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# Efficacy of Osteoporosis Drugs Anabolic and Antiresorptive Classes in Post Menopause Women

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## ABSTRACT

Osteoporosis is a degenerative bone disease that affects many postmenopausal women. Antiosteoporosis drugs consist of antiresorptive and anabolic groups. So far, there is still controversy over the administration of antiosteoporosis drugs, therefore researchers conducted a systematic review study aimed at determining which one is more effective. This research was conducted by reviewing several studies through the PubMed and Science Direct databases. The results showed that abaloparatide, teriparatide, and SERM (Selective Estrogen Receptor Modulators) were more effective than bisphosphonates. In conclusion, the anabolic class is more effective than the antiresorptive class in postmenopausal women.

**Keywords :** Anabolic, Antiosteoporosis Drugs, Antiresorptive, Osteoporosis, Postmenopausal.



## INTRODUCTION

Osteoporosis is a worldwide public health problem. Osteoporosis is a degenerative disease(Waseso, Supartono and Fauziah, 2018). The interaction between etiology and risk factors can cause cellular defects in the form of an increase in the number and activity of osteoclasts compared to osteoblasts, where according to the World Health Organization, osteoporosis is characterized by a decrease in bone mass along with disruption of the bone microarchitecture tissue that causes bones break easily (Resnasari, Supartono and Ekapurwani, 2020).

Osteoporosis affects elderly people and women are more at risk than men. This is evidenced by the probability of osteoporosis fracture, especially in patients aged 50 years, which is

almost 50% for women and 22% for men (Gorter et al., 2020). Osteoporosis affecting elderly women is also often associated with menopausal conditions, namely the last bleeding from the uterus that is still affected. by reproductive hormones (especially low estrogen) and usually occurs between the ages of 45-55 years (Humaryanto, 2017).

According to the World Health Organization (2003), one of the gold standards for diagnosing osteoporosis is by examining bone mineral density (BMD) to determine bone density (Resnasari, Supartono and Ekapurwani, 2020). Bone density is expressed as a comparison of the results of bone mineral density with the normal value of average bone density in people of the same age. Young adults expressed with a standard deviation score (T-score) (Resnasari, Supartono and Ekapurwani, 2020). Bone density was obtained from measurements using a bone densitometry tool and would be divided into three categories, namely normal (BMD> -1 SD), osteopenia (BMD between -1 to - 2.5 SD), and osteoporosis (BMD <-2.5 SD) (Resnasari, Supartono and Ekapurwani, 2020). Prevention and therapy of osteoporosis is necessary to reduce the prevalence of osteoporosis (Yunita, Imananta and Suryana, 2017). Osteoporosis therapy aims to increase bone density and reduce additional bone loss and/ or fracture and control pain (Hidayati, 2019). Untreated osteoporosis can lead to an increased risk of death, as a higher risk of all-cause death has been found among patients with osteoporosis compared to who do not have osteoporosis (Cai et al., 2020). There are various pharmacological treatment options for the management of osteoporosis, namely using drugs from the antiresorptive group which are drugs that reduce bone loss (for example bisphosphonates, calcitonin, strontium ranellate, denosumab, and romosuzumab) and/or anabolics. which are drugs that increase bone mass (eg estrogen replacement therapy, teriparatide, abaloparatide, and SERMs);with calcium and vitamin D supplementation (Bethel, 2019). On the other hand, there is still controversy over the administration of antiosteoporosis drugs between the antiresorptive and anabolic groups for the management of osteoporosis in postmenopausal women.

Therefore, the authors would like to conduct a literature study to find out which one is more effective for the management of osteoporosis in postmenopausal women, namely antiresorptive or anabolic drugs. By finding this, it is hoped that this study can provide useful information to reduce the prevalence of osteoporosis, improve the prognosis of osteoporosis patients in Indonesia, and reduce the mortality rate due to osteoporosis, so that it can help improve the public health status to support the national development of the nation and state.

## METHODS

Protocol and Registration

This study uses a literature review research design with a systematic review type. The protocol used in this systematic review is based on The PRISMA statement for reporting systematic reviews and meta-analyzes of studies that evaluate health care interventions: explanation and elaboration (Liberati et al., 2009) and has been registered in PROSPERO (https://www.crd.york.ac.uk/PROSPEROFILES/229651_STRATEGY_20210106.pdf). This systematic review research uses the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes). The PRISMA method includes a checklist of items that should be contained in a systematic review study (with or without meta-analysis), of which there are 27 items. Apart from that, the PRISMA method also includes 4 phases information flowin a literature search for systematic review research.

### Inclusion and Exclusion Criteria

The inclusion criteria in this study were literature discussing or relating to the efficacy of anti-resorption and anabolic osteoporosis drugs for osteoporosis management, particularly in postmenopausal women and literature published in the last 10 years.The exclusion criteria in this study were literature that did not have DOI and ISSN and literature that was not published in English.

### Data source

The search was conducted using a research database, namely PubMed and Science Direct.

### Literature Search

Literature search was carried out using the keywords [(Efficacy) AND (antiresorptive) OR (bisphosphonate) OR (calcitonin) OR (strontium ranelate) OR (denosumab) AND (osteoporosis) AND (therapy) OR (treatment) AND (post menopause)], [(Efficacy) AND (antiresorptive) OR (bisphosphonate) OR (calcitonin) OR (strontium ranelate) OR (denosumab) AND (antiosteoporosis) AND (drug) AND (post menopause)], [(Efficacy) AND (anabolic) OR (teriparatide) OR (abaloparatide) AND (osteoporosis) AND (therapy) OR (treatment) AND (post menopause)], and [(Efficacy) AND (anabolic) OR (teriparatide) OR (abaloparatide) AND (antiosteoporosis) AND (drug) AND (post menopause)].

**Study Selection**

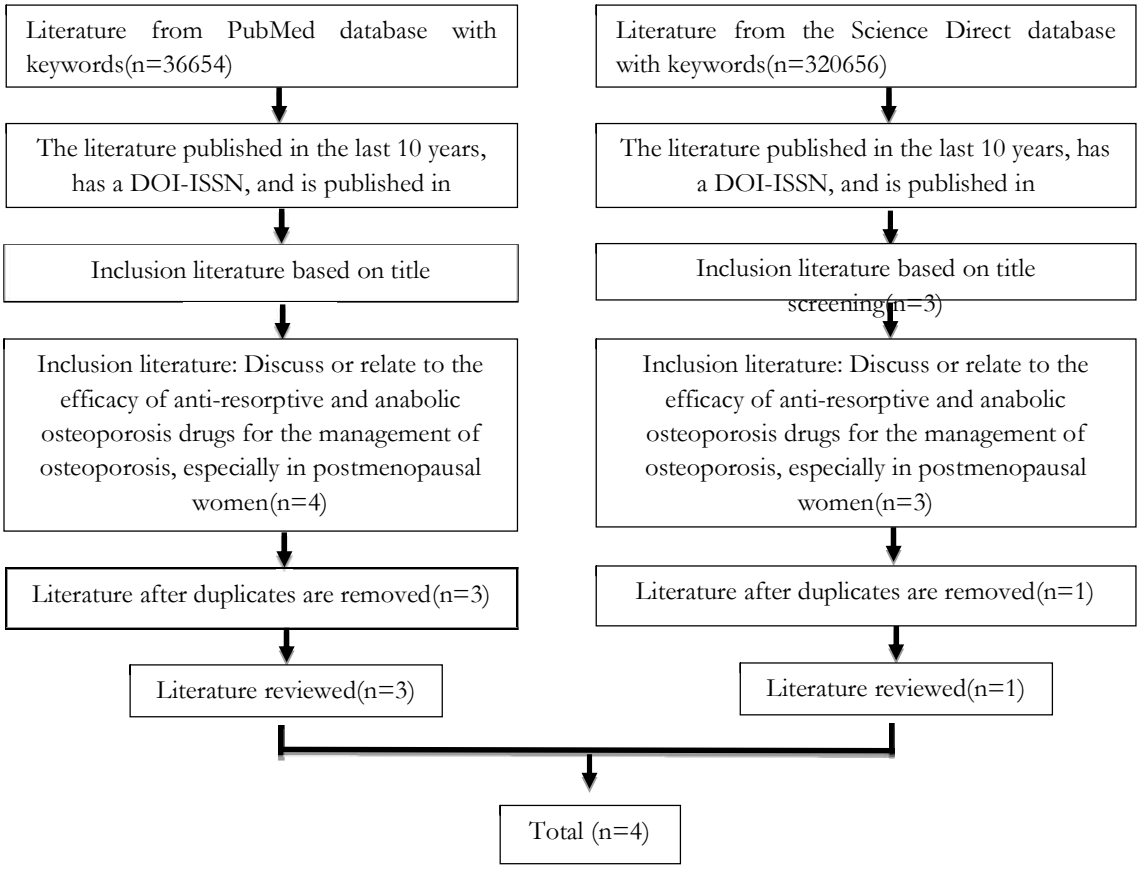


**Figure 1.** Study Selection

**Data Items**

The characteristics of the study are studies published in the last 10 years, have a DOI-ISSN, and published in English. Patient characteristics were osteoporosis patients, especially postmenopausal women (age ≥ 45 years). The characteristics of the intervention were to analyze the efficacy of osteoporosis drugs in the antiresorptive and anabolic classes and compare them. Type of outcome measure, which describes the comparison of the efficacy (efficacy) between antiresorptive and anabolic osteoporosis drugs for the management of osteoporosis in postmenopausal women (for example, it can be seen from the bone mineral density and/or patient prognosis, before and after the intervention).

**Bias Risk Assessment**

The Joanna Briggs Institute (JBI) critical appraisal checklist consisting of questions that can be answered with "yes", "no", or "unclear" (The Joanna Briggs Institute, 2020). The quality of the journals reviewed in this study can be classified as good because it meets 80% of the JBI criteria.

**Data Synthesis**

The author classifies the literature that has been obtained based on research objectives and compares them according to the characteristics, methods and results of the study. After that, the

authors summarize the conclusions obtained from the literature that match the inclusion criteria, then put them in the conclusion table.The data synthesis in this systematic review focuses on the analysis of the efficacy of anti-resorption and anabolic osteoporosis drugs for the management of osteoporosis in postmenopausal women.

## RESULTS AND DISCUSSION

**Table 1.** Data Extraction

| No | Researcher Name and Year of Research | Research Title | Research purposes | Research Method or Design | Population (Research Sample) | Clinical Outcomes |
|---|---|---|---|---|---|---|
| 1 | McClung et al. (2018) | Effects of Abaloparatide-SC on Bone Mineral Density and Risk of Fracture in Postmenopausal Women Aged 80 Years or Older with Osteoporosis | Describe the effect abaloparatide-SC in a subgroup of patients aged 80 years or over ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints) | Randomized controlled trial (RCT) | Postmenopausal women aged 49-86 years with osteoporosis | • Patients ≥80 years in placebo (n = 43) and abaloparatide-SC (n = 51) groups<br>• (95% CI) The increase in BMD at 18 months with abaloparatide-SC treatment was 3.9% in total hip (P <0.001), 3.6% in the femoral neck (P <0.01), and 12.1% in lumbar spine (P <0.001), and similar to that observed in the overall population.<br>• There was a numerical, but not statistically significant, reduction in the risk of vertebral and non-vertebral fractures in this subpopulation, compared with placebo. |
| 2 | Shin et al. (2016) | Effectiveness of Osteoporosis Drug in Postmenopausal Women with Spinal Compression Fracture: Combined Consecutive Therapy of Teriparatide and Raloxifene | Evaluating bone mineral density (BMD) before and after treatment with anti-osteoporosis drugs, to compare the therapeutic effectiveness of combination teriparatide and selective estrogen receptor | Cohort study | 85 postmenopausal women were concurrently diagnosed with osteoporosis and spinal compression fractures. Group treated with teriparatide and SERM | • The mean age was 70.25 ± 9.03 years, the mean body mass index was 23.90 ± 3.30 kg / m2.<br>• The TS group was treated for 3.23 ± 1.63 months.<br>• Group B was treated for 19.03 ± 7.76 months.<br>• In the TS group there was no change in BMD at the femoral neck (0.54 ± 0.12 vs. 0.54 ± 0.11), but the T-score increased slightly from -2.47 ± 1.11 to -2.45 ± 1.00. |

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| | | versus Bisphosphonate Single | modulator (SERM) VS bisphosphonates | | (group TS, n = 26) and bisphosphonates (group B, n = 59) | • In contrast, in group B, femoral neck BMD and T-score decreased from 0.60 ± 0.11 to 0.54 ± 0.10, and from -2.26 ± 0.87 to -2.38 ± 1.00.<br>• BMD and T-score of the lumbar spine were increased in the TS group, while the B group showed a decrease in BMD.<br>• Particularly in the TS group, all lumbar spine T-scores increased significantly.<br>• The femoral neck BMD ratio increased in the TS group (2.00 ± 16.29) but decreased in the bisphosphonate group (-8.39 ± 13.08) (p = 0.002). |
| 3 | Marozik et al. (2019) | Bone metabolism genes variation and response to bisphosphonate treatment in women with postmenopausal osteoporosis | Analyzing the effects of SOST, PTH, FGF2, FDPS, GGPS1, and LRP5 gene variants on response to aminobisphosphonates treatment | Cohort study | Postmenopausal women with osteoporosis and taking aminobisphosphonate for at least 12 months | • The 201 women on BPs therapy found no statistically significant differences observed in age, menopausal age, body weight, height, BMI and baseline BMD levels between respondents (122 subjects) and non-responders (79 subjects).<br>• As a single marker, SOST rs1234612 T / T (OR = 2.3; P = 0.02), PTH rs7125774 T / T (OR = 2.8, P = 0.0009), FDPS rs2297480 G / G (OR = 29, 3, P = 2.2 × 10-7), and GGPS1 rs10925503 C / C + C / T (OR = 2.9; P = 0.003) gene variants were overrepresented in the non-respondent group.<br>• No significant association between FGF2 rs6854081 and LRP5 gene variant rs3736228 and response to BPs treatment was observed.<br>• Carriers of the combination of the |

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| | | | | | | TTGC allele (from rs1234612, rs7125774, rs2297480, and rs10925503) tended to respond negatively to BPs treatment (OR = 4.9, 95% CI 1.7–14.6, P = 0.005).<br>• The CCTC combination was significantly more represented among respondents (OR = 0.1, 95% CI 0.1-0.5, P = 0.006). |
| 4 | Saag et al. (2020) | Effect of Abaloparatide on Bone Mineral Density and Fracture Incidence in a Subset of Younger Postmenopausal Women with Osteoporosis at High Risk for Fracture | Analyzed the efficacy and safety of abaloparatide in postmenopausal women who were younger and considered to be at high risk of fracture. | Randomized controlled trial (RCT) | Patients <65 years of age with baseline T-score ≤ -2.5 (any site] and ≥ 1 vertebrae prevalent and / or ≥ 1 previous clinical fracture within 5 years of randomization) | • 296 women (age range 49-64 years) had increased BMD at 3 sites at 6 months (p <0.01 for total hip and femoral neck; p <0.0001 for lumbar spine), 12 months (p <0.0001 at 3 sites), and 18 months (p <0.0001 at 3 sites).<br>• The fracture rate was numerically lower for abaloparatide compared to placebo, consistent with the results of the overall trial, although the difference was not statistically significant.<br>• The numbers needed to prevent and treat 1 additional vertebral fracture after 18 months of treatment were 18 for abaloparatide and 21 for teriparatide. |

Pharmacological therapy for the management of osteoporosis consists of antiresorptive and/or anabolic drugs; with calcium and vitamin D supplementation (Bethel, 2019). In the first article, the pharmacological intervention given to a subgroup of patients aged 80 years or over was abaloparatide-SC therapy. PTH is type 1 and exhibits a potent effect on anabolic activity leading to lower bone resorption (Kristiningrum, 2020). In this study, therapy with abaloparatide-SC was associated with a significantly increased BMD of the lumbar spine and proximal femur, fewer vertebral and nonvertebral fractures, and there is no difference in the security profile.

The results of research by McClung et al. This is also supported by similar evidence in another study, in which a phase 2 study of 222 post-menopausal women with osteoporosis for 24 weeks showed that abaloparatide 80 mcg/day was associated with a significant increase in BMD in

total pelvic bone, femoral neck, and lumbar bone compared with placebo (Kristiningrum, 2020). In addition, the 18-month ACTIVE (Abaloparatide Comparator Trial in Vertebral Endpoints) study for 18 months showed that abaloparatide increased BMD and decreased the risk of vertebral and non-vertebral fractures compared to placebo (Kristiningrum, 2020).

Apart from abaloparatide, there are other drugs from the anabolic class, one of which is teriparatide (Tu, Kristie et al., 2018). Teriparatide is a recombinant human parathyroid hormone called PTH peptide and is the only anabolic drug currently approved for osteoporosis therapy that stimulates osteoblastic bone formation, thereby improving quality and bone mass (Kristiningrum, 2020). This drug activates osteoblasts by binding to the PTH / PTHrP type 1 receptor, thereby directly stimulating bone formation at previously active remodeling sites and inactive bone surfaces, as well as initiating new remodeling sites (Kristiningrum, 2020). In addition, there are SERMs (Selective Estrogen Receptor Modulators) as other drugs of the anabolic class (An, 2016). The mechanism of action of the SERM group of compounds relies on tissue-selective estrogen receptor agonists or antagonistic activity in their interaction with estrogen receptors, and these properties include a certain degree of molecular and functional complexity (An, 2016). With regard to bone loss and osteoporosis, the action of SERMs on estrogen receptors influences bone homeostasis by decreasing osteoclast activity in a growth factor-dependent manner and reducing bone resorption (An, 2016). This effect is possible in preventing and treating osteoporosis.

In a related study that tested teriparatide treatment in severe osteoporosis patients with Duchenne Muscular Dystrophy, stable bone health results were obtained and there was a slight increase in P1NP, without safety concerns. However, in the fourth article examining the pharmacological intervention of abaloparatide in a subgroup of younger postmenopausal women and compared to teriparatide, we found that abaloparatide appears to be effective and well tolerated compared to teriparatide (Saag et al., 2020). However, there are limitations to this study, where the number of patients those included in this subgroup analysis were relatively small and there was no follow-up for some errors that could also occur due to subjective conditions (Shin et al., 2016).However, research by McClung et al. and Saag et al. it has been shown that anabolic drugs have good efficacy for the management of osteoporosis in postmenopausal women, and further, when compared between abaloparatide and teriparatide, abaloparatide has been shown to be more effective than teriparatide.

Meanwhile, the related efficacy of the antiresorptive class for the management of osteoporosis is described in a related study examining the efficacy of bisphosphonate therapy in patients with primary osteoporosis and osteopenia binds hydroxyapatite and inhibits bone resorption by osteoclasts in several ways, namely cytotoxic or metabolic injury to mature osteoclasts, inhibits osteoclast adherence to bone, inhibits osteoclast differentiation and recruitment, and affects the osteoclast structure required for bone resorption (cytoskeleton component) (Kristiningrum, 2020).Results of the study Yunita et al. showed changes in the Bone

Mineral Density (BMD) score that increased significantly in the femoral neck, ward's triangle, and g. trochanter after the second BMD score measurement 6-18 months apart on bisphosphonate therapy (Yunita, Imananta and Suryana, 2017).

Furthermore, when viewed from the comparison of the efficacy between anabolic and antiresorptive drugs, the study in the second article proved that the combination therapy of teriparatide and SERM was very effective in treating the lumbar spine, compared to bisphosphonates (Shin et al., 2016). According to a study conducted by Shin et al. Although the period of teriparatide treatment is relatively short, the preventive effect of compression fractures is substantial (Shin et al., 2016). Therefore, the combination therapy of teriparatide and SERM is highly recommended for patients concerned with osteoporotic spinal compression fractures (Shin et al., 2016). The study results of the second article further elaborate on the results related research by Yunita et al. who only studied the effects of bisphosphonate therapy without direct comparison with drugs of the anabolic class.

From a pharmacological point of view of the two drug classes, drugs from the antiresorptive group were chosen as the first line drugs in osteoporosis therapy in Indonesia because the mechanism of action to reduce bone loss or inhibit bone resorption by osteoclasts is considered more effective than the anabolic group that increases bone mass or increase bone formation by osteoblasts (Kristiningrum, 2020). Meanwhile, studies in Korea suggest that bisphosphonates have traditionally been the first choice for treating osteoporosis, but recent trials have shown teriparatide to be more effective for elderly patients with compression fractures diagnosed with osteoporosis (Shin et al., 2016).

Some studies show 20 μg daily subcutaneous teriparatide injection reduces the risk of vertebral fracture. In one study, BMD of the lumbar spine and neck of the femur was determined at 4, 12, and 24 months after 21 months using teriparatide injection; then compared with a control group of patients treated with a placebo. The results of clinical trials proved that teriparatide was more effective at reducing the risk of fractures compared to the placebo group. Teriparatide increases cancellous bone volume and cortical bone thickness, and improves trabecular morphology. In the research of Shin et al. also proved that the BMD of the lumbar spine of the TS group (treatment with anabolic group: teriparatide + SERM) was significantly higher than that of group B (treatment with the antiresorptive group: bisphosphonates) (Shin et al., 2016). Therefore, it can be said that the anabolic group is more effective than antiresorptive in treating osteoporosis in postmenopausal women based on the results of recent clinical trials, so that theories regarding pharmacology including the mechanism of action of each drug class need to be examined more deeply. The author recommends that doctors choose anabolic drugs for osteoporosis therapy in postmenopausal women according to the situation and condition of the patient.

The limitations of this study include, the number of articles reviewed in this study is still quite small because there are not many studies with limited inclusion criteria that are expected and can be downloaded in full text. The large number at the beginning of the search was due to the sum of articles from all keywords that after being searched, it turned out that there were many duplications (finding the same article) between keywords.

In this systematic review, research on the efficacy of anabolic drugs is more numerous than that of the antiresorptive group, and the variants of anabolic drugs are more diverse (abaloparatide, teriparatide, and SERM) than the antiresorptive group involved (bisphosphonates only). Factors that can affect the efficacy of osteoporosis drugs, namely genetic factors, are not explained in studies that discuss the efficacy of anabolic drugs. In addition, this systematic review was not maximal because of the limited research time and human resources who carried out the systematic review.

## CONCLUSION

Based on this systematic review, it has been shown that anabolic osteoporosis drugs are more effective in postmenopausal women, where after intervention there is an increase in bone mineral density and a reduced risk of fractures due to osteoporosis. Meanwhile, no significant differences were found after intervention with bisphosphonate (antiresorptive) drugs in postmenopausal women with osteoporosis.The author advises the next researchers to conduct a more holistic and comprehensive observational study related to the comparison of the efficacy of osteoporosis drugs in the anti-resorption and anabolic classes in postmenopausal women. In addition, if you want to carry out a systematic literature review to continue this research, it must be done by expanding the inclusion criteria for the appropriate study and the database used, and sharpening the literature search strategy with appropriate keywords.

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