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Comparative Effectiveness of Different Osteoporosis Medications in Enhancing Bone Mass

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Purpose: To compare the spine and non-dominant hip bone mineral density before and after treatment with different categories of osteoporosis medications.
Methods: In this retrospective cohort study, we analyzed the medical records of patients with osteoporosis who were prescribed anti-resorptive agents (bisphosphonates, alendronate, risedronate, intravenous ibandronate, and denosumab) or bone-forming agents (teriparatide). Patients were selected using purposive sampling. Descriptive statistical analysis was performed, including calculations of percentages, means, and standard deviations, along with hypothesis testing using Wilcoxon signed-rank and t-tests.
Results: Among the 80 participants treated with these medications and monitored over 3–5 years, with at least 2 years of continuous treatment, none had hip or spine fractures. In the bisphosphonate group (n = 59), both the spine and non-dominant hip bone mineral density showed significant improvements. The denosumab group (n = 17) demonstrated a significant increase in spine bone mineral density, whereas the increase in nondominant hip bone mineral density was not significant. The teriparatide group (n = 4) showed improvements in both the spine and non-dominant hip bone mineral density, although not significant, possibly because of the small sample size.
Conclusions: All medication categories had positive effects on bone mineral density. Antiresorptive agents, particularly bisphosphonates, showed significant improvements in both spine and hip bone mineral density, whereas denosumab showed significant improvement, specifically in spine bone mineral density. The bone-forming agent teriparatide showed a positive trend, although not significant, likely because of the limited sample size.

Keywords: Osteoporosis, anti-resorptive agents, bone-forming agents, bone mineral density, bisphosphonates, denosumab, teriparatide

Osteoporosis is a condition in which the bone strength decreases, making individuals more susceptible to fractures. It is a widely accepted fact that bone strength depends on both bone density and bone quality. Usually, after peak bone mass, the bone density declines by 0.3%–0.5% annually, and then rapid bone loss occurs during the menopausal period, with bone density loss of 3%–5%. Involutional bone loss in the elderly is another factor[3]. During this period, bone formation slows, leading to a gradual decline in bone mineral density (BMD). This decline is particularly obvious in

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women, as bone resorption rates increase rapidly after menopause. Non-modifiable risk factors for osteoporosis include age ≥ 65 years, Caucasian and Asian ethnicity, early menopause (< 45 years) , bilateral oophorectomy, small body frame, and a family history of osteoporosis. Modifiable risk factors include inadequate calcium intake, lack of physical activity, smoking, excessive alcohol and caffeine consumption, body mass index (BMI) < 19 kg /m^2, and estrogen deficiency before menopause. Epidemiological statistics estimate that osteoporotic fractures affect approximately 40% of women and 13% of men worldwide. Statistical predictions indicate that the number of hip fractures will increase from 1.7 million in 1990 to 6.3 million in 2050, with the majority occurring in Asia[2]. Indeed, by 2050, Asia is projected to account for more than 50% of all osteoporosis-related hip fractures.

In Thailand, the prevalence rate of female osteoporosis in the menopausal clinic at Chulalongkorn Hospital is 15.7%[3], whereas that of male osteoporosis (Pongchaikul Chatlert and team[4]) is 12.6% from small subjects. Thailand has become an aging society and the number of osteoporosis patients is expected to increase. Most osteoporosis treatments are original drugs, and studies on the efficacy of drug regimens are limited. Our Province has one of Thailand's highest proportions of elderly residents, with 24.24%[5] of the older population. Osteoporosis is a significant musculoskeletal disorder that is becoming increasingly prevalent in this population, making it crucial to implement preventive measures and establish a comprehensive care system. Our hospital founded the Osteoporosis Clinic, to investigate diseases and use osteoporosis drugs with standard protocol under Nation Osteoporosis Foundation[2] policy for specific patients with osteoporosis. In this study, we aimed to assess the effectiveness of different groups of osteoporosis medications and compare the mean BMD of patients at the osteoporosis clinic before and after treatment with these medications.

METHODS

This was a retrospective cohort study that analyzed data from medical records. The study utilized a sample group from the osteoporosis clinic consisting of individuals who underwent treatment between January 1, 2015, and May 31, 2021. The study received IRB approval from the Ethic Committee of our hospital in 012/2565 coding. Our hospital established a dedicated osteoporosis clinic in October 2014, which continues to operate to the present day. The clinic's service model relies on a multidisciplinary team approach, emphasizing screening activities to identify individuals at risk for osteoporosis (Appendix 1).

First, the hospital's multidisciplinary team developed a screening protocol specifically for individuals aged > 50 years. The screening protocol was as follows:

1. General risk factors include weight, height, BMI, dietary habits, physical activity, and underlying health conditions.

2. Specific risk factors include menstrual history[6], history of oophorectomy, history of minor trauma, and history of steroid use.

3. OSTA screening (Osteoporosis Self-assessment Tool Asian) check list for at risk patients.

4. Quantitative Ultrasound (QUS) Screening[7]: A QUS score < –2.5 is required for 1 risk point. However, the QUS is only a screening tool. For confirmation, the DXA, which is the main diagnostic tool according to WHO standards, is still required. After screening, if the patient is identified to be at risk (Two points out of four.), the patient underwent osteoporosis diagnostic testing using DXA scan as a standard diagnostic test, which measures the BMD as a representative of bone mass. A BMD score between + 1 and –1 is considered normal; a score below –1 but not lower than –2.5 indicates osteopenia (low bone mass); and a score below –2.5 is classified as osteoporosis[8,9]. The BMD T-score is essential for assessing the risk of fractures, with studies showing that the risk of fractures increases by 1.4 to 2.6 times for each standard deviation change in the T- Score[10]. Treatment decisions are not solely based on a BMD T-Score of ≤ –2.5 but also consider clinical factors when deciding whether to admit a patient to the clinic for further treatment.

Finally, the patients in the Osteoporosis Clinic at our hospital were treated with three categories of medications along with the National Osteoporosis Foundation regulation[2]. Bisphosphonate is the first-line drug used for treatment. A follow-up DXA scan will be considered after 2 years. If the results remain the same or do not improve, the treatment will need to be changed from bisphosphonate to Denosumab. Teriparatide was another drug considered in patients with hip or spine osteoporosis with a T-score < –3.5. The three categories of medications were as follows:

1. Bisphosphonates, which reduce the activity of the osteoclasts involved in bone resorption. The medications administered in the hospital include Actonel®, Fosamax®, and Ostex®.

2. Denosumab, a monoclonal antibody (mAb) and biologic agent that targets the cytokine RANKL to prevent bone loss and reduce bone resorption by inhibiting its activity. Our hospital uses Prolia®, but patients with hypocalcemia should not receive it.

3. Teriparatide is an analog of parathyroid hormone that stimulates the cyclic adenosine monophosphate/ protein kinase A (cAMP/ PKA) pathway to promote bone formation. Our hospital uses Forteo®.

Currently, this clinic has a total of 300 patients, including 195 patients with normal bone density and osteopenia. Only patients who were diagnosed with osteoporosis (n = 105) received osteoporosis medication, all of whom were provided with a guide for self-care, exercise instructions, and calcium and vitamin D supplementation. The patients received a DXA scan once a year for monitoring from the National Osteoporosis Foundation, as recommended[1,2].

Population and Sample Size

The study included 300 patients treated at the osteoporosis clinic of our hospital between January 1, 2015, and May 31, 2021. The medical records from this period were reviewed to analyze and categorize the population based on treatment. The inclusion criteria were as follows: diagnosed with osteoporosis; BMD ≤ –2.5 SD, as determined by DXA scan once a year[1,2]; and received continuous treatment with the same osteoporosis medication for at least 2 years without any missed doses. Initially, the study included 105 osteoporotic patients who met the criteria; however, Twenty-five patients were excluded from the study due to treatment discontinuation, medication use for less than 2 years, or fewer than two DXA scans (at least one per year) performed consecutively.

Therefore, 80 patients who qualified for the study were divided into three groups according to the medications available at the Osteoporosis Clinic (Table 1).

Table 1 Number of patients with osteoporosis in the study group, categorized by medication received.

Patient Group	Medication Group	Number of Patients (Sample Size)
1	Anti-resorptive (osteoclast) (bisphosphonate) including: - Actonel® (150 mg), taken orally once monthly - Fosamax® (70 mg), taken orally once weekly - Ostex® (3 mg), taken intravenously every 3 months	59
2	Anti-resorptive (RANKL) (denosumab), (60 mg), taken subcutaneously every six months.	17
3	Bone forming agent (teriparatide), (20 micrograms), taken subcutaneously once daily.	4
	Total	**80**

Data Analysis

The SPSS statistical software package was used to analyze the data using descriptive statistics (percentage, mean, and standard deviation), paired sample t-tests, and Wilcoxon signed-rank tests. Analyses were conducted separately for the spine and hip to compare the effectiveness of the four types of medications.

RESULTS

Characteristics of the Sample Group

The sample group consisted of 80 individuals, including five males (6.67%) and 75 females (93.33%). The majority of the participants (42; 52.50%) had been attending the clinic for 5–6 years, followed by 30 people (37.50%) for 3–4 years and 80 people (10%) for 7 years. In terms of BMI[12], most participants were within the normal range (55; 68.75%), followed by 17 people (16.25%) above the normal range and eight people (10%) below the normal range. Among the female participants, the majority experienced menopause after the age of 45 (76; 88.37%), while 10 persons (11.63%) experienced menopause before the age of 45. On average, menopause occurs at a young age in these patients, and the earlier it occurs, the greater is the risk[3]. Most female participants (67, 89.33 %) had no history of oophorectomy, while eight (10.67%) had undergone the procedure. None of the participants (100 %) had a history of alcohol or tobacco use. The majority of the participants (52; 65%) had a history of regular exercise, while 28 (35%) reported no exercise routine. The majority of participants had no family history of hip fractures (75 people, 93.75%), while five people (6.25%) reported a family history of fractures. The majority of participants (73, 91.25 %) had no history of hip, spine, or wrist fractures, whereas seven (8.75%) had a history of minor fractures. Most participants had no history of steroid use (71; 88.75%), followed by six people (7.50%) with a history of steroid use and three people (3.75%) who did not specify their steroid use history.

Comparison of BMD Before and After Treatment

The paired sample t- test with a 95% confidence level revealed a significant improvement in the BMD of the spine and hip following bisphosphonate treatment compared to that before treatment ($p < 0.05$; Tables 3 and 4).

The Wilcoxon signed-rank test was used to evaluate spine and non-dominant hip BMD in the groups treated with denosumab and teriparatide, with a 95% confidence level. The results revealed a statistically significant difference in spine BMD before and after treatment with denosumab ($p < 0.05$), whereas the non-dominant hip BMD did not show a significant difference, as shown in Table 5.

There were no significant differences in spine and non-dominant hip BMD before and after teriparatide treatment, as shown in Table 6.

Table 2 Characteristics of the sample group.

Category	Number (n)	Percentage (%)	Category	Number (n)	Percentage (%)
Sex			**Oophorectomy (female only)**		
Male	5	6.67	Yes	6	8.00
Female	75	93.33	No	69	92.00
Duration of Clinic Attendance			**Alcohol/tobacco use**		
3–4 years	30	37.50	Yes	0	0
5–6 years	429	52.50	No	80	100
7 years	8	10.00	**Exercise**		
Age (years)			Yes	52	65.00
< 70	26	32.50	No	28	35.00

Table 2 Characteristics of the sample group. (Cont.)

Category	Number (n)	Percentage (%)	Category	Number (n)	Percentage (%)
≥ 70	54	67.50	**Family history of hip fractures**		
BMI			Yes	5	6.25
Below normal (< 18.5)	8	10	No	75	93.75
Normal (18.5–22.9)	55	68.75	**History of hip, spine and wrist fractures**		
Above normal (23.0)	13	16.25	Yes	7	8.75
Menopause before 45 years (female only)			No	73	91.25
Yes	8	10.67	**Steroid use history**		
No	67	89.33	Yes	6	7.50
			No	71	88.75
			Not Specified	3	3.75

Table 3 Mean and standard deviation of bone mineral density before and after treatment with bisphosphonates paired samples statistics.

		Mean (gm/cm²)	N	Percent change (%)
Spine bone mineral density	Before	−2.38	59	↑ 61.34
	After	−1.46	59	
Hip bone mineral density	Before	−1.94	59	↑ 76.80
	After	−1.49	59	

Table 4 Comparison of bone mineral density before and after treatment with bisphosphonates in the sample group paired samples test.

		Paired Differences					t	df	Sig. (2-tailed)
		Mean Difference	SD	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Spine bone mineral density	Before - After	−0.92	1.07	0.139	−1.20	−0.65	−6.633	58	0.000*
Hip bone mineral density	Before - After	0.45	1.23	0.160	−0.77	−0.13	−2.786	58	0.007*

*$p < 0.05$

Table 5 Comparison of bone mineral density before and after treatment with denosumab using Wilcoxon signed ranks test.

Denosumab (n = 17)		**Mean**	**Std. Deviation**	**Mean Rank**	**Asym.Sig (2-tailed)**
Spine bone mineral density	Before Min -4.40, Max -0.90	-2.72	1.03	6.50	0.002*
	After Min -2.30, Max 0.00	-1.01	0.74		
Non-dominant hip bone mineral density	Before Min -4.10, Max 0.60	-2.31	1.33	6.30	0.060
	After Min -3.10, Max 1.00	-1.59	1.22		

*p < 0.05

Table 6 Comparison of bone mineral density before and after treatment with teriparatide using Wilcoxon signed ranks test.

Teriparatide (n = 4)		**Mean**	**Std. Deviation**	**Mean Rank**	**Asym.Sig (2-tailed)**
Spine bone mineral density	Before Min -5.70, Max 1.30	-2.95	3.00	2.50	0.068
	After Min -3.00, Max 2.60	-0.33	2.42		
Non-dominant hip bone mineral density	Before Min -3.60, Max -1.70	-2.68	0.84	3.50	0.465
	After Min -3.90, Max 0.00	-2.20	1.62		

*p < 0.05

DISCUSSION

Until now, there have been no comparative studies on the effectiveness of different osteoporosis medications in Thailand. In this study, we evaluated the effectiveness of these medications for different types of patients, focusing on the spine and hip, at our osteoporosis clinic. Ultimately, the goal is to ensure that patients receive the most appropriate medication based on their symptoms and affected bone area. However, the response to bone density changes may differ among different patient profiles, such as that identified between male and female patients, as well as those who were treatment naïve and those who had received other treatments. This study adds to the existing evidence on the comparative effects of various osteoporosis medications on non-dominant hip and spine BMD. Empirical evidence supports the effectiveness of osteoporosis medications in reducing fracture rates, increasing BMD, and decreasing bone turnover[12-21]. The included patients were diagnosed and treated with osteoporosis medications, and the BMD increased across all groups; however, some osteoporosis medications did not significantly increase BMD. Most patients in the osteoporosis clinic at our hospital were women aged between 70 and 79 years. This is due to the significant hormonal changes that postmenopausal women experience, leading to physical changes during this period, including concerns about decreasing BMD[22,23]. Almost all of the participants (68.75%) had a BMI[24] between 18.5 and 23, which is within the normal

range. While BMI is a recognized risk factor for fractures[25], it did not appear to influence changes in BMD in this study, as the average BMI across different groups was similar. The desired outcomes of osteoporosis medications include reducing the rate of bone fracture[26], increasing bone mineral density, and decreasing bone turnover.

A comparison of the mean spine and nondominant hip BMD in the sample group treated with bisphosphonates before and after treatment showed a significant difference ($p < 0.05$). As shown in Table 1, bisphosphonates used in this study were obtained from three manufacturers. Although the methods of administration differed to ensure better patient compliance, the antiresorptive mechanism of action was consistent across all three medications[27-30], leading to similar effects on both the spine and non-dominant hip BMD[31-36].

For patients treated with denosumab, we found a statistically significant increase in spine BMD ($p < 0.05$), whereas the increase in nondominant hip BMD was not statistically significant. Several studies have demonstrated that denosumab can increase BMD in both the spine and hips . However, it has a more significant impact on increasing BMD in the spine, often resulting in a 2–3 times greater benefit compared to its impact on the hip, as reported by McClung MR[37], Cumming SR[38], and McCloskey EV[39]. However, the relatively small sample size of patients treated with denosumab may have limited the statistical power of the findings. Nonetheless, there was still an increase in hip bone mass compared to pre-treatment levels.

Before and after teriparatide treatment, there were no significant differences in the spine and non-dominant hip BMD. The primary indication for teriparatide is combination[40,41] or switch therapy, particularly for severe osteoporosis (BMD < –3.5). The small number of patients treated with teriparatide in this study, together with the high cost of the medication and restrictive guidelines, likely contributed to the lack of statistically significant results. However, there is a trend suggesting that teriparatide may have a better outcome on spine BMD, as indicated by the greater reduction in BMD.

A limitation of this study was the small sample size of each group, which resulted in low statistical power. This may lead to findings where certain medications show an increase in BMD but do not reach statistical significance, making it difficult to conclude that these medications are ineffective. Another limitation was the National Osteoporosis Foundation regulations. Furthermore, most of the treatments were bisphosphonates as a first-line drug, and patient drug compliance and transportation that cause incorrect drug doses and might lead to loss of patient follow-up at the osteoporosis clinic, respectively. The follow- up period of patients also varied owing to the realities of service delivery; therefore, comparisons of the effectiveness of different medications must be made with caution. Additionally, because this study was conducted at a single hospital, the results cannot be generalized to broader patient populations in other settings.

CONCLUSIONS

Since 2015, our hospital has been offering services at its osteoporosis clinic with efforts to promote BMD screening and provide treatment for patients with abnormal BMD. We conclude that all medication groups at the osteoporosis clinic of our hospital demonstrated an increase in BMD following treatment. Specifically, the groups treated with the bisphosphonate or denosumab showed a statistically significant increase in spine BMD. In addition, bone mineral density of the non-dominant hip increased significantly in the group treated with bisphosphonates but did not increase in the group treated with denosumab. However, due to limitations in the study population size, this outcome is inconsistent with previous studies.

However, another the limitations of this study include the National Osteoporosis Foundation regulations, and most of the treatments were bisphosphonates as a first-line drug, which resulted in different treatment outcomes. As Thailand transitions into an aging society, osteoporosis poses a significant economic threat with the potential for substantial costs associated with an increase in osteoporotic fractures. Therefore, it is crucial to promote health literacy among the older

population, emphasizing the importance of the early detection and treatment of osteoporosis to prevent fractures. For individuals diagnosed with osteoporosis, insurance coverage should not restrict access to services, such as bone mass screening and medication. It is essential to develop a system that supports the financial needs of this vulnerable population, ensuring that all older individuals have equitable access to the necessary osteoporosis care.

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Appendix 1 Osteoporosis clinic screening.

1. General History

Name _____ Surname _____ HN. _____

Birth Date _____ Age _____ year. Weight _____ kg. Height _____ cm. BMI. _____ (Below than 19 is not ok.)

Consumer Behavior ☐ cigarettes, ☐ alcohol, Coffee, Soft drink

Exercise Behavior ☐ more than 3 time/week.

Underlying disease _____

2. History of risk.

2.1 Menopause before 45 yrs or amenorrhea more than 1 yr. ☐

2.2 oophorectomy both side or on Hormonal drug irregularly ☐

2.3 Fracture around the hip in parent ☐

2.4 Fracture on minor trauma ☐

2.5 On steroid drug more than 3 month. ☐

3. Osteoporosis Self Assessment Tool for Asian (OSTA)

Age	Weight (kg.)										
(year)	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94
40-44											
45-49											
50-54											
55-59								Low risk			
60-64											
65-69				Moderate risk							
70-74											
75-9											
80-84		High risk									
85-86											
90-94											
95-99											

4. Quantitative Ultrasound (QUS) ☐ **Screening** **T-score ..... (<-1.0)**

Processing (2 in 4) ☐ Risk ☐ Not risk

- Go to DEXA scan, Date of appointment

_____ (Doctor Sign) Date _____