Registry on the management of postmenopausal and corticosteroid-induced osteoporosis in Egypt

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Objectives
Osteoporosis is a systemic disease which is characterized by low bone mineral density and abnormal bone architecture, which subsequently leads to bone fractions. The most common types of osteoporosis are postmenopausal osteoporosis and corticosteroid-induced osteoporosis. Long-term treatment and high compliance are required in treatment of osteoporosis to successfully achieve the beneficial goal of reducing future fractures and enhancing quality of life. Hence, the primary objective of this disease registry study was to describe the therapeutic management trends for postmenopausal and corticosteroids-induced osteoporosis and to improve our understanding of the choice of medication prescribed by the physicians, whereas the secondary objectives were to characterize the factors influencing patient compliance and to collect inefficacy data and fracture data in compliant and noncompliant patients over long term (over 6 months of treatment).
Patients and methods
This study was a local, multicenter, observational disease registry. The study comprised a single baseline visit and four follow-up phone calls over 6 months of duration. A total of 571 patients were enrolled who fulfilled the inclusion and the exclusion criteria of the study.
Results
The most commonly prescribed osteoporosis treatment class was bisphosphonates in 523 (91.6%) patients, followed by calcium in 458 (80.18%) patients, vitamin D3 or vitamin D in 288 (50.4%) patients, and calcitonin in 35 (6.1%) patients. The assessment of patient compliance showed that 409 (71.6%) patients were fully compliant throughout the 6-month follow-up period, whereas 162 (28.4%) patients were noncompliant. The most frequent causes of noncompliance were gastritis, missing doses, poor improvement, and patient on several medications. Patients who were compliant to their medications showed lower fracture rates than those who were noncompliant.
Conclusion
Bisphosphonates and calcium were the most frequently prescribed medications. Lower numbers of fractures were noticed in compliant patients than in noncompliant patients.

Keywords:
bisphosphonates, corticosteroid, Egypt, osteoporosis, postmenopausal, registry

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Introduction

Osteoporosis is a condition in which bone strength decreases and broken bones rate increases. It is a frequent disease among old people [1]. Osteoporosis is accompanied with low bone mineral density, and thus increased bone fragility [2,3]. Osteoporosis increases the risk of fractures, the most common of which are vertebral column, rib, and wrist fractures. Vertebral fractures may lead to many complications as it causes chronic neurogenic pain. Though fractures associated with osteoporosis have a clear pattern and heal normally, these fractures are associated with an increased risk of serious functional deterioration and hospitalization [4,5]. Therefore, patient with osteoporosis experienced impaired quality of life [6,7]. Osteoporosis could be secondary to many conditions. The most common of which are increasing age, female sex, long-term corticosteroid therapy, chronic inflammatory disease, malabsorption, and untreated premature menopause [8]. The wide use of corticosteroids in treatment of different medical disorders increases the risk of those patients developing osteoporosis. Postmenopausal women and early menopausal women are also at high risk owing to estrogen deficiency and thus loss of bone mass. Moreover, the risk of osteoporosis is

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higher in women than in men [9]. Many treatments are usually prescribed to manage osteoporosis, which typically involves the use of pharmacological agents. The most common of which are bisphosphonates [10], calcitonin [11], calcium, and vitamin D [12]. Bisphosphonates play an important role in managing of osteoporosis owing to their ability to reduce bone turnover and increase bone mineral density, and thus decrease the incidence of fractures. However, several studies provided evidence of poor and inadequate use of bisphosphonates [13–18]. This poor compliance and persistence are of concern because of its negative effects on patients' health as well as their quality of life [19].

Reasons for noncompliance and persistence are multiple. Usually, they can be separated into external factors and internal factors. Examples of external factors could be the interaction of the treating physician, the dosing frequency [20,21], and inadequate education among patients regarding their medication [22,23]. However, specific patient characteristics may influence adherence to treatment [19,24,25]. Moreover, the occurrence of untoward adverse effects during treatment can be a reason for patients to stop their treatment [19,26]. In elderly patients, because of their common deficits in physical dexterity, cognitive skills and memory, and the high number of medications they are prescribed, simpler dosing regimens and closer assistance might improve compliance and persistence [22].

Another particular concern is that patients with osteoporosis are often not convinced of the diagnosis and the need for therapy. Gold *et al.* [19] have described three different profiles of patients with osteoporosis undergoing treatment. Only 35% of the patients are worried about their osteoporosis status. A large group (58%) is not concerned by their health status and ignores the risk of it. Also, 6% of patients seem reluctant to any kind of treatment [19,23].

These data underline the crucial need to identify patient's characteristics and perceptions of osteoporosis therapy. Identifying characteristics in (none) persistent patients could be the basis for developing tools to improve persistence. The use of medications for the treatment of postmenopausal osteoporosis (PMO) and corticosteroid-induced osteoporosis (CIO) require long-term treatment with high compliance to successfully achieve the beneficial goal of reducing the incidence of future fractures and enhancing quality of life.

Hence, in this observational study, we aimed at assessing of the choice of osteoporotic treatment regimens in real life, patients' compliance, and treatment inefficacy.

Patients and methods

Study participants

Enrolled participants were male and female with osteoporosis, aged 21 years and over. Patients were required to meet the following inclusion criteria at visit one: patients experiencing PMO and/or CIO and were willing to sign the Data Release Consent Form. Exclusion criteria included the following: patients with secondary osteoporosis and participants of another study.

Study design and data collection

This was a local, multicenter, noninterventional, observational, prospective, disease registry. A total of 572 patients were recruited from 38 sites. The first patient included was on 6 June 2009, and the last patient exited was on 28 November 2010. Enrollment duration was extended owing to low recruitment rates or high numbers of inactive sites. Patients with PMO and CIO were treated at the investigators' discretion. No treatment was imposed by the study nor was recommended.

Study was conducted over one cross-sectional baseline visit and four phone calls to follow-up patient's adherence to treatment over a 1.5 month interval for 6 months.

Study objectives

The primary objective of this study was to assess the osteoporosis treatment classes and trends. Secondary objectives included assessing patients' compliance to treatment by the investigator for 6 months through phone calls over 1.5 month each, number and types of fractures, and treatment inefficacy (Table 1).

Patients tolerability and compliance to their medications was assessed by both the physician and the patients themselves on a three-point scale: excellent, fair, and poor.

Statistical analysis

The study population consists of all patients who fulfilled the eligibility criteria. One patient was excluded for not meeting the inclusion criteria. Statistical analysis was performed using frequency tables (number and %) and χ^2-tests. Descriptive summary statistics were provided for both continuous and categorical variables. Data were summarized using mean, SD, minimum, maximum, and median for continuous parameters, whereas counts and percentages were used for ?categorical parameters.

Ethical considerations

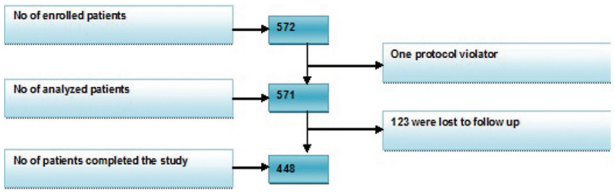
This study was conducted in accordance with the principles established by the 18th World Medical

Table 1 Study objectives

Objectives	Day 0 (V 1) baseline	Follow-up (four phone calls)
Informed consent	✓	
Inclusion/exclusion criteria	✓	
Demographics	✓	
Marital status, education, and occupation	✓	
Vital signs	✓	
Height, weight, and body mass Index	✓	
Osteoporotic risk factors	✓	✓
Confirmatory tests of osteoporosis (if available)	✓	
New fractures		✓
Other medications and treatments	✓	✓
Osteoporosis management and type of osteoporosis treatment	✓	✓
Medication usage and compliance		✓
End of study		✓ (after last phone call only)

Assembly (Helsinki, 1964) and all applicable amendments laid down by it, as well as the ICH guidelines for good clinical practice. This study was conducted in compliance with all international laws and regulations, as well as Egyptian national laws and regulations. Ethics committees' approvals and MOH approval were obtained before starting this study.

Figure 1



Patients disposition.

Results

Recruitment

A total of 572 patients were included in this study. One patient was excluded from the final analysis as he was below the age range specified in the protocol. The analysis was done on 571 patients. A total of 123 patients were lost to follow-up (Fig. 1).

Patients' baseline characteristics and demographics

The mean age of the 571 eligible patients was 57.53 ±10.897 years. Number of female patients was higher than males, representing 89 and 11%, respectively (Table 2). The mean weight was 80.94±14.56 kg. The mean height was 163.34±9.37 cm. The mean BMI was 30.29±5.339 kg/m^2.

Regarding the educational level, 37.1% held university degrees, 22.6% had secondary school degrees, 19.3% were patients who can read and write, 8.2% were illiterate 8.2%, 7.4% had primary school degrees, and 5.3% had preparatory school degree.

Regarding vital signs, the mean heart rate was 80±9.236 beats/min, the mean systolic blood pressure was 133 ±14.991 mmHg, whereas the mean diastolic blood pressure was 85±9.272 mmHg. As for the patients' marital status, 93.5% were married and 4.4% were single.

The osteoporosis risk factors included history of bone and joint disease in 54.6%, positive family history of osteoporosis or brittle bones in 45.7%, menopause before 45 years of age in 22.6%, previous fracture in 27.5%, long-term use of oral corticosteroids (more than 3 months) in 18.2%, current smoking in 14.7%, history of hyperthyroidism or hyperparathyroidism in 4.2%, and low BMI in 1.2%.

Regarding the level of activity, 54.3% of the study population were moderately active, 40.8% were inactive, and 4.9% were vigorously active.

A total of 135 (23.61%) patients presented with previous history of osteoporotic fractures, the most common of which were spine fractures in 56 (9.8%) patients, followed by wrist fractures in 51 (8.9%) patients, hip fractures in 36 (6.3%) patients, and other fracture sites in 18 (3.2%) patients.

Regarding the concomitant disease, 60.4% of patients experienced hypertension, 31% diabetes mellitus, and 21.4% musculoskeletal disease. The most frequent concomitant medications were antihypertensive in 31.5% of the patients, antidiabetics in 22.6%, anti-inflammatory in 9.8%, and corticosteroids in 8.4%.

Osteoporosis medications

Five classes of osteoporosis medications were reported: bisphosphonates were the most frequently prescribed,

Table 2 Baseline characteristics and demographics

Patients' baseline characteristics and demographics	Mean±SD
Age (years)	57.53 ±10.897
Sex (%)	
Male	11
Female	89
Weight (kg)	80.94 ±14.56
Height (cm)	163.34 ±9.37
BMI (kg/m^2)	30.29 ±5.339
Educational level (%)	
University degrees	37.1
Secondary school	22.6
Read and write	19.3
Illiterate	8.2
Primary school	7.4
Preparatory school	5.3
Vital signs	
Heart rate (beats/min)	80±9.236
Systolic blood (mmHg)	133±14.991
Diastolic blood (mmHg)	85±9.272
Osteoporosis risk factors (%)	
History of bone and joint disease	54.6
Positive family history of osteoporosis or Brittle bones	45.7
Menopause before 45 years	22.6
Previous fracture	27.5
Oral corticosteroids	18.2
Current smoking	14.7
Hyperthyroidism or hyperparathyroidism	4.2
Low BMI	1.2
Level of activity (%)	
Vigorously active	4.9
Moderately active	**40.8**
Inactive	54.3
History of osteoporotic fractures (%)	
Total	23.61
Spine fractures	9.8
Wrist fractures	8.9
Hip fractures	6.3
Other fracture sites	3.2
Concomitant diseases (%)	
Hypertension	60.4
Diabetes mellitus	**31**
Musculoskeletal disease	31.4
Concomitant medications (%)	
Antihypertensive	**31.5**
Antidiabetics	**22.6**
Anti-inflammatory	**9.8**
Corticosteroids	**8.4**

Bold means these significance not done for these values.

for 523 (91.6%) patients, followed by calcium was prescribed for 458 (80.18%) patients, vitamin D3 or vitamin D was prescribed for 288 (50.4%) patients, and calcitonin was prescribed for 35 (6.1%) patients (Table 3). Then comes other medications in the fifth rank, representing prescription in eight (1.58%) patients, namely, strontium ranelate for eight (1.4%) patients and ossein-hydroxyapatite for one (0.18%) patient. Some patients were on more than one osteoporotic treatments.

Table 3 Distribution of different medications

Osteoporosis medications	%
Bisphosphonates	91.6
Calcium	**80.18**
Vitamin D3 or vitamin D	50.4
Calcitonin	6.1
Other medications	1.58

Bold means these significance not done for these values.

Hormone replacement therapy and selective estrogen receptor modulators were not prescribed to any patient.

The new concomitant medications included analgesics for five (0.9%) patients, nonsteroidal for four (0.70%) patients, and vitamin B complex for one (0.18%) patient.

Assessment of treatment compliance

Patient compliance was analyzed through four phone calls in a period of 6 months (Table 4). At the first phone call, 451 (79%) patients were compliant to osteoporosis medication as reported, 454 (79.5%) patients were compliant at the second phone call, 453 (79.3%) patients at the third phone call, and 435 (76.2%) at the fourth phone call. A total of 409 (71.6%) patients were fully compliant throughout the 6 months follow-up period.

Patients' compliance was affected by the patient tolerability according to physicians' assessment. Of the 372 patients who showed excellent tolerability, 93.3% were compliant and 6.7% were noncompliant. Alternatively, of the 73 patients who showed fair tolerability, 86.3% were complaint and 13.7% were noncompliant, and of three patients who showed poor tolerability, one patient was compliant and two patients were noncompliant.

The most frequent cause for noncompliance appeared to be 'gastritis,' representing 19 (3.2%) patients, followed by 'missing doses' representing 13 (2.3%) patients, 'poor improvement' representing 11 (1.9%) patients, and finally 'several medications (polypharmacy)' representing 10 (1.8%) patients.

Highest percentage of compliance was for calcitonin (74.3%) and then calcium and vitamin D (72.9%), whereas the least percentage was for bisphosphonates (72.2%).

Table 4 Treatment compliance

Assessment of treatment compliance	%
Physician assessment at phone call 1	
Compliance	**79**
Physician assessment at phone call 2	
Compliance	**79.5**
Physician assessment at phone call 3	
Compliance	**79.3**
Physician assessment at phone call 4	
Compliance	**71.6**
Reasons for noncompliance	
Gastritis	3.2
Missing doses	2.3
Poor improvement	1.9
Several medications	1.8
Compliance according to drug classes	5.3
Calcitonin	74.3
Calcium and vitamin D	72.9
Bisphosphonates	72.2

Bold means these significance not done for these values.

Assessment of treatment tolerability

Physicians' assessment

At the first follow-up phone call, the tolerability was excellent in 331 (58%) patients, fair in 118 (20.7%) patients, and poor in 27 (4.7%) patients (Table 5). However, assessment at the end of the study (fourth phone call) was excellent in 373 (65.1%) patients, fair in 72 (12.6%) patients, and poor in three (0.5%) patients.

Regarding patient treatment tolerability according to their treatment, excellent tolerability was seen in 66% patients for vitamin D, 65.9% for bisphosphonates, 64.8% for calcium, and 57.1% for calcitonin.

Patients' assessment

At first follow-up phone call, the tolerability was excellent in 289 (50.6%) patients, fair in 139 (24.3%) patients, and poor in 48 (8.4%) patients. However, assessment at the end of the study (fourth phone call) was excellent in 341 (59.7%) patients, fair in 98 (17.2%) patients, and poor in nine (1.6%) patients.

As regards to patient treatment tolerability according to their treatment; excellent tolerability was 60.9% in bisphosphonates, 59% in calcium, 58.7% in vitamin D, and 45.7% in calcitonin.

Switching of osteoporosis prescriptions

Switching osteoporosis medication was seen in 20% of patients on calcitonin, representing the highest percentage among the three classes of medications prescribed during this study; 9.2% of patients on calcium; 6.6% of patients on vitamin D; and 6.1% of patients on bisphosphonates (Table 6).

Table 5 Treatment tolerability

Assessment of treatment tolerability	%
Physician assessment at phone call 1	
Excellent	**58**
Fair	**20.7**
Poor	**4.7**
Physician assessment at phone call 4	
Excellent	**65.1**
Fair	**12.4**
Poor	**0.5**
Patient assessment at phone call 1	
Excellent	50.6
Fair	24.3
Poor	8.4
Patient assessment at phone call 4	
Excellent	59.7
Fair	17.2
Poor	1.6
Excellent tolerability regarding each treatment	
Bisphosphonates	60.9
Calcium	**59**
Vitamin D	58.7
Calcitonin	45.7

Bold means these significance not done for these values.

Table 6 Switch between durgs

Switching of osteoporosis prescriptions	%
Bisphosphonates	6.1
Calcium	9.2
Vitamin D	6.6
Calcitonin	20

The drivers for switching the antiosteoporosis prescription were poor improvement in 28 (4.9%) patients, gastritis in 12 (2.1%) patients, and noncompliance in eight (1.5%) patients.

Sites and incidence of fractures

Only 40 (7.0%) patients experienced fractures at different sites, with 56 (9.8%) fractures (Table 7). Of the 40 patients who experienced fractures, 28 (4.9%) patients had one fracture, 10 (1.75%) patients had two fractures, and two (0.35%) patients had four fractures.

The incidence of fractures was the highest in patients on calcitonin (11.4%), followed by bisphosphonates (6.8%), calcium (5.0%), and vitamin D (4.9%).

Regarding the fracture sites, three sites were predominant as follows: femoral neck, pelvic spinal, and wrist fractures, representing 2.9% (16 fractures), 2% (11 fractures), and 1.5% (eight fractures), respectively. These were followed by radius, upper humeral, tibia, and fifth metatarsal bone fractures, representing 1.1% (six fractures), 0.8% (four fractures), 0.4% (two fractures), and 0.2% (one fracture) for each of the later fractured sites.

Table 7 Description of fractures

Sites and incidence of fractures	%
Incidence	**9.8**
Types of fractions	
One fracture	**4.9**
Two fractures	**1.75**
Four fractures	**0.35**
Fractures in relation to treatment	
Bisphosphonates	**6.8**
Calcium	5
Vitamin D	**4.9**
Calcitonin	11.4
Sites of fractures	
Femoral neck	2.9
Pelvic spinal	2
Fracture vs. compliance status (number of patients)	
Compliance	**22**
Noncompliance	**18**

Bold means these significance not done for these values.

Of the 40 patients who experienced fractures, 22 patients were compliant to their medications during the 6 months follow-up period, whereas 18 patients were noncompliant.

Discussion

Osteoporosis is defined as 'a skeletal disease characterized by loss of bone strength susceptible to increased risk of fracture', which is frequent in women and the elderly [27].

In postmenopausal osteoporosis, bone loss results from increased bone turnover associated with a negative bone balance (bone resorption exceeding bone formation). Antiresorptive agents are the predominant class of currently available osteoporosis therapeutic agents. Among them, the nitrogen-containing bisphosphonates alendronate and risedronate were shown to reduce the risk of both vertebral and nonvertebral fractures, and they are widely used in clinical practice [28]. Corticosteroid-induced osteoporosis is the most common secondary cause of osteoporosis [29].

In patients taking corticosteroids, osteonecrosis commonly occurs in the humeral head [30], the femoral head, and the knee [30].

This study showed that bisphosphonates were the most frequently prescribed medications for the treatment of osteoporosis (89.5% of the patients), followed by calcium-containing preparations and vitamin D3 or vitamin D. Results of meta-analysis showed that bisphosphonates are beneficial in avoidance of corticosteroid-induced osteoporosis, with first choice for its prevention being a potent oral bisphosphonates, for example alendronate or risedronate [31,32]. Furthermore, in a study evaluating improving compliance and persistence of bisphosphonate therapy for osteoporosis, data indicate that patients with osteoporosis who have good long-term medication compliance experience substantially lower risk of fracture [33].

Intravenous bisphosphonates should be considered for patients intolerant of the oral route. The use of long-term low-dose corticosteroids treatment with calcium and vitamin D among patients may prevent further bone loss. Moreover, the use of parathyroid hormone also showed promising results [34]. However, treatment with calcium in postmenopausal women is mostly beneficial in patients with low calcium intake [35].

Compliance to osteoporosis medication is crucial to prevent fractures and to ensure efficacy. However, patients' compliance to osteoporotic medications is seen to be low. In this study, high compliance rates were noticed over a follow-up period of six months. Compliance rates ranged from 74.3 to 72.2% in all treatment classes. Common reason for noncompliance in this study were gastritis, low awareness of the patients of their medications, poor improvement, and patients on several medications.Overall tolerability assessment showed that patients were tolerable to their medications, with a high number of excellent and fair tolerable patients and a small number of poorly intolerable patients.

Osteoporosis medications aim at reducing the risk of fractures. Meta-analysis study showed that bisphosphonates are effective at avoiding and treating corticosteroid-induced bone loss at the lumbar spine. However, efficacy regarding fracture avoidance was not concluded from this analysis [31].

Moreover, studies on calcium in postmenopausal women with osteoporosis showed that calcium is highly beneficial mainly in preventing osteoporosis. But once osteoporosis occurred, its benefits decline [35].

Calcitonin administration in osteoporosis results in reduction of the frequency of subsequent fractures, in both the spine and the hip [36].

The main concern in patients with osteoporosis is the risk of fractures. The most common fractures in patients with osteoporosis are vertebral column, rib, and wrist fractures. All medications are aimed on decreasing the incidence of fractures in patients with osteoporosis. In this study, only 7% of the patients experienced fractures.

Higher numbers and percentages of fractures were seen in noncompliant patients than in compliance patients. It suggests that patients' compliance and awareness of their medications may play a valuable role in decreasing fracture rates in patients with osteoporosis. The most common types of fractures in this study were femoral neck, pelvic spinal, and wrist fractures. The incidence of fractures was the highest in patients on calcitonin, followed by bisphosphonates, calcium, and vitamin D.

Regular physical activity and exercise also play a crucial role in patients with osteoporosis, as prolonged periods of inactivity endorses reduced bone mass, whereas mechanical loading through exercise increases bone mass [10]. In this study, assessing of the patients' activity through follow-up periods and comparing it with fracture rates was not done.

Furthermore, the number of female patients were significantly higher than male patients, thus an depth analysis of disease characteristics in male patients was not achieved.

A higher number of patients were planned to be included in this study, but owing to low recruitment rates, this could not be achieved. Further studies are required to improve our understanding of the choice of the medication in patients with osteoporosis.

Also, educational programs are needed to educate patients about their illness and the need for persistent treatment and to increase awareness among high-risk groups about prophylaxis and preventive measures against fractures.

Conclusion

Osteoporosis is a frequent disease that affects both males and females. In our study, the most common prescribed pharmacological treatments were bisphosphonates and calcium. Patients' compliance was high in all treatment groups. Reasons for noncompliance were gastritis, low awareness, poor improvement, and patients on several medications. The number of fractures witnessed in this study is small; the most common of which were femoral neck, pelvic spinal, and wrist fractures. Patients' compliance decreased the rates of fractures. Osteoporosis disease requires compliance to medications, regular exercise, and decreasing the risk of fractures.

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Conflicts of interest
There are no conflicts of interest.

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