Overview of the Pharmacological Management of Osteoporosis in Postmenopausal Women

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aim: The aim of the study is to assess the Pharmacological management of osteoporosis in postmenopausal women.
Objective: The purpose of this study is to evaluate the treatment of osteoporosis in postmenopausal women.
Methodology: This is an observational prospective study, carried out in a tertiary care hospital.
Results: A total of 300 postmenopausal women were enrolled in the study. The mean ± standard deviation, of the age of postmenopausal women included in this study was 55.5 ± 5.0 years. 68.1% were prescribed with the combinational therapy of Teriparatide+Bisphosphonates. 39.2% of subjects were using acetaminophen for pain.
Conclusion: Antiresorptive drugs (hormonal therapy, bisphosphonates, and denosumab) and, the anabolic agents (teriparatide) are commonly prescribed, in this study it is obvious that Sequential Therapy is highly prevailing in the clinical practice, with 68.1%.

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1. INTRODUCTION

Osteoporosis is paving to be a serious public health problem in India. Currently, it is estimated, over 200 million people worldwide suffer from this disease. [1] The prevalence of osteoporosis in postmenopausal women varies between 25% and 62%, in India. [2-4]

According to World Health Organization (WHO), BMD (bone mineral density) 2.5 standard deviations or more below the mean value for young adults (T score ≤ −2.5) is defined as osteoporosis, and BMD below this limit and one or more fractures is defined severe osteoporosis [5]. Osteoporosis is classified as clinical osteoporosis (involves the identification of a fragility fracture and does not need densitometry for treatment to begin), and densitometry osteoporosis (identified via an assessment of bone mineral density) [6]. As women have a lower peak bone mass, which is compounded by the hormonal changes that occur at the time of menopause, osteoporosis is more common in women [7].

The WHO definition applies to postmenopausal women and men aged 50 years or older. This diagnostic classification should not be applied to premenopausal women, men younger than 50 years or children [8].

Chart 1: WHO (World Health Organization) CRITERIA FOR CLINICAL DIAGNOSIS OF OSTEOPOROSIS [9]

BMD T-score	Diagnosis
T-score ≥ -1	Normal
-1 > T-score > -2.5	Low bone mass
T-score ≤ -2.5	Osteoporosis
T-score ≤ -2.5 with existing fracture	Severe osteoporosis

The T-score is the patient's bone density compared with the BMD of control subjects who are at their peak BMD, while the Z-score reflects a bone density compared with that of patients matched for age and sex [10].

As ovarian function declines with age, the combined effects of estrogen deprivation, and increased follicle - stimulating hormone (FSH) production cause marked stimulation of bone resorption and a rapid bone loss. Calcium and Vat-D together play a major role in building up strong bones in women after menopause. Lack of proper supplementation of calcium after menopause spikes osteoporotic conditions. In a cross-sectional study from South India, 74.5% of the postmenopausal women take less amount than the recommended daily calcium dose [11]. Increased physical activity, done routinely, helps improve the skeletal system's mechanical ability [6]. Vitamin D deficiency is prevalent in 70% of the general population in India [12]. Vit-D supplementation for post-menopausal women with or without osteoporosis is mandatory. The treatment emphasizes on decreasing fracture risk, implying systemic bone loss and the stabilization or increasing BMD [13]. For centuries, several molecules have been developed and proved effective [14,15]. Antiresorptive agents (reducing the osteoclastic bone resorption) and anabolic agents (increasing the osteoblastic bone formation activity.) are used in clinical therapy of osteoporosis. [6,15]

Antiresorptive agents include Bisphosphonates, Denosumab, Estrogen replacement and selective estrogen receptor modulators, and Calcitonin. Bisphosphonates inhibit osteoclastic bone resorption, they are most widely used for treating osteoporosis among which zoledronic acid a nitrogen-containing bisphosphonate which act as a potent inhibitor of bone resorption by inhibiting osteoclast proliferation and induces osteoclast apoptotic cell death, has a high affinity for mineralized bone and especially for sites of high bone turnover, followed by pamidronate > alendronate > ibandronate > risedronate > etidronate > clodronate. [16] Denosumab is an antiresorptive Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, targets and binds RANKL there by inhibiting osteoclast formation, function, and survival. Estrogen replacement therapy at different doses rapidly normalizes turnover, preserves BMD at all skeletal sites, leading to a significant reduction in vertebral and nonvertebral fractures. The most frequently used Selective estrogen receptor modulators (SERMs), raloxifene, lasofoxifene, and bazedoxifene are nonsteroidal synthetic drugs with similar effects as estrogen [17]. Calcitonin inhibits bone resorption by increasing osteoblast activity. Teriparatide, a recombinant Human Parathyroid Hormone (1–34) is an anabolic agent, it increases both bone formation and resorption balancing the levels of osteoclasts and osteoblasts and is advised to give bisphosphonates after completing the course of PTH therapy.

Combination or Sequential therapy, the combination of anabolic and antiresorptive

agents, due to their synergistic activity improves bone density and bone strength. However, results of sequential therapy were mixed, [18-27]. this was not confirmed in the earlier trials [18,19,23,25-27] but recent trials reported positive effects of sequential therapy [20-22,24].

2. MATERIALS AND METHODS

2.1 Study Design and Study Setting

An observational prospective study, conducted during August 2018 to January 2019 in a tertiary care hospital in Vijayawada. Post-Menopausal women of age between ≥ 45 years, who attained natural menopause and are menopausal for at least 1 year were included and Premature menopausal (ovarian failure), surgical menopausal women, Menopausal women with osteoporosis are excluded from the study.

2.2 Study Procedure

Elaborate information of age, obstetric history, history of fractures in the past, any history of fracture in the parents, history of chronic diseases such as diabetes, hypertension, thyroid disorders etc., drug history specifically with respect to glucocorticoids, daily sun exposure, dietary history and exercise history were noted. Details about common symptoms of menopause and perimenopause such as hot flashes, night sweats, sleep disturbances, vaginal dryness, lack of concentration, mood swings, menstrual disturbances etc. were taken. The height and weight of all subjects was recorded in the outpatient department using digital apparatus. The weight in kilograms was divided by the square of the height measured in meters to calculate the Body Mass Index (BMI) for each subject and then subjects were informed to undergo bone mineral densitometry using Dual-energy X-ray absorptiometry (DEXA) scan.

Daily physical activity was assessed moderate for subjects performing only household tasks, heavy for those involved in some form of exercise such as walking, jogging or yoga for at least 30 min a day for at least five days a week, in addition to household work. Those responders, who were walkable but claimed to undertake no significant routine physical activity, were classified as sedentary. Daily sun exposure was divided into less than one hour, one to five hours and more than five hours of exposure during day time.

2.3 Statistical Analysis

Data was expressed as means, SD and frequencies (%) using Microsoft Office Excel 2010, 15.0.

3. RESULTS

A total of 300 postmenopausal women who were referred for DEXA participated in this study. The mean ± SD age of the post-menopausal women included in this study was 55.5±5 years. The mean ± SD age of menopause was 47.3±1.4 years. 75% of subjects assessed have the normal BMI, 18.5-24.9 kg/m $^{2.}$ The mean (SD) BMD (g/cm2) was 0.24(0.04) for Osteoporotic and 0.43 (0.09) for Non-Osteoporotic. Table 1, depicts the demographic and clinical characteristics of the women. A total of 207 subjects (69%) were osteoporotic postmenopausal and 93(31%) were postmenopausal but non-osteoporotic. The majority of the study participants had completed High school education (n = 104(34.7%),54(18%) of them were illiterate, and 70(23.3%) of them had received college education.

67% of women in our study had insufficient levels of serum 25-hydroxyvitamin D3 and abnormal thyroid levels. 66% women in the study population had abnormal parathyroid hormone values.181(60.3%) of subjects are Diabetic, 167(55.6%) were Hypertensive and 145(48.3%) were suffering with Osteoarthritis, 143(47.4%) of subjects do Moderate physical activity. Minimal sun exposure recorded in 35(11.6%) subjects and 69(23%) have >5 hours of sun exposure as depicted in Table-1. 167(55.6%) subjects take regular Vit-D and Calcium, Vit-D and Calcium alone is taken by 69(23%), 64(21.4%) of subjects respectively depicted in Table-1.

Percentages of Age groups and Duration of menopause in postmenopausal women is shown in Table-2 and 3.

The mean (SD) of T-scores depicted in Table-4 are 2.60 (0.18), -2.58 (0.23), -2.61 (0.16) for Lumbar spine (L1-L4), Femoral neck (left), Total hip (left) respectively.

Pharmacotherapy for osteoporosis is depicted in Graph-1, 19 (9.3%) on other combinations, 24 (11.59%)and 23 (11.1%) on Calcium+ Vit-D and HRT+ Denusomab respectively, 141(68.1%) of subjects were prescribed with the combinational therapy of Teriparatide and Bisphosphonates.

Graph-2 shows prevalence of NSAIDS for pain management, 81(39.2%) of subjects were using acetaminophen, 63 (30.5%), 32(15.4%), 31(14.9%) use Ibuprofen, Tramadol, Aspirin respectively.

Table 1. Demographic and Clinical characteristics

Characteristics	N=300(100%)
Osteoporotic	207(69%)
Non-osteoporotic	93(31%)
Age [Mean ± SD]	55.5 ±5.0
Age at Menopause [Mean ±SD]	47.3 ± 1.4
Duration of Menopause [Mean ± SD]	8.2 ± 4.5
Education [n (%)]	
College	70(23.3%)
High School	104(34.7%)
Primary School	72(24%)
Illiteracy	54(18%)
BMI, Kg/m^2 [n (%)]	
Obese (equal or >30 kg/m^2)	8(2.6%)
Overweight (25.0-29.9 kg/m^2)	55(18.4%)
Normal (18.5-24.9 kg/m^2)	225(75%)
Underweight (<18.5 kg/m^2)	12(4%)
BMD, g/cm^2 [Mean (SD)]	
Osteoporotic	0.248 ± 0.040
Non-Osteoporotic	0.438 ± 0.092
Physical Activity	
Sedentary	50(16.8%)
Moderate	143(47.4%)
Heavy	107(35.8%)
Endocrine Parameter	
Hypovitaminosis D	201(67%)
Hyperparathyroidism	198(66%)
Hypothyroidism	201(67%)
Chronic diseases	
Diabetes mellitus	181(60.3%)
Hypertension	167 (55.6%)
Osteoporosis	145(48.3%)
Sun exposure [n (%)]	
<1 hr	35(11.6%)
1-5 hr	196(65.4%)
>5 hr	69(23%)
Regular intake of	
Vit-D	69(23%)
Calcium	64(21.4%)
Vit-D + Calcium	167(55.6%)

**Table 2. Prevalence of osteoporosis of postmenopausal women according to different age group**

Age group	N (%) (N=207)
45-54	23(11.1%)
55-64	158(76.4%)
>65	26(12.5%)

Table 3. Duration of menopause

Duration(years)	N=207(%)
<5	5 (2.4%)
5-10	114(55%)
>10	88(42.6%)

Table 4. Bone parameters in osteoporotic participants

Location	T-score Mean (SD)
Lumbar spine (L1-L4)	-2.60 ±0.18
Femoral neck (left)	-2.58 ±0.23
Total hip (left)	-2.61 ±0.16
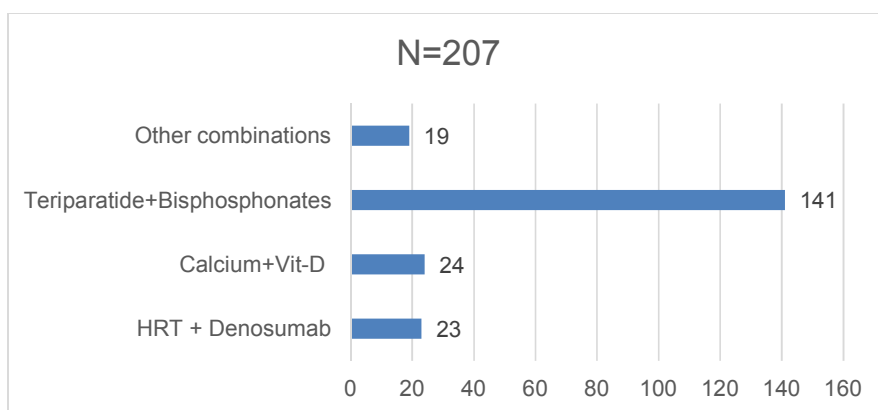
Graph 1. Pharmacotherapy for osteoporosis
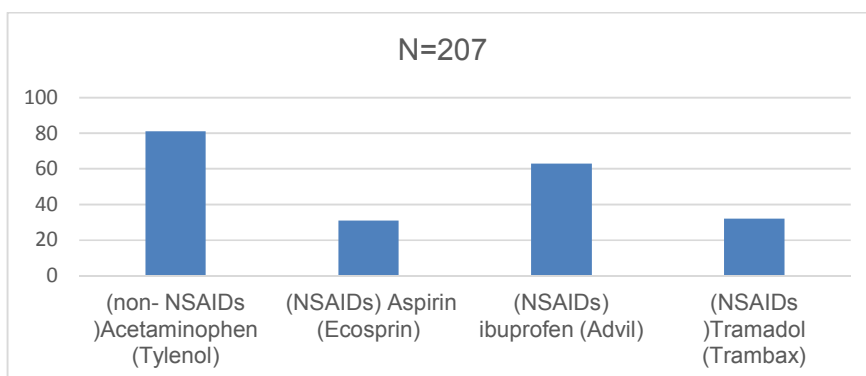
Graph 2. Prevalence of analgesics being used for pain management

4.DISCUSSION

The objective of the study was to assess the Pharmacological treatment and level of awareness of osteoporosis among postmenopausal women especially with respect to risk factors, treatment options, and consequences, the explanation for choosing postmenopausal women as study participants was that they are at the highest risk for osteoporosis and fragility fractures, and this warrants early and precautionary screening in this group. In this study, the mean age of attaining menopause was 47.3 years. This is consistent with the study conducted by Ahuja et al., in which the average age of menopause of an Indian woman was 46.2 years [28] and is also related with the study conducted by Manickavasagam Senthilraja et al., in which the average age of menopause was 49 years. [29]

The median age at menopause among white women from industrialized countries ranges between 50 and 52 years. [30-33]. The OP prevalence increased progressively after the age of 55 years in postmenopausal women. A survey reported that the prevalence of osteoporosis was 10.3% in the population older than 50 years in the US. [34] The rate of osteoporosis in Caucasians women older than 50 years varies from 7.9% to 22.6%. [35] In Italy, nearly 34% in a cohort of 4000 women experienced osteoporotic fractures. [36]. Aging is associated with an increased risk of osteoporosis. [37,38]. The association between menopausal duration and Osteoporosis as seen in the present study was agreed with other studies. [39,40]. It's obvious that the participants with lower education levels were more likely to have osteoporosis than individuals with higher education level, especially postmenopausal women. The finding agreed with the previous research that demonstrated the association between educational level and risk of osteoporosis.[39,41–45] Although little is known of the definitive reasons why educational level may have an effect on BMD and OP, it may be explained by the more knowledge of prevention of osteoporosis in the participants with high educational level,[46] the greater level of physical activity and nutritional intake of more educated individuals, lower dietary calcium intake,[47] environmental factors such as sun exposure.

67% of women in our study were found to have insufficient levels of Vitamin D. 84.9% postmenopausal osteoporotic women from Middle East were found to be Vitamin D deficient, as reported by Marie-Helene Gannag e-Yared et al. [48] A Columbian study reported the prevalence of low serum Vitamin D to be 54.3% in women with osteoporosis [49]. Hypovitaminosis D prevails in all age groups in India and it is certain that Vitamin D deficiency is treated adequately, especially in postmenopausal women and elderly men with osteoporosis who are candidates for anti-osteoporotic treatment. [12,49-51]. 66% (n= 198) had hyperparathyroidism in our study, many researchers have reported on the frequent association of hyperparathyroidism and low BMD [52, 53]. 67 %(n=201) of our cases had hypothyroidism. Lopez et al. from Spain have reported the prevalence of osteopenia to be 87% and osteoporosis 14% in subjects with subclinical hypothyroidism [54].

In our study 60.3% (n=181) are complicated with diabetes mellitus. Diabetes mellitus as well as hypertension were significantly associated with low BMD in a study from Jordan [55]. In a systematic review Sugimoto et al. Drew a conclusion that diabetes is an independent risk factor for the development of fracture in the Asian population. However, the relationship between diabetes and low BMD was equivocal [56]. 48.3 %(n=145) women were suffering from Osteoarthritis in the present study. 55.6% (n=167) of our subjects had hypertension. In a study of metabolic factors and low BMD, hypertension was found to be associated significantly with poor T-scores. The association amid these two diseases mediated via low dairy product intake has been proposed by Varenna et al. [57].

Inadequate sun exposure and sedentary lifestyle have been postulated to contribute to low BMD, even in tropical countries [57]. In our study 68.1% (n=141) were on combination therapy of anabolic agents and bisphosphonates. Currently, combination therapy is at the second step, switching from monotherapy (anabolic or antiresorptive agents) which might be appropriate. [18,24,58-60] Moreover, anabolic agents could be used concomitantly combined with other antiresorptive agents. The effects of combination therapy, also, seem to be affected by the potency of antiresorptive agents. [61] In a study by Schafer et al., combined monthly IBN (150 mg/month) and PTH (1-84) (100 µg/d) therapy using two different dosing regimens as follows

a. Combination therapy: combination with PTH and IBN for 6 months, followed by 18 months of IBN alone.
b. Sequential therapy: PTH alone for 3 months followed by 9 months of IBN for two sequential courses. Using Quantitative computed Tomography (QCT), the volumetric BMD of the hip in the sequential therapy showed a higher volumetric BMD after two years.

In the first few months, concurrent therapy resulted in a rapid increase in the bone turnover marker, followed by a gradual decrease after 2 years. Markers increased to a maximal value at 3–4 months in the sequential therapy group, followed by a gradual decrease when IBN was used alone. However, in the second 3-months PTH therapy, the bone turnover marker increased again though the increase was inferior to the first course, perhaps benefiting BMD. [62].

Based on the findings from the studies, combination therapy may not be an alternative option for osteoporosis therapy due to a lack of additive effects. However, as noted in studies, data focusing on the reduction of the risk of the fracture using combination therapy are largely lacking.

The use of NSAIDs is sometimes unavoidable in the control of pain. In our study 30.5% (n=63) subjects were on Ibuprofen for Pain management. Raisz reported in 1977 for the first time that prostaglandins exerted marked resorption effect on the bone tissue in rats. [63] However, Chambers in 1985 claimed that the agents depressed the rate of resorption by osteoclasts in vivo experiment [64].

CONCLUSION

Osteoporosis is quite a common clinical situation, with an increasing incidence within the next decades due to the global aging of the population. Fractures and Bone loss, follows due to the reduction of estrogen levels in the postmenopausal period, leading to increased osteoclast activity and, subsequently, bone resorption. Bisphosphonates are widely used for treating osteoporosis as they inhibit the resorption of bone by osteoclasts and may have an effect on osteoblasts. Calcium and Vit-D together play a major role in building up strong bones in women after menopause and these should be mandatory supplement for all postmenopausal women. The challenge today is to advance the detection of osteoporosis and induce healthcare professionals to refer at-risk patients for treatment.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee, Reg. No IHEC/SIMS/2018/030.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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