <5 mg are efficacious (23).

Fracture risk is positively related to daily dose and increases during the first 6 months of therapy (24). The relative risk of fractures for patients in GCs therapy is higher for forearm, hip and vertebral sites (24). Some confounding factors such as activity of the disease, age of the patient, sex, baseline BMD, previous fracture history, may influence the rate of bone loss (25). The effects of GCs on fracture risk as well as being dose-related, also depend on the duration of the therapy (26).

Reliable information regarding the epidemiology of GC induced osteoporosis (GIOP) comes exclusively from the placebo group of randomized clinical trials while observational studies are generally lacking data on the real prevalence of vertebral fractures, GC dosage and primary diagnosis.

The main objective of this multicenter study was to evaluate, with a transversal and longitudinal approach, in real life, the prevalence and incidence of osteoporotic fractures and to identify their major determinants in a sample of patients with

different rheumatic diseases in chronic treatment with GCs. Secondary objectives were to quantify the prevalence of the major risk factors for osteoporotic fracture: age, underlying disease, sex, bone mineral density (BMD), dietary intake of calcium, specific anti-osteoporotic therapy, estimate of vitamin D, physical activity, smoking, alcohol, family history, comorbidity and falls.

■ MATERIALS AND METHODS

This is a national multicenter cross-sectional and longitudinal observational study (The Glucocorticoid Induced OsTeoporosis TOol, GIOTTO Study). 553 patients suffering from RA, PMR and CTDs and in chronic treatment with GCs were enrolled in the Italian rheumatologic centers of Verona, Vercelli, Mantova, Pavia, Modena, Bologna, Florence, Pisa, Siena, Ancona, Rome, Naples, Foggia, Lecce, Reggio Calabria, Catania, and Cagliari.

The study was purely observational so no additional treatments or tests other than those normally applied to these patients, were provided or requested.

Each center enrolled patients arriving consecutively in their outpatients clinics and within the following inclusion criteria:
– for the *cross-sectional phase*: women or men age >21 years and receiving GCs for at least one year at a dose of at least 5 mg/day of PN or equivalent
– for the *longitudinal phase*: patients in therapy with GCs (at least 5 mg/day) for less than three months and in which a therapy with GCs was expected for at least one year at a dosage of at least 5 mg/day of PN or equivalent.

All subjects with at least one of the following characteristics were excluded from the study: a diagnosis of metabolic bone diseases or other forms of secondary osteoporosis (uncontrolled hyperthyroidism, M. Cushing, malabsorption syndrome, primary hyperparathyroidism), severe renal insufficiency (serum creatinine >2 mg/dl), severe liver failure. Patients on aromatase inhibitors, androgen deprivation therapy and heparin were also excluded.

Additional diagnostic tests (instrumental or biochemical) deemed appropriate by the investigator for the clinical practice were provided. The prevalence and incidence of fractures were referred to so-called clinical fractures (but also to any vertebral fractures detected incidentally by radiographic investigation of the spine).

The data collection cards (CRF) included information about medical history, clinical, diagnostic and therapeutic data, in particular: demographics; physiological and pathological history; assessment of the state of the rheumatic disease and concomitant Health Assessment Questionnaire; previous drug therapy; previous and ongoing GC therapy; specific medical history for osteoporosis (date of first diagnosis; date of first fragility fracture; previous vertebral and non-vertebral fractures before the start of GC treatment; new fractures on GC treatment; recurrence of vertebral fractures; risk factors for osteoporosis or fracture); outcome of laboratory examinations; previous/ongoing drug therapy for osteoporosis; assessment of the quality of life (EQ-5D); simplified questionnaire on calcium and vitamin D intake and physical activity.

The study was approved by the Ethics Committee and by the local coordinator. All patients provided written informed consent.

Descriptive statistics analysis included: sample size, mean, standard deviation, median and range for continuous vari-

Table I - Features of Patients depending on the Rheumatic Disease (Mean ± SD).

Rheumatic diseases	No.	F/M	Age (yrs)	BMI (kg/m^2)	Cumulative dose (g)	Length of therapy (mo)
AR	183	157/26	64±13*	25±5	20.3±22.9	108±91
CTDs	249	206/43	57±16*	25±4	23.9±42.9	79±84*
PMR	91	71/20	74±6*	26±5*	6.3±10.1*	29±53*

*p<0.05 between groups.

ables; absolute and relative frequency distributions for categorical variables.

■ RESULTS

A total of 553 patients with RA, CTDs (mainly SLE =93%) or PMR in chronic treatment with GCs were recruited. Table I shows the main clinical features of the patients depending on the disease.

The prevalence of the main risk factors for osteoporosis and fracture, according to the disease that requested GCs chronic therapy, is shown in Table II.
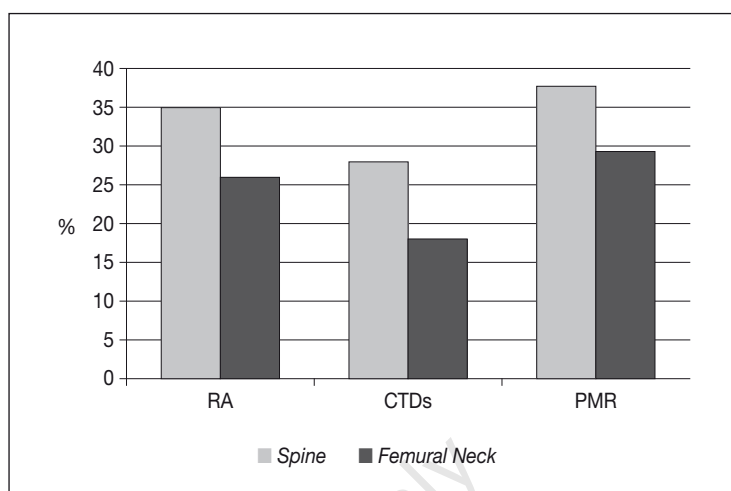
The prevalence of osteoporosis according to DXA (T-score <-2.5) was at the spine in 28%, 38% and 35% of patients with CTDs, PMR or RA; at the femur, on the other hand, it was respectively 18%, 29% and 26% (Figure 1).

A prevalence of previous clinical fractures was found in 12%, 37% and 17% of patients suffering respectively from CTDs, PMR, or RA before any treatment with GC (Figure 2A).

During treatment with GC new clinical fragility fractures were reported in 12%, 10% and 23% of patients suffering respectively from CTDs, PMR and RA (Figure 2B).

The prevailing type of fragility fracture was vertebral, in particular multiple vertebral fractures in patients suffering from PMR (Figure 3A).

More than 30% of patients had recurrence of vertebral fracture. A second relapse of a vertebral fracture was found in


**Figure 1 -** Prevalence of osteoporosis at spine or femoral neck depending on the Rheumatic Disease.

Table II - Prevalence of risk factors for osteoporosis or fracture, according to the Rheumatic Disease.

| Risk factors	RA	CTDs	PMR
Family history of fractures	15%	23%	13%
Alcohol habits	20%	19%	34%
Smoking habits (currently/previous)	19%/23%	19%/17%	9%/26%
Falls during last 6 months	20%	15%	19%
No physical activity	42%	42%	39%
Sunlight exposure <1/week	37%	35%	18%
No seaside holiday	66%	63%	60%
Low calcium intake	30%	23%	34%
Comorbidities	78%	76%	98%
VAS-EQ-5D<50%*	23%	18%	20%

*Visual analogue scale for recording European Quality of Life-5 Dimensions.
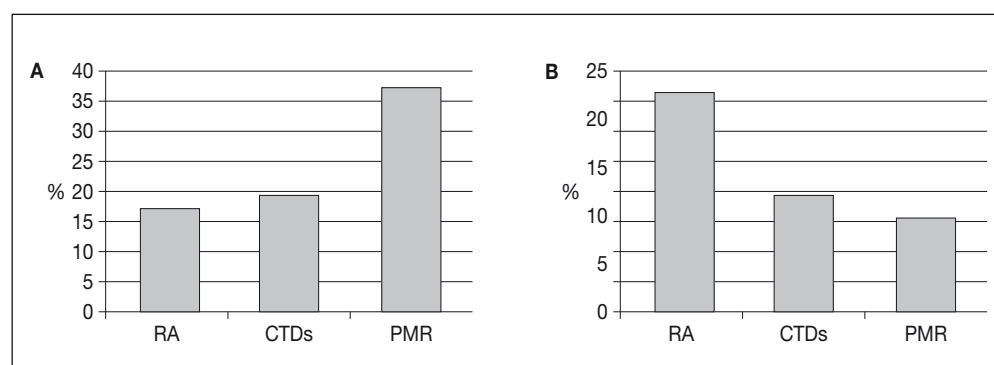
Figure 2 - A) Prevalence of patients with fractures pre-GC treatment, according to the Rheumatic Diseases; B) Prevalence of patients with new clinical fragility fractures in the different Rheumatic Diseases during GC treatment.
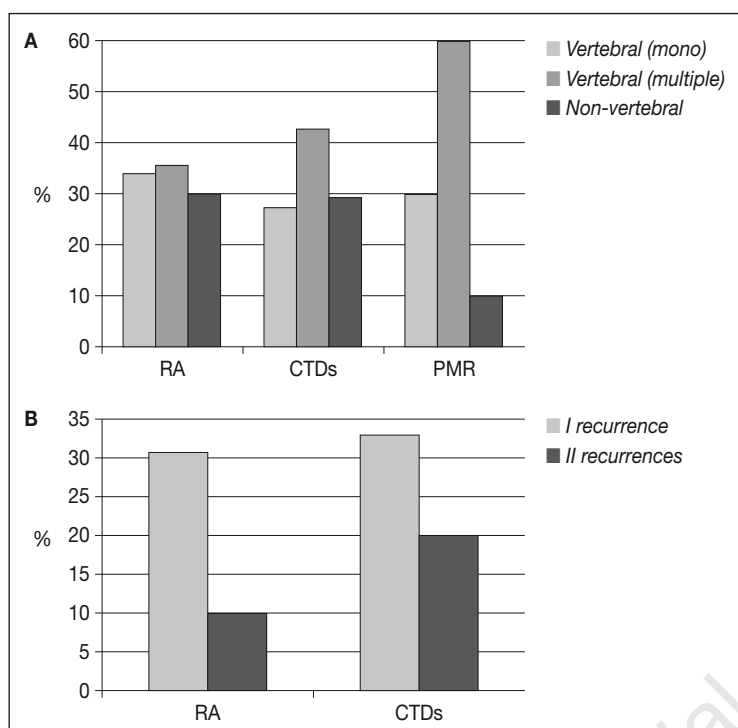
Figure 3 - A) Distribution of different types of fractures, in the different diseases, during GC treatment; B) Prevalence of RA or CTDs patients with recurrence of fractures during GC treatment.
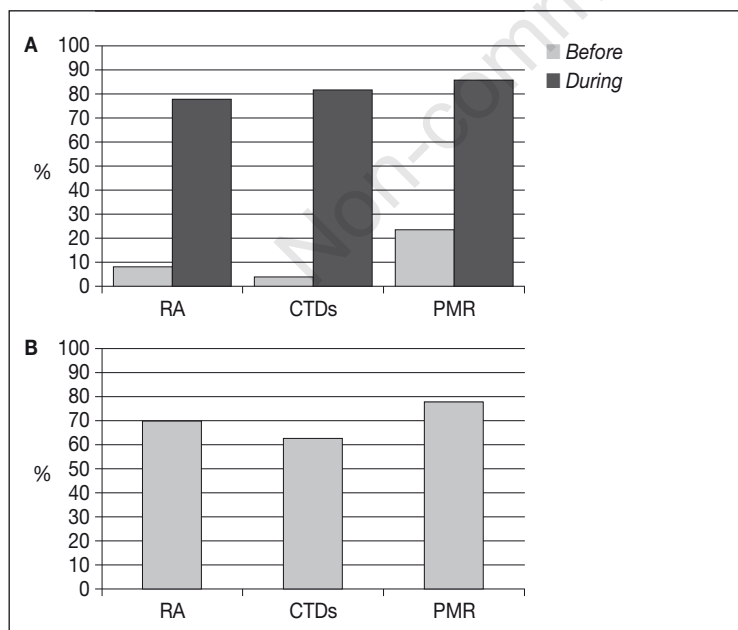
Figure 4 - A) Prevalence of patients with calcium and/or vitamin D supplementation, before or during GC treatment, according to the Rheumatic Disease; B) Prevalence of patients on prevention or treatment of osteoporosis with specific drugs, depending on the Rheumatic Disease.

20% of patients with CTDs and 10% of those with RA (Figure 3B).

In addition, considering only calcium and/or vitamin D, an average of 80% of patients were in supplementation during treatment with GCs; only few of them were already on treatment before the beginning of the GCs treatment (Figure 4A).

64% of patients with CTDs, 80% of patients with PMR and 72% of patients with RA, were treated with specific drugs for the prevention or treatment of GIOP, and in particular with anti-resorptive drugs (alendronate or risedronate) (Figure 4B).

The patients included in the prospective longitudinal phase of the study, which met the inclusion and exclusion criteria, were 83. Their assessment did not show any significant results in addition to those shown by the retrospective longitudinal analysis of 553 cases.

■ **DISCUSSION
AND CONCLUSIONS**

The main aim of this multicenter study was to evaluate the prevalence and the incidence of osteoporotic fractures in a cohort of patients with different rheumatic diseases and in therapy with chronic GCs.

In this study we have observed that in RA patients in treatment with GCs, the prevalence of osteoporosis according to DXA, in terms of T-score <-2.5, was of 35% at the spine, while it was 26% at the femur. In previous studies the frequency of generalized osteoporosis in the global population of patients with RA, with or without GC treatment, ranged from 12.3 to 38.9% in the lumbar spine and from 6.3 to 36.3% in the hip (27-29). The frequencies of osteoporosis in the subgroups of RA patients according to current prednisolone use were 26.6% and 24.7% at the spine and femoral neck, respectively (27). The KORONA database (including 77.7% GCs users) showed that the frequency of osteoporosis was 46.8% (30), a higher percentage in comparison to some other studies, which reported a prevalence of 22-24 %, but with a lower prevalence of GC use (31, 32). In a large Italian multicenter cross-sectional study that in-

cluded 925 female RA patients, the authors reported that the frequency of osteoporosis in the whole sample was 28.8% at the lumbar spine and 36.2% at the femoral neck. GC use was associated with significantly lower lumbar and femoral BMD (28).

In our study the prevalence of osteoporosis in patients with CTDs (mainly SLE) was of 28% at the spine and 18% at the hip. Recently, Carli et al observed that more than 50% of SLE patients chronically treated with GCs had a reduced BMD and 28% had osteoporosis (33). In previous studies the prevalence of osteoporosis in GC treated patients with SLE ranged from 1.4 to 68% (34, 35). Two recent studies have demonstrated that bone loss occurs mainly in SLE patients treated with at least 7.5 mg/day prednisone, while treatment with lower doses of prednisone is not associated with bone loss (36, 37).

The frequency of osteoporosis in patients with PMR in previous studies ranges between 14.9 and 85%. In our experience, in these elderly patients osteoporosis was generally found in 38% at the spine and 29% at the hip.

Risk of fracture in patients who received long-term GC is about 33-50%, depending on daily and cumulative dose (38). This variability can be explained by the use of different age groups in the study populations, the menopausal status of the participants, and the use of GCs. In addition, we observed that the prevalence of previous clinical fractures before any GCs treatment was 12% in patients with CTDs, 37% in patients with PMR and 17% in patients with RA. This finding may be determined by the role of an underlying inflammation, with the exception of PMR where other factors such as an older age or a higher prevalence of comorbidities could play a role. In the general population, even small elevations of C reactive protein within the normal range increase non-traumatic fracture risk (39). In some studies, the levels of inflammatory markers and cytokines predicted bone loss and were predictive for fractures (40, 41). There is a strong biological rationale for these observations. Osteoclastogenesis is under the control of

RANK-ligand, which is mainly produced by osteocytes in normal bone remodelling, but also by lymphocytes and fibroblasts in other conditions such as inflammation (42). Osteoclastogenesis can be enhanced by many cytokines: interleukin (IL) IL-6, IL-23, Tumor necrosis factor α (TNF-α). TNF-α transgenic mice are models of osteoporosis with dramatic decrease in bone mass and deterioration of bone microarchitecture. In addition, an over-expression of a Wnt inhibitor, sclerostin, has been observed in these models, with a consequence of inflammation-related decrease in bone formation (43). Moreover, alterations in other Wnt inhibitors, such as DKK1, might be involved in inflammation-related bone loss (44). These findings show that inflammation has a deleterious effect on bone remodelling, inducing increased resorption and decreased formation, before any effect of GCs themselves. Paradoxically, GCs might play a dual role: they induce bone loss and on the other hand they suppress systemic inflammation with a subsequent beneficial effect on bone mass (3).

Autoimmunity, too, might have a role in bone remodelling. For example, in RA the adaptive immune system produces antibodies against rheumatoid factor (RF) and/or against cyclic citrullinated peptides (antibodies to citrullinated protein antigens or ACPA). The plasma levels of ACPA are an index of disease activity and joint damage (45). A recent study has shown that ACPA can stimulate osteoclast differentiation, and that in ACPA-positive patients with RA there is more frequent evidence of bone loss and thinning of cortical thickness than in APCA-negative patients with RA (46-48). Recently, a significant correlation has been observed between RA related osteoporosis and risk of erosions (49, 50).

The incidence of new fragility fractures during GCs treatment in our cohort of patients was 12% in CTDs, 10% in PMR, and 23% in RA. The prevailing type of fracture was vertebral, in particular multiple vertebral fractures, especially in patients with PMR. It is known that the risk of fractures is doubled in patients with GCs, and the risk of vertebral fractures is even higher.

In a study comparing 244,235 oral GCs users *versus* controls, the relative risk of hip fracture was 1.6, and the relative risk of vertebral fracture was 2.6. Many studies have confirmed these results (24, 51, 52). The global prevalence of fractures in patients receiving long-term GCs has been reported as 30-50%. In 551 patients receiving long-term GCs, the prevalence of vertebral fractures was 37%, with 14% of patients having 2 or more asymptomatic vertebral fractures; 48% of patients aged ≥70 years and 30% of those aged <60 years had at least one vertebral fracture (53). The increase in fracture risk is immediate, as early as 3 months after the initiation of therapy and it reverses sharply after discontinuation of GCs (24). This can be related to the added effects of GCs on bone remodeling previously unleashed by the inflammation itself, and the dramatic effect on bone strength through induced apoptosis of osteocytes. Data also suggest a rapid increase in the rate of falls after the start of oral GCs (24). In epidemiological studies, the increased risk of fractures is observed even at low doses of prednisone, that is, 2.5-5 mg per day. The appropriate care of patients receiving such low doses is not well defined. There is a dose-dependent increase in fracture incidence. Interestingly, the fracture risk is related to the current daily dose, more than to the cumulative dose (54): this may be related to the difficulty of an accurate calculation of this cumulative dose.

Secondary objectives of this study were to quantify the prevalence of the principal risk factors for osteoporotic fractures. The prevalence of comorbidities was very high, especially in PMR. No physical activity was found in about 40% of the patients, independently of the rheumatic disease, and the prevalence of falls was high, in particular in RA and PMR (about 20%). Immobilization due to pain from inflamed joints and impairment of physical activity are known key factors related to low BMD and are common in patients suffering from rheumatic diseases (55). The risk of falls may be higher in RA patients because of lower limb joint disease and muscle weakness (due to GCs therapy and disuse) (56). An increased fall risk in 89% of the RA patients was found (57). Potential interventions to reduce falls in this kind of patient include control of disease activity, rehabilitation or exercise therapy, balance training, occupational therapy, home assessment and treatment of vitamin D deficiency. A study by Bearne et al. suggested that a *brief rehabilitation* can improve the quadriceps sensorimotor function (58).

In addition, in our patients we found high prevalence of low sunlight exposure and low calcium intake. Vitamin D deficiency is common in patients with rheumatic disease, and associated with disease activity (59-61). We also evaluated the regular intake of calcium and vitamin D supplements before and during therapy with GCs. We observed that only a few patients were on supplementation before starting GCs therapy, while about 80% of patients were taking calcium or vitamin D supplements during GCs therapy, as recommended (62). In our study, prevention or treatment of GIOP with specific drugs for osteoporosis appear sub-optimal, and generally restricted to anti-resorptive approach with bisphosphonates (63), despite it is well known that inhibition of bone formation and increased apoptosis of osteocytes play a consistent and crucial role in the pathogenesis, while changes in bone resorption during GCs use are variable. Although it has been shown that bisphosphonates reduce vertebral fractures during the first 2 years of GC treatment, there are no data on long-term use, and, it is known that they reduce bone turnover, including bone formation, which is already downwards regulated by GCs. Effectively, the use of the anabolic agent teriparatide was found more successful in reducing vertebral fractures than alendronate (64).

This study has a number of limitations, mainly linked to its cross-sectional design and patient selection bias. Moreover, in order to define severe renal insufficiency, a glomerular filtration rate would have been better than serum creatinine cut off, given the muscle wasting in rheumatic chronic diseases (65).

In conclusion, the GIOTTO study might provide relevant contributions to clinical practice, in particular by highlighting and quantifying in real life the prevalence of GIOP and relative fractures, the frequency of the main risk factors, and the currently sub-optimal prevention. Moreover, these results emphasize the importance of the underlying rheumatic disease on the risk of GIOP associated fractures.

Conflict of interest: the authors declare no potential conflict of interest.

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