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Original Article

# Assessment of Glucocorticoid-Induced Osteoporosis Treatment by Prevailing Guidelines in a Tertiary Care Hospital

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## Abstract

**Background:** Glucocorticoids are the primary drugs used in various disorders across the world. Long-term use of glucocorticoids opens a new Pandora's box filled with several side effects, especially glucocorticoid-induced osteoporosis (GIOP). Patients with GIOP are seldom given treatment as per guidelines.

**Methods:** This was a prospective observational study that included patients on glucocorticoids (dose equivalent to ≥ 2.5 mg prednisolone daily for at least 3 months). Fracture Risk Assessment (FRAX) tool scores were calculated for patients above the age of 40 years, and patients were segregated into low-, medium-, and high-risk categories of hip fractures and major osteoporotic fractures (MOPs).

**Results:** This study included 116 patients, 85 (73.3%) of whom were females. The average dose of prednisolone was 8.39 mg/day. Only 15.5% of patients on glucocorticoids were ever evaluated for glucocorticoid-induced osteoporosis. This study showed that 44.8% and 23.3% of patients had a moderate to high risk of hip fracture and MOP, respectively. Only 7.8% of patients received bisphosphonate treatment.

**Conclusion:** Glucocorticoid-induced osteoporosis is a prevalent yet neglected malady that acts as a slow knife, adding to the morbidity and mortality risk of an individual. The unchecked use of glucocorticoids in current clinical practice warrants greater concern from clinicians. This study serves as another reminder of the abyss of osteoporosis due to steroid use and how prevalent it is despite the vast amount of existing literature.

**Keywords:** FRAX score, glucocorticoid-induced osteoporosis, glucocorticoids, osteoporotic fractures, steroids

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## Introduction

Rheumatological diseases have come a long way from being less known and understood to a field with breakthrough advances in both diagnosis and management. In its infancy, it was thought to be a branch with diseases that were destined to decrease the quality of life despite any intervention. Now, the field has an arsenal with a variety of pharmacological agents that can not only treat the symptoms but also alter the pathophysiology at the molecular level, providing assurance of healthy living with the disease. The top spot among these pharmacological agents is still held by glucocorticoids. They are the wonder drugs of this era and bridle the fast pace of disease activity in various rheumatological diseases and their varied organ manifestations. However, they do come with a red note, the most common yet undermined issue being glucocorticoid-induced osteoporosis. It takes the first spot among the list of secondary causes of osteoporosis. It is also evident that neither its propensity to cause long-term havoc nor any act to prevent it is under requisite scrutiny, and hence requires a sincere and methodical redress.[1,2]

## Review of Literature

Long-term consumption of these drugs has been shown to increase the risk of osteoporosis; in fact, around 50% of patients receiving glucocorticoids are susceptible to osteoporosis, which ergo raises the incidence of both vertebral and hip fractures (160% and 60% respectively).[3,4] Osteoporosis due to glucocorticoids thwacks the trabecular bone, which is rapidly progressive initially and then plateaus. Simultaneously, it also increases the risk of fracture. The daily dose of glucocorticoids correlates with the risk of fracture.[1,5] Bone Mineral Density (BMD) is widely used to scan a patient for the presence of osteoporosis. However, not

all accountability of GIOP can be attributed to BMD; the risk of fracture seems higher among patients on glucocorticoids, even more than postmenopausal women having similar BMD. This suggests that apart from the density of bone, the quality of bone is also affected by glucocorticoids. Some studies also revealed that a cumulative dose of glucocorticoids greater than 1 gm increases the risk of fracture.[6,7] Bone metabolism that involves both resorption and formation is targeted by glucocorticoids; in addition, they also have a toll on muscular strength. They do so because, being lipophilic they go through the cellular membrane unhindered and into the nucleus, thereby affecting various genes.[8] They affect multiple cells—osteoblasts (decreasing osteoblastogenesis), osteocytes (increasing sclerostin and Dickkopf-1 (DKK-1) and inducing apoptosis), and increased osteoclast maturation. Some indirect effects, like increased urinary excretion of calcium and lower intestinal absorption, also contribute to decreased bone mass and concomitant hyperparathyroidism. Their effect on sex steroids and Insulin-like Growth Factor-1 (IGF-1) similarly promotes osteoporosis. Glucocorticoids also affect the quality of life by decreasing muscle mass, particularly in axial joints—shoulders and hips. This in turn increases the propensity to fall, which adds to the fracture risk.[9,10]

BMD at the lumbar spine and distal forearm measures bone mineralization but does not quantify the total loss of bone in these areas. Trabecular bone score is another method showing better credibility in determining at-risk patients for GIOP-induced fractures. It can also help follow-up with patients on treatment for GIOP and has shown that teriparatide gave a better response trajectory than bisphosphonates.[11] Biochemical markers of osteoclastic activity like osteocalcin can point out osteoporosis secondary to glucocorticoids, and similarly, osteoblastic activity can be estimated via biomarkers like urinary-free deoxypyridinoline and N-telopeptide type-1 collagen in serum and urine samples.[12,13]

### Main Points

- Glucocorticoid-induced osteoporosis is an often-overlooked entity and given the prevalence of glucocorticoid use in departments across the medical field, the gap between available literature on guidelines for managing glucocorticoid-induced osteoporosis (GIOP) and clinical practice is immense.
- On evaluation, it was found that as per the Fracture Risk Assessment (FRAX) score, 22.4% of patients were at high and moderate risk of hip fracture, respectively. Similarly, 6% and 17.3% of patients were at high and moderate risk of major osteoporotic fracture. All these patients should have received bisphosphonates to prevent osteoporotic fractures.
- In this study, only 7.8% of patients received bisphosphonates for the prevention of osteoporotic fractures.
- Previous studies have revealed that only around 15% of patients are evaluated and treated for GIOP. A similar outcome was seen in this study, where only 14.7% of patients received treatment as per the American College of Rheumatology (ACR) 2017 guidelines.
- Fracture Risk Assessment is a bedside tool that should be the first assessment method to calculate fracture risk among patients and is the preferred method as per ACR 2017 guidelines. This study revealed that none of the patients were ever evaluated via FRAX, few of them underwent dual-energy X-ray absorptiometry scans for measuring their bone mineral density which is not standardized and does not provide any information on bone architecture.

### ACR 2017 Guideline

ACR 2017 guides in a practical way in identifying, stratifying, and managing patients at risk of GIOP. It can reduce the probability of missing and mistreating such patients, especially patients with a higher risk of GIOP-related fractures. Individuals under the age of 40 are at low risk unless and until they have had fragility fractures before or very low BMD. However, no other clinical risk factors are accounted for in this group of patients. In contrast, patients above the age of 40 years are segregated based on the basis of FRAX score, which, of course has its own limitations. The guideline does recommend multiple BMD estimations for older individuals; however, the impact of which is questionable. Hence, BMD for assessment of osteoporosis is warranted only if it adds extra information to management. The ACR 2017 also recommends treating all patients with moderate to high risk of fractures with bisphosphonates, which is again a bit controversial as bisphosphonates should not be used in younger age and in older individuals, it may paradoxically increase the risk of fractures.[14]

### Fracture Risk Assessment Tool

Fracture Risk Assessmentis a tool that can be used bedside in clinics to ascertain fracture risk in the form of a 10-year probability of risk of fracture involving the hip, humerus, forearm, and vertebra. It takes into account the use of glucocorticoids and is apt even without BMD. It is advised to evaluate FRAX at the time of starting glucocorticoids, followed by the next estimation at 6 months, and then yearly thereafter. Fracture Risk Assessment, according to ACR guidelines 2017, is central for GIOP management. This composite tool includes factors such as a family history of fractures, substance abuse like cigarette smoking and alcohol, endocrinopathies, etc.[14]

It was developed by the World Health Organization and incorporates various variables that play a key role in a holistic evaluation of osteoporosis-associated risk of fractures. Although glucocorticoids are also subsumed into this calculator, there are indeed some limitations as the duration of glucocorticoid use is not part of the computation. If the dose of steroids is greater than 7.5 mg/day, there is a 20% higher risk of hip fractures and a 15% higher risk of major osteoporotic fractures.[13]

In a study in Taiwan, participants were asked to fill out a questionnaire about medications provided for osteoporosis and various variables used in the FRAX tool. The study had 2 groups: a study group of patients on glucocorticoids (807 patients) and a control group who were not on any steroids (7897 patients). The study showed that BMD failed to provide any difference between the 2 groups. However, patients on glucocorticoids had significantly higher risk factors according to FRAX. The steroid group also had a higher risk of hip and major osteoporotic fractures. Only 20.3% of patients among the glucocorticoid users received treatment. The study recommended the use of FRAX rather than BMD to assess and treat GIOP.[15]

There are some limitations with FRAX, such as:

1. The dosage and duration of glucocorticoids are not accounted for in the calculator.
2. Past and current users of glucocorticoids are not segregated.
3. It projects a risk of steroid use between 2.5 and 7.5 mg/day. For anything above 7.5 mg/day, it may underestimate and for anything below 2.5 mg/day, it may overestimate the risk of fractures.
4. Although glucocorticoids impact vertebrae more, FRAX is basically validated for non-vertebral fractures.
5. FRAX cannot be applied for people with age < 40 years, premenopausal, or if already on any anti-osteoporotic drugs.

6. For postmenopausal females and age > 50 years in men, in case of lower than 2.5 mg/day of steroids, FRAX is adjusted by a factor of 0.8 and 0.65 for MOP and hip fracture respectively.
7. For a steroid dose of more than 7.5 mg/day, FRAX is adjusted by a factor of 1.15 and 1.20 for MOP and Hip fractures, respectively.[16]

### Treatment of Glucocorticoid-Induced Osteoporosis

For preventing GIOP, initiating with a low-dose glucocorticoid is an opening gambit. The least possible dose, for the shortest duration, may do the trick along with lifestyle modifications and patient education. Hyperglycaemia too should be kept in check as it may further add to increased fracture risk. Calcium supplements alone have been shown to be exiguous in improving bone quality. Studies have shown that active metabolites of vitamin D along with calcium supplements do maintain BMD and reduce vertebral fractures.[17]

Bisphosphonates are the drug of choice for GIOP and are backed by their low cost and efficacy. Their key role is the apoptosis of osteoclasts. They may have an additional role in osteoblast protection and improving BMD. A Cochrane study brought bisphosphonates into the limelight, describing a reduction in the incidence of vertebral fractures with BMD improvement.[18] Intravenous bisphosphonates emerged as the preferable choice over oral counterparts as they bypass the adverse effects of the latter. However, they are not risk-free and may lead to atypical femoral fractures and jaw osteonecrosis in the long term.[18] Denosumab, a Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL) human monoclonal antibody, is another drug used for the treatment of GIOP. It appreciably attenuates BMD. Studies have shown it to be superior to bisphosphonates with similar adverse effects. A major drawback with RANKL inhibition is the recurrence of fracture risk following discontinuation. Hence, after stopping denosumab, it must be followed with bisphosphonate therapy.[19] Parathyroid hormone has a central role in calcium metabolism; hence, its anabolic action of promoting osteoblast production is useful in GIOP. Teriparatide has been tried in postmenopausal cases of osteoporosis. When compared with bisphosphonates, teriparatide showed higher BMD improvement and subsequently lower vertebral fracture risk.[20] One major drawback is the cost and the fact that daily subcutaneous injections require far more compliance than other treatment options. Saag et al[21] compared alendronate and teriparatide in patients with GIOP. They found that at the end of 36 months, the group on teriparatide showed a higher rise in BMD (11%) than the alendronate group of alendronate (5.3%) in the lumbar spine. Similarly, there was a higher rise in BMD at the total hip (5.2% vs. 2.7%). Concomitantly Teriparatide group showed fewer fractures in vertebrae (1.7% vs 7.7%). A humanized monoclonal antibody to sclerostin, romosozumab, is another option to consider for GIOP patients. Glucocorticoids increase sclerostin, thereby inhibiting the Wnt pathway that moderates the activation of osteoblasts, ultimately leading to bone formation. Randomized controlled trials comparing romosozumab to other therapies for GIOP showed a higher rise in BMD.[22] After these medical modalities in managing GIOP, vertebroplasty and kyphoplasty can be advocated if features such as pain not responding to medical management and the persistence of vertebral fractures are present. Although patients with GIOP are more prone to developing fractures post-procedure, these interventions are not recommended.[23]

## Material and Methods

### Study Design

A prospective observational study. This study was conducted on all patients on glucocorticoids visiting the Outpatient Department (OPD) of the Department of Rheumatology, Max Institute, Saket. The study was initiated after the institutional Scientific Committee [Max Healthcare Institute, Saket, New Delhi, India] approval (Reference No. TS/MSSH/MHIL/ISC/RHEUMAT/21 – 38) and subsequently from the Institutional Ethics Committee Max Healthcare Institute, Saket (Ref No. BHR/TS/MSSH/MHIL/SKT-1/MHEC/RHEUMATO/22-01 Date: 07/02/2022). All participants were provided with complete information regarding the study, explained in Hindi/English at their convenience. The patients were also provided with consent forms (Hindi/English) to sign after they had completely understood the study's purpose and methodology. The candidate(s) had full autonomy over their involvement.

### Inclusion Criteria

All patients on a prednisone dose ≥ 2.5 mg/day for a period ≥ 3 months who fall under the moderate to high-risk category for glucocorticoid-induced osteoporotic fracture according to 2017 ACR guidelines for prevention and treatment of glucocorticoid-induced osteoporosis were included in this study.[14]

### Exclusion Criteria

All patients visiting the Rheumatology OPD, Max Institute, Saket not on glucocorticoids, patients on glucocorticoids with dose <2.5 mg/day, on glucocorticoids with dose ≥ 2.5 mg/day for less than 3 months, and patients already on anti-osteoporotic therapy were included in the study. The study was carried out from October 2021 to December 2022 in the Department of Rheumatology, Max Institute, Saket. All patients included in the study were subjected to FRAX scoring. Each participant/guardian was given complete information about the purpose and objective of the study and was provided with informed consent. A detailed review of the patient's medical and pharmacological history and physical examination was done. Height and weight were measured using a standard medical scale. The overall assessment of the patient's risk for developing osteoporosis was done by FRAX and calculated using the FRAX India tool (https://www.sheffield.ac.uk/FRAX/tool.aspx).

### Sample Size

All consecutive patients visiting the Rheumatology OPD, Max Institute, Saket, from October 2021 to December 2022 were included in this study.

### Cochran Sample Size Formula with Desired Error of Margin

- Formula for calculating a sample for proportions
- For populations that are large, Cochran (1963:75) developed Equation 1 to yield a representative sample for proportions

$$n_0 = Z^2pq/e^2 \quad (1)$$

Where;

$Z_{\alpha/2}$ is the level of significance at 5%, i.e., 95% CI = 1.96

p = Proportion of chronic glucocorticoid users receiving optimal care = 15% = 0.15

d = Error of margin = 7% = 0.07

$$n = \frac{1.96^2 * 0.15 * (1 - 0.15)}{0.07^2}$$

= 99.96 = 100 patients needed in each group

### Study Reference
Alexandra O Kobza et al.[23]

### Formula Reference
Cochran, W. G. (1977). Sampling techniques (3rd ed.). New York: John Wiley and Sons.

### Power of the Test
80%

### Level of Significance
5%

### Statistical Methods
Chi-square test, Student's paired and unpaired *t*-test, Pearson's correlation coefficient.

### Software Used
SPSS 27.0 version (IBM SPSS Corp.; Armonk, NY, USA), GraphPad Prism 7.0 version.

### Sample Allocation
Convenient Selection of Patients

Descriptive statistical analysis was performed to calculate the means with corresponding SD, medians, and ranges. The test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference in proportions, and chi-square ($X^2$) test was performed to find the associations. The corrected chi-square ($X^2$) test was used in case one of the cell frequencies was <5. The *t*-test was used to compare 2 means. A *P*-value <.05 was taken to be statistically significant.

## Results
Over the period of 1 year, a total of 2982 patients were screened for the study. However, only 116 patients met the inclusion criteria. Of the remaining 2866 patients, 1280 patients were on steroids irregularly or at variable dosages, 940 patients were on prednisolone for less than 3 months duration, 548 patients were not on any steroids, and 98 patients were on prior anti-osteoporotic medications. The distribution of patients into different disease categories is as such: Rheumatoid Arthritis (RA) = 22, Spondyloarthropathies = 64, Gout = 5, Systemic Lupus Erythematosus = 12, Scleroderma = 5, Sarcoidosis = 4, Wegener's Granulomatosis = 2, and Takayasu Arteritis = 2.

In this study, out of 116 patients, 31 (26.7%) were male, and 85 (73.3%) patients were female. The mean age in this study was 56.89 years, the mean dose of prednisone was 8.39 mg, and the mean duration of prednisone was 3.77 months. Out of 116 patients, 3 (2.6%) patients had secondary osteoporosis, 9 (7.8%)

**Table 1.** Baseline Characteristics

| Parameters | Number | % | *P* |
|---|---|---|---|
| Age (in years) | | | |
| <50 | 24 | 20.7 | <.0001 S |
| ≥50 | 92 | 79.3 | |
| Gender | | | |
| Male | 31 | 26.7 | <.0001 S |
| Female | 85 | 73.3 | |
| Prednisone Dose (mg) | | | |
| <10 | 83 | 71.60 | <.0001 S |
| ≥10 | 33 | 28.50 | |
| Duration of Medication of Prednisone (in months) | | | |
| <5 | 93 | 80.2 | <.0001 S |
| ≥5 | 23 | 19.8 | |
| Evaluation for Glucocorticoid-Induced Osteoporosis | | | |
| Yes | 18 | 15.5 | <.0001 S |
| No | 98 | 84.5 | |
| Body Mass Index (kg/m$^2$) | | | |
| <18.5 | 8 | 6.9 | <.0001 S |
| 18.5-24.9 | 44 | 37.9 | |
| ≥25.0 | 64 | 55.2 | |
| Associated Factors | | | |
| Secondary osteoporosis | 3 | 2.6 | .07 NS |
| Drinking of alcohol | 9 | 7.8 | |
| Habit of smoking | 11 | 9.5 | |
| Rheumatoid arthritis | 22 | 19.0 | |
| Dual Energy X-Ray Absorptiometry (DEXA) | | | |
| Yes | 8 | 6.9 | <.0001 S |
| No | 108 | 93.1 | |
| Fracture Risk Assessment Score of Hip fracture | | | |
| High | 26 | 22.4 | <.0001 S |
| Low | 64 | 55.2 | |
| Moderate | 26 | 22.4 | |
| Fracture Risk Assessment Score of Major Osteoporotic Fracture | | | |
| High | 7 | 6.0 | <.0001 S |
| Low | 89 | 76.7 | |
| Moderate | 20 | 17.3 | |
| Treated with | | | |
| Calcium | 53 | 45.7 | .0019 S |
| Vitamin D | 29 | 25.0 | |
| Bisphosphonates | 9 | 7.8 | |
| Teriparatide | 1 | 0.9 | |
| Denosumab | 0 | 0.0 | |
| Treatment as per Guideline | | | |
| Yes | 17 | 14.7 | <.0001 S |
| No | 99 | 85.3 | |

NS, not significant; S, significant.

had a history of alcohol intake, 11 (9.5%) had a history of current smoking, 22 (19%) had diagnosis of RA, and only 8 (6.9%) had their Dual Energy X- ray Absorptiometry (DEXA) done. Fracture Risk Assessment scores were calculated for all 116 patients. Only 9 (7.8%) out of 116 patients received bisphosphonates for the treatment of glucocorticoid-induced osteoporosis, and only 17 (14.7%) were treated as per prevailing guidelines for the treatment of GIOP (Table 1).

In this study, out of 116 patients, only 18 (15.5%) were evaluated for glucocorticoid-induced osteoporosis. The remaining 98 (84.5%) patients who received glucocorticoids (prednisolone > 2.5 mg/day for 3 months) were never evaluated for glucocorticoid-induced osteoporosis (Table 2 and Figure 1). Fracture Risk Assessment score showed 64 (55.2%) patients at low risk of hip fractures, 26 (22.4%) patients at moderate risk of hip fractures, and 26 (22.4%) patients at high risk of Hip fractures (Table 3 and Figure 2).

As per FRAX score, 89 (76.7%) patients at low risk of major osteoporotic fractures, 20 (17.3%) patients at moderate risk of Major osteoporotic fractures, and 07 (6%) patients were at high risk of Major osteoporotic fractures (Table 4 and Figure 3). None of the patients with moderate to high risk of Hip fractures as per FRAX received Bisphosphonates (Table 5 and Figure 4). Out of 20 (17.3%) patients with moderate risk of Major osteoporotic fractures, only 1 patient received bisphosphonates, and out of 7 (6%) patients with high risk of Major osteoporotic fractures, no one was prescribed Bisphosphonates (Table 6 and Figure 5). Out of a total 116 participants, only 17 (14.7%) patients were treated as per ACR 2017 guidelines for prevention and treatment of glucocorticoid-induced osteoporosis (Figure 6).

## Discussion

Glucocorticoid-induced osteoporosis is a frequently undermined major health concern given the widespread use of steroids across various medical specialties. Individuals on long-term glucocorticoids for various reasons must undergo screening for the risk of osteoporosis and related complications, such as increased risk of fractures, and should be managed according to the guidelines.

**Table 2.** Percentage of Patients Evaluated for Glucocorticoid-Induced Osteoporosis

| Evaluation for Glucocorticoid-Induced Osteoporosis | Number | % |
|---|---|---|
| Yes | 18 | 15.5 |
| No | 98 | 84.5 |
| Total | 116 | 100.0 |

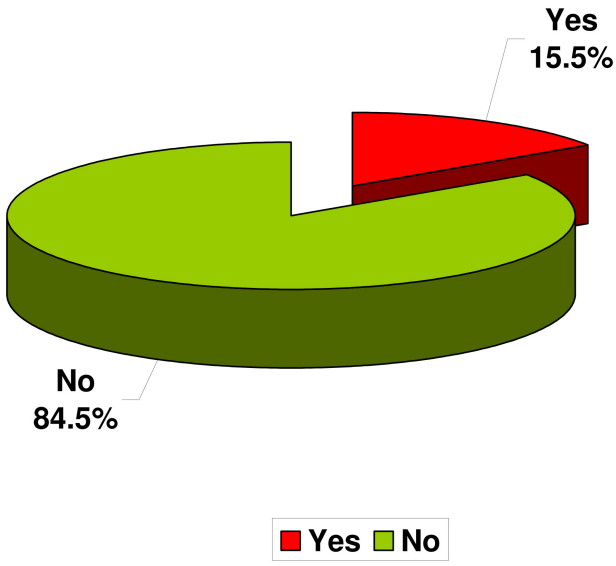


**Figure 1.** Percentage of people evaluated for glucocorticoid-induced osteoporosis.

In a Japanese study conducted between April and December 2017 by Shinoda K. K. Taki H., they evaluated whether physicians followed guideline-based evaluation and treatment for glucocorticoid-induced osteoporosis in female patients who had a diagnosis other than RA and had been on glucocorticoids for at least 12 months. They calculated GIO scores via bone mineral density at femoral neck and lumbar spine for all patients, as per the 2014 Japanese guidelines for osteoporosis. Ninety individuals were included in this study and were considered liable for osteoporosis treatment if the GIO score was greater than 3. Based on femoral neck and lumbar BMD, a GIO score of more than 3 was seen in 66% and 63% of patients, respectively. Of these, 93% (56 patients) received treatment for osteoporosis. Fifteen of them were on bisphosphonates, 12 on denosumab, 3 on teriparatide, and 11 on vitamin D3 supplements alone. Although this study showed 93% adherence to osteoporosis treatment, in this study, patients were evaluated based on recent 2017 ACR guidelines and used FRAX scoring to divide the patients into different categories with low, intermediate or high risk of osteoporotic fractures. No such division was done in the Japanese study, and

**Table 3.** Risk of Hip Fractures as per Fracture Risk Assessment Tool

| Fracture Risk Assessment Score of Hip fracture | Number | % |
|---|---|---|
| High | 26 | 22.4 |
| Low | 64 | 55.2 |
| Moderate | 26 | 22.4 |
| Total | 116 | 100.0 |
| Mean ± SD | 2.28 ± 3.52 | |
| Median | 0.9 | |
| Range | 0 - 21 | |

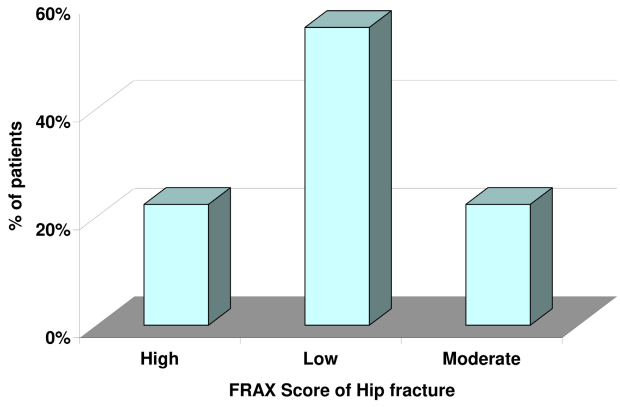


**Figure 2.** Percentage of people at risk of hip fracture (as per Fracture Risk Assessment score).

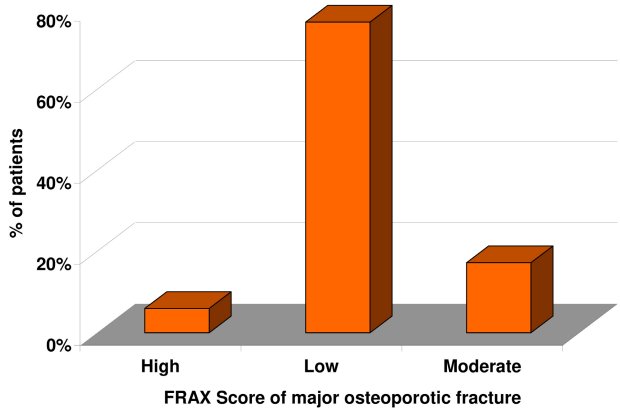


**Figure 3.** Percentage of people at risk of major osteoporotic fractures (as per Fracture Risk Assessment score).

it used BMD to evaluate fracture risk, which is an insufficient tool for the correct estimation of the actual risk of osteoporotic fracture.[24]

Srinivasulu et al[25] conducted a retrospective analysis of patients on long-term steroids with a dose ≥ 7.5 mg/day for ≥ 3 months duration. Patients were evaluated based on the basis of ACR guidelines for GIOP 2001. A total of 151 patients were included in the study. Forty-two of these patients had rheumatological disorders, while the remaining patients were from various other branches like respiratory, renal, endocrine, etc. The mean age of these patients was 52.5 years. Forty-two patients, i.e., 29%, did not receive any medications for the prevention of osteoporosis. Of the remaining 107 patients, only 34 patients, i.e., 32%, received medications as per the guidelines. None of these patients were advised to undergo a bone mineral density scan. This study, however, was conducted in 2010 and there were no recommendations for FRAX back then. In this study, the latest ACR 2017 guidelines were used to evaluate the patients for GIOP, which includes FRAX calculations. Also, the minimum dosage of steroids as a threshold for GIOP was different from this study (7.5 mg/day in Srinivasulu et al[25] and 2.5 mg/day in this study).

Song et al[26] conducted a retrospective study in Korea to evaluate the management of GIOP in patients above the age of 20 years. They included all the patients who were on any dose of steroids for a period of 90 days or more. They described high-quality care of GIOP as a bone mineral density test, calcium and vitamin D prescription, and initiation of other anti-osteoporotic medications. However, they did not mention any particular guidelines that they used as a benchmark. The mean age of their patients was 49.8 years, and approximately 50% of them were females. This was contrary to this study, which had majority of females, possibly due to the inclusion of patients with rheumatological disorders only. Their study showed that high-quality care for the prevention of GIOP was given to only 3.7% of the patients. A critical nuance between the study of Song et al[26] and this study was the use of proper guidelines to evaluate GIOP (ACR 2017 guidelines in this case).

Tory et al[27] did a systematic literature review to analyze adherence to GIOP preventive care and performed a descriptive analysis. Initially, they identified 661 articles, and after exclusion, 38 articles were screened. Only 7 articles remained for analysis after further exclusions from the screened articles. There were 2 system-based and 5 education-based intervention studies. All these studies focused on improving the management of GIOP; however, they showed unanimously that these measures had little impact on GIOP treatment. The study revealed differences in the prescription of long-term glucocorticoids among physicians and rheumatologists. The adherence to and methodology

**Table 4.** Risk of Major Osteoporotic Fractures As Per Fracture Risk Assessment Tool

| Fracture Risk Assessment Score of Major Osteoporotic Fracture | Number | % |
|---|---|---|
| High | 7 | 6.0 |
| Low | 89 | 76.7 |
| Moderate | 20 | 17.3 |
| Total | 116 | 100.0 |
| Mean ± SD | 6.46 ± 5.38 | |
| Median | 5.1 | |
| Range | 0.8 - 31.0 | |

**Table 5.** Treatment Received By Patients At High To Moderate Risk of Hip Fractures

| | Hip Fracture Risk | | | |
|---|---|---|---|---|
| Treatment | High | Moderate | Low | Total |
| Calcium | 6 | 5 | 12 | 23 |
| Row % | 26.1 | 21.7 | 52.2 | 100.0 |
| Col % | 23.1 | 19.2 | 18.8 | 19.8 |
| Biphosphate | 1 | 0 | 0 | 1 |
| Row % | 100.0 | 0.0 | 0.0 | 100.0 |
| Col % | 3.8 | 0.0 | 0.0 | 0.9 |
| Calcium + Vitamin D | 4 | 4 | 14 | 22 |
| Row % | 18.2 | 18.2 | 63.6 | 100.0 |
| Col % | 15.4 | 15.4 | 21.9 | 19.0 |
| Calcium +Vitamin D +Biphosphate | 3 | 1 | 4 | 8 |
| Row % | 37.5 | 12.5 | 50.0 | 100.0 |
| Col % | 11.5 | 3.8 | 6.3 | 6.9 |
| Teriparatide | 1 | 0 | 0 | 1 |
| Row % | 100.0 | 0.0 | 0.0 | 100.0 |
| Col % | 3.8 | 0.0 | 0.0 | 0.9 |
| Nil | 11 | 16 | 34 | 61 |
| Row % | 18.0 | 26.2 | 55.7 | 100.0 |
| Col % | 42.3 | 61.5 | 53.1 | 52.6 |
| Total | 26 | 26 | 64 | 116 |
| Row % | 22.4 | 22.4 | 55.2 | 100.0 |
| Col % | 100.0 | 100.0 | 100.0 | 100.0 |

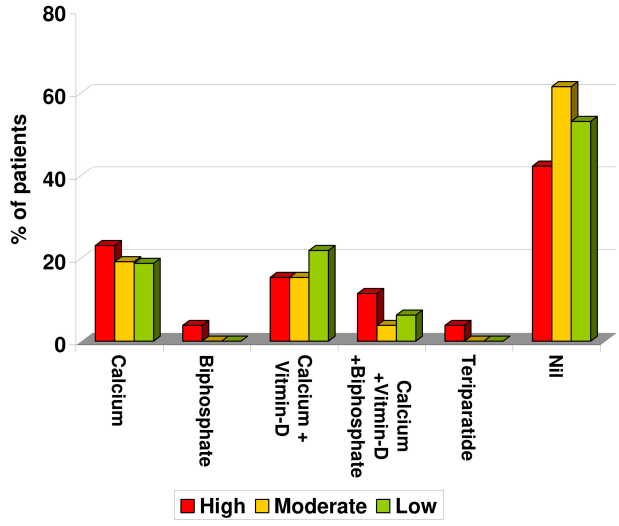


**Figure 4.** Anti-osteoporotic treatment received by patients at risk of hip fracture.

used for GIOP management differed from one clinician to another. Educational efforts to improve GIOP management seemed to have a suboptimal impact, and GIOP remained an under-recognized entity. The article highlighted that perhaps an amalgamation of robust changes in the system, clinicians' perspectives, and patient education would be necessary to tackle this situation. In this study, patients referred from various specialties were included. Many of these patients were on long term steroids. Most of them were not prescribed medications to prevent osteoporosis, and many who were on some medications were inadequately treated. This reveals that despite various guidelines that have been published in the past and have updated the management of GIOP based on recent evidence, awareness and recognition of the severity and impact of GIOP still elude daily practice.[27]

**Table 6.** Treatment Received by Patients at High to Moderate Risk of Major Osteoporotic Fractures

| | Hip Fracture Risk | | | |
|---|---|---|---|---|
| Treatment | High | Moderate | Low | Total |
| Calcium | 3 | 5 | 15 | 23 |
| Row % | 13.0 | 21.7 | 65.2 | 100.0 |
| Col % | 42.9 | 25.0 | 16.9 | 19.8 |
| Biphosphate | 0 | 1 | 0 | 1 |
| Row % | 0.0 | 100.0 | 0.0 | 100.0 |
| Col % | 0.0 | 5.0 | 0.0 | 0.9 |
| Calcium + Vitamin D | 1 | 6 | 15 | 22 |
| Row % | 4.5 | 27.3 | 68.2 | 100.0 |
| Col % | 14.3 | 30.0 | 16.9 | 19.0 |
| Calcium +Vitamin D + Biphosphate | 0 | 3 | 5 | 8 |
| Row % | 0.0 | 37.5 | 62.5 | 100.0 |
| Col % | 0.0 | 15.0 | 5.6 | 6.9 |
| Teriparatide | 1 | 0 | 0 | 1 |
| Row % | 100.0 | 0.0 | 0.0 | 100.0 |
| Col % | 14.3 | 0.0 | 0.0 | 0.9 |
| Nil | 2 | 5 | 54 | 61 |
| Row % | 3.3 | 8.2 | 88.5 | 100.0 |
| Col % | 28.6 | 25.0 | 60.7 | 52.6 |
| Total | 7 | 20 | 89 | 116 |
| Row % | 6.0 | 17.2 | 76.7 | 100.0 |
| Col % | 100.0 | 100.0 | 100.0 | 100.0 |

Soen et al[28] did a retrospective study of patients above the age of 18 years on glucocorticoids for a period of 92 days or more. Patients were divided into different categories as per the dosage of glucocorticoids (prednisolone): < 5 mg/day, 5 to 7.5 mg/day, and > 7.5 mg/day. They included patients over a 10-year period (2009 to 2019). The study population included 25 569 patients, and among them, 13 342 patients did not have cancer. About 4185 patients had RA, and annual bone density measurement was done in only 6.6% of patients in the cancer-free population. Around 51.8% of patients received treatment for GIOP during the entire period. This study revealed a need for programs to increase awareness of GIOP among clinicians. The study also illuminates that only 15.5% of patients were evaluated for GIOP, and even fewer received appropriate treatment for the same.[28]

A study by Gera and Vij[29] did a retrospective analysis of whether patients on long-term glucocorticoids were prescribed prevention measures for prevention of GIOP. They included patients who were on a prednisolone dose greater than or equal to 7.5 mg/day for at least 3 months. 105 patients, 67 being females, were included in this study, and the mean age was 42 years.

The study revealed that assessment for the risk of osteoporosis was negligible and only 3 patients received bisphosphonates as treatment. Bone mineral density was measured in only 4 patients. The key difference from this study was the threshold for evaluation of GIOP (7.5 mg/day in this study vs. 2.5 mg/day in this study) and no mention of FRAX as an assessment tool for GIOP.[29]

In a study by McCloskey et al,[30] they revealed that only 50% of elderly females received adequate treatment for osteoporotic fractures. The 10-year risk estimated for a major osteoporotic fracture was around 18.3%, and for hip fracture, it was around 8%. The study revealed that depending on the country in Europe, the gap in the treatment of glucocorticoid-induced osteoporosis varied from 53.1% to 90.8%.[30]

The study by Rossini et al[31] included 553 patients suffering from RA, connective tissue diseases (CTD), and polymyalgia rheumatica (PMR) and were on glucocorticoids at a dose of at least 5 mg daily for at least 1 year. The prevalence of osteoporosis in this study was assessed using a Dual Energy X-Ray Absorptiometry (DXA) scan (T score less than -2.5). The prevalence of osteoporosis in the spine was around

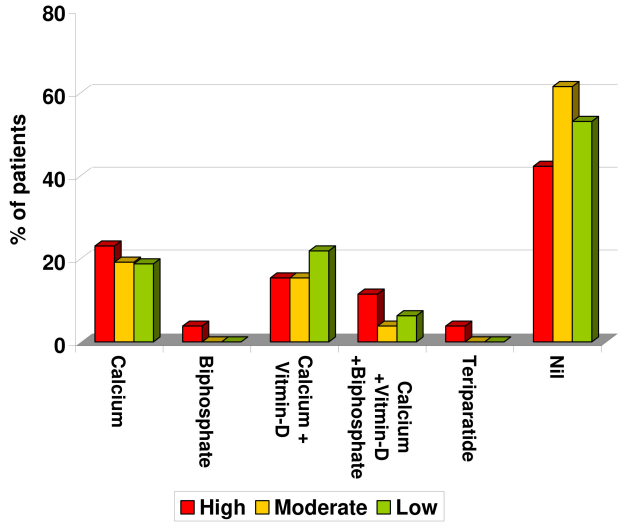


**Figure 5.** Anti-osteoporotic treatment received by patients at risk of major osteoporotic fracture.

28%, 35%, and 38% and in the femur it was 18%, 26%, and 29% in connective tissue disease, RA, and Polymyalgia Rheumatica respectively. For the treatment of osteoporosis, 64%, 80%, and 72% of patients with CTD, PMR, and RA respectively received bisphosphonates.[31]

In Sapkota et al,[32] they did a retrospective study on patients with systemic lupus erythematosus. Patients who received glucocorticoids at a dose greater than 7.5 mg for at least 3 months were included in this study. For patients older than 40 years of age, the risk of fracture was calculated using the FRAX online tool. The key outcome measures presented were vitamin D dosage and levels, use of bisphosphonates, and incidences of osteoporotic fractures on follow-up. The ACR 2017 guideline for glucocorticoid-induced osteoporosis was used as the gold standard. Out of 654 patients with SLE, 203 were found to be at the inclusion dosage of glucocorticoids. In patients below 40 years of age, the median dose of prednisone was 15 mg daily, and in patients above 40 years of age, the median dose was 12.5 mg daily. The median FRAX score for major osteoporotic fractures was 7.8 and for hip fractures was 0.6. In this study, in patients below the age of 40 years, 1 patient received bisphosphonates even though it was not indicated, and in the group of patients above 40 years, almost 36% of patients were eligible for bisphosphonate therapy, but only 14.6% received it. Bisphosphonates were given to another 10% of individuals who did not require it as per the guidelines.[32]

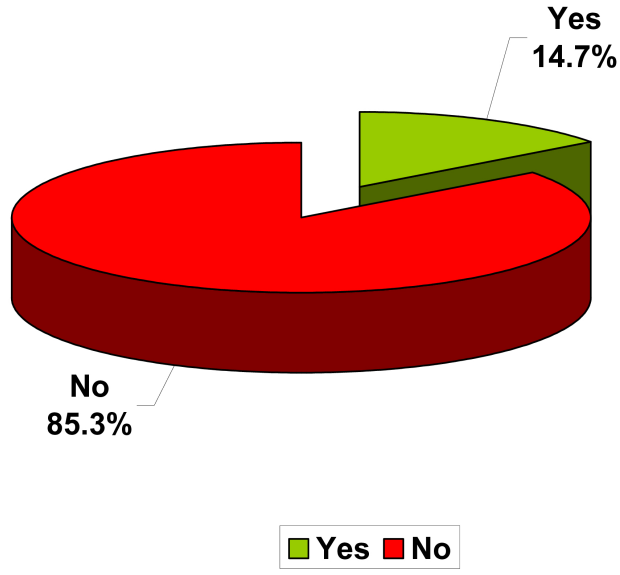


**Figure 6.** Percentage of people treated for glucocorticoid-induced osteoporosis as per ACR 2017 Guidelines.

Ma et al[33] included 790 patients with RA, 60.9% (481) of whom were on glucocorticoids. For the evaluation of glucocorticoid-induced osteoporosis, they measured bone mineral density at femoral neck, greater trochanter, and lumbar spine and divided patients into groups of normal, osteopenic, and osteoporotic patients. The study found that osteoporosis was more prevalent among patients with RA as compared to the control group. Among patients with RA on glucocorticoids, osteoporosis was seen in 41.6%. This study also noted the prevalence of osteoporotic fractures in their cohort, but the evaluation for glucocorticoid-induced osteoporosis was based solely on bone mineral density.[33]

In Yamasaki et al,[34] they conducted a retrospective analysis on patients aged more than 70 years who were diagnosed with Immune Thrombocytopenia (ITP) and were on glucocorticoids. Patients were then evaluated for the risk of future development of osteoporotic fractures based on Japanese guidelines, which included scores based on parameters such as age, dose of prednisone, lumbar spine BMD, and a history of prior fragility fractures (a score of 3 was kept as the threshold for pharmacological intervention). The study also measured FRAX for assessment of fracture risk scores in patients during the phase of loading doses of prednisone and the tapering phase. However, they did not provide any data on the number of patients at low, intermediate, and high risk of osteoporotic fractures. Also, the treatment for osteoporosis in this study was primarily based on BMD.[34]

Another study by Hmamouchi et al[35] estimated the prevalence of GIOP in African patients suffering from rheumatic disorders. They found that the overall prevalence of GIOP was around 47%. However, they used only BMD as a tool to ascertain the presence of GIOP.

What can be summarized from the above studies is that although the risk of GIOP in patients has been evaluated in all of them, the methodologies were inconsistent and not according to ACR 2017 guidelines.

In this study, the focus is on patients who were on glucocorticoids for a duration of greater than 3 months and at a dose greater than 2.5 mg per day, which is the inclusion criteria for evaluating patients for GIOP. This study also provides statistics on how many of the patients were at medium to high risk of fractures due to GIOP, as per FRAX which is indeed a validated tool and has been used in some studies described above.

### Limitations

1. The study was conducted in the Rheumatology OPD only; hence, there could have been a referral bias.
2. It was a single-centre study; hence, the actual percentage of people evaluated for GIOP may be lower than depicted in this study.
3. A number of factors could contribute to osteoporosis in the patients apart from the use of glucocorticoids, such as age (mean age of 56.8 years), height, weight, history of previous fractures, alcohol, smoking, etc. It is uncertain what percentage each of these factors would have contributed to the overall risk of osteoporotic morbidity. However, the focus of this study was to determine if these patients, apart from having other contributory factors for osteoporosis (like age), were on glucocorticoids, had been evaluated for the risk of GIOP, and managed as per the prevailing guidelines. That is where it should be highlighted that FRAX should have been done, as it includes age as a factor along with glucocorticoids in evaluating fracture risk in these patients.

Glucocorticoid-induced osteoporosis is an often-overlooked entity and given the prevalence of glucocorticoid use in departments across the medical field, the gap between available literature on guidelines for managing GIOP and clinical practice is immense. Lack of awareness among practicing physicians and the hustle of daily OPD (outpatient department) make matters worse and difficult to tackle, as it has been mentioned in the discussion that previous efforts to address these issues have created very minimal impact. It requires a certain degree of shift in the mindset of clinicians during their training itself, along with some improvisation from pharma companies to bring attention to this quotidian issue and make it a routine practice that is uniformly adhered to.

In this study, only 7.8% of patients received bisphosphonates for the prevention of osteoporotic fractures. This study further emphasizes the lack of proper evaluation and management of GIOP.

Fracture Risk Assessment is a bedside tool that should be the first assessment method to calculate fracture risk among patients and is the preferred method as per ACR 2017 guideline. This study revealed that none of the patients were ever evaluated via FRAX, few of them underwent DXA scans for measuring their BMD, which is not standardized and does not provide any information on bone architecture. Hence, awareness of FRAX as the first assessment tool is lacking among treating physicians. This study illuminates the need to adapt medical practice as per guidelines for GIOP, especially in a resource-constrained country like India, and use FRAX for risk stratification of individuals with GIOP.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Institutional Ethics Committee Max Healthcare Institute, Saket (Ref No. BHR/TS/MSSH/MHIL/SKT-1/MHEC/RHEUMATO/22-01 Date: 07/02/2022).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – P.D.R., A.K.A.; Design – P.D.R., S.C.; Supervision – P.D.R., S.C.; Resources – H.K., R.B.; Materials – A.K.A., H.K.; Data Collection and/or Processing – A.K.A., J.B.; Analysis and/or Interpretation – A.K.A., P.D.R.; Literature Search – A.K.A., J.B.; Writing Manuscript – A.K.A., J.B.; Critical Review – P.D.R., S.C.

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