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Impact of the Use of Cox-2 Inhibitors on Bone Mass of Menopause Women

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Abstract: Pharmacologically non-steroidal anti-inflammatory drugs have the main target of the cyclooxygenase (COX) enzyme as a good pain therapy in patients with chronic inflammation such as osteoarthritis and Rheumatic arthritis. COX-2 can be induced by cytokines, growth factors, and other stimuli based on the inflammatory response. There is an increase in the consumption of non-steroidal anti-inflammatory drugs in postmenopausal women. The purpose of this study was to determine the impact of using COX-2 inhibitors on bone mass in postmenopausal women. The study used an analytical observational research technique with a cross sectional design. The sample was carried out by purposive sampling on 33 postmenopausal women who taking COX-2 inhibitors for more than 6 months and 33 postmenopausal women who did not take COX-2 inhibitors.The research instrument measures bone mineral density using the technique Dual energy X-ray Absorptiometry (DXA) or tool Bone Mineral Density (BMD) Sonography namely OsteoSysSonost 3000. The Mann-Whitney test showed that the value of p = 0.000 <0.05, there was significant difference in the BMD (Bone Mineral Density) measure between postmenopausal women using COX-2 Inhibitors and menopausal women not using COX-2 Inhibitors. There is an effect of the use of COX-2 Inhibitors on bone mass in postmenopausal women. On average, the Bone Mineral Density Sonography of postmenopausal women using COX-2 Inhibitors was significantly lower, compared to postmenopausal women without COX-2 Inhibitors. It is necessary to supervise postmenopausal women regarding the long-term use of COX-2 inhibitors.

Keywords: Cyclooxygenase II Inhibitor, Bone Mass, Menopause.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are available in drug stores and purchased as over-the-counter pain relievers. Causes some side effects when used irrationally. NSAIDs are divided into conventional NSAIDs that are not selective in inhibiting the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, and NSAIDs that are selective for cyclooxygenase-2 (COX-2) enzymes. (Febriyanti, 2021).

The 2013 Basic Health Research was conducted in 33 provinces and 497 districts in Indonesia to study medicines stored in households. Shows that East Java is the highest user of NSAIDs (15%). Non-selective COX-2 and partially selective COX-2 drugs were 38.3% purchased from drug stores and 14.4% from drug stores. For the treatment of rheumatism all used for more than a month. The widespread use of NSAIDs as pain relievers shows the need for appropriate drug use information to avoid the side effects of NSAID drugs (Soleha, *et al*., 2018).

Cyclooxygenase-2 is a physiological enzyme that plays a key role in various biological functions in the mechanisms of pain and inflammation. The COX 2 enzyme is induced during inflammatory or cancerous processes and does not reflect a role in maintaining the stomach lining. Selective COX-2 inhibition can significantly reduce side effects including gastrointestinal tract damage and hepatotoxic effects ofTraditional NSAIDs such as aspirin, ibuprofen. Recent developments in COX-2 inhibitors have mainly focused on increasing the selectivity index of drugs for COX. -2 along with increasing the potency of the drug by modifying the Coxib scaffolds on the market such as Celecoxib. (Sharma, *et al*., 2019)

Accuracy of indication for useNon-steroidal anti-inflammatory drugs (NSAIDs) were adjusted for symptoms in patients by comparing with The Monthly Index of Medical Specialties according to the doctor's diagnosis. (Isngadi, 2018)

Pharmacologically non-steroidal anti-inflammatory drugs (NSAIDs) are proven to be the best painkillers to control pain due to chronic inflammation such as osteoarthritis and rheumatic arthritis which usually occurs in postmenopausal women. However, these analgesic preparations are often purchased over-the-counter and result in fatal side effects (Zahra, *et al*., 2017).

Some depressed patients do not respond well to standard anti-depressant therapy. Using celecoxib, a COX 2 inhibitor, as an add-on therapy. Celecoxib is effective in reducing depressive symptoms, lowers blood concentrations of pro-inflammatory cytokines, lowers HDRS scores, and is well tolerated (Pratako, 2019).

The use of non-steroidal anti-inflammatory drugs (NSAIDs) in a long time, causes side effects of gastrointestinal injuries resulting in upper gastrointestinal bleeding (Soleh, 2018).

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The side effects of using other NSAIDs can be delayed-union or non-union. Disruption of the prostaglandin-biosynthesis process due to cyclooxygenase-inhibitors can have an impact on the process of callus formation when fractured. Long-term use of COX-2 inhibitors has a negative effect on the bone healing process (Pinandita, *et al*., 2018).

Some depressed patients do not respond well to standard anti-depressant therapy. Using celecoxib, a COX 2 inhibitor, as an add-on therapy. Celecoxib is effective in reducing depressive symptoms, lowers pro-inflammatory cytokine concentrations in the blood, lowers HDRS scores, and is well tolerated.

The technique is an extension of the previous imaging technique called Dual energy Photon Absorptiometry (DPA) using DXA. The main application of DXA is measuring bone mineral density to assess the risk of fractures and osteoporosis. DXA bone mass assessment was performed in the central part of the lumbar spine and the peripheral bones of the ankle, medial malleolus, and lateral malleolus. (sung, 2018). The purpose of this study was to determine the impact of using COX-2 inhibitors on bone mass in postmenopausal women.

METHOD

Study Osteoporosisat Murni Teguh Hospital, Medan City, North Sumatra-Indonesia, using an analytical observational research technique with a cross sectional design. Based on randomly selected longitudinal population. The data are presented by sampling using purposive sampling to 33 postmenopausal women who have under gone taking COX-2 inhibitors for more than 6 months, in 33 postmenopausal women not taking COX-2 inhibitors.

Primary data collection is done by taking the results of BMD (Bone Mineral Density) Sonography in postmenopausal women taking COX-2 inhibitors who underwent BMD (Bone Mineral Density) measurement using structured interviews. The research instrument that will measurebone mineral density using the technique Dual energy X-ray Absorptiometry (DXA) ortoolBMD (Bone Mineral Density) Sonography is OsteoSysSonost 3000. The measurement results look at the percent difference in BMD (g/cm2). Measurement of BMD (Bone Mineral Density) rated on the density of bone compositionbody frame with a score that is normal (>-1 SD), osteopenia (-1 SD to 2.5 SD), osteoporosis (<-2.5 SD) and severe osteoporosis (<-2.5 SD+).

Data analysis in this study was to obtain an overview of the bone mass comparison of postmenopausal women between COX-2 inhibitor users and non-COX-2 inhibitor users. Data analysis was tested normality of the data using the Shapiro-Wilk test. If the data is normally distributed, it is continued by using Independent T-Test. If it is not normally distributed, it is continued using the Mann-Whitney test.

RESULT

The results of the study are based on table 1, based on the age of the respondents using COX-2 inhibitors and not users of COX-2 inhibitors, which are known to be 55-59 years old (33.3%), followed by 60-64 years (25.8%), age 50-54 years (24.2%), and age 65-69 years (16.7%).

Table 1: Percentage of Age distribution of respondents using COX-2 inhibitors (n=66)

Age	Frequency	Percentage (%)
50-54 Years	16	24.2%
55-59 Years	22	33.3%
60-64 Years	17	25.8%
65-69 Years	11	16.7%
Total	66	100%

Source: Primary Data from the medical records

Based on table 2, it is known that the average measurement of Bone Mineral Density (BMD) in postmenopausal women using COX-2 inhibitors is -3.161, with a standard deviation of 0.454. Meanwhile, postmenopausal women without COX-2 inhibitors were -1.827, with a standard deviation of 0.508. On average, the measurement of Bone Mineral Density (BMD) in postmenopausal women using COX-2 Inhibitors was lower than the BMD in menopausal women without COX-2 Inhibitors.

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Table 2: Percentage of Average Bone Mineral Density inCOX-2 Inhibitor Users (N=66)

User COX-2 Inhibitor	No	Average	Standard Deviation
Not	33	-1.827	0.508
Yes	33	-3.161	0.454

Source: Primary Data from the medical records

Based on Table 3, the results of the normality test show that the BMD (Bone Mineral Density) measurement value in postmenopausal women using COX-2 inhibitors is not normally distributed with a p value = 0.042 < 0.05, so the test is continued by using the Mann-Whitney test.

Table 3: Normality TestCOX-2 Inhibitor Users

COX-2 Inhibitor Users	P-Value (Normality Test)
Not	p=0.181
Yes	p=0.042

Based on Table 4, the Mann-Whitney test was used to test whether there was a difference in the measurement of BMD (Bone Mineral Density) in menopausal women who used COX-2 Inhibitors with menopausal women without COX-2 Inhibitors.

The results of the Mann-Whitney test, obtained p value = 0.000 <0.05, it was concluded that there was a significant difference in the BMD (Bone Mineral Density) measurement value between postmenopausal women using COX-2 Inhibitors and postmenopausal women not using COX-2 Inhibitors.

Table 4: Mann-Whitney Test COX-2 Inhibitor Users

COX-2 Inhibitor	P-Value (Mann-Whitney Test)
Yes	p = 0.000 < 0.05 (Significant)

DISCUSSION

Based on the research results, there is an effect of the use of COX-2 Inhibitors on bone mass in postmenopausal women. Bone mass in postmenopausal women taking COX-2 inhibitors was significantly lower than bone mass in postmenopausal women without COX-2 inhibitors.

The use of cyclooxygenase-2 (COX-2) inhibitors has been shown to not only impair bone formation under stress, but also to prevent menopause-related bone loss. The use of COX-2 inhibitors is associated with increased bone mineral density in postmenopausal women not taking estrogen therapy. COX-2 Inhibitorscan suppress bone repair and formation by inhibiting angiogenesis and impairing the function of osteoblasts and osteoclasts. (Nakata, *et al*., 2018)

In postmenopausal women not taking estrogen replacement therapy, use ofCOX-2 Inhibitor every day associated withhigher bone mass. Effects of using COX-2 Inhibitor depending on the dose, judging by the clinical benefits and safety, if there are serious side effects then do not use again. (Puljak, *et al*., 2017).

A series of salicylic acid derivatives have higher analgesic activity than aspirin on a molar basis. Screened to investigate its analgesic activity and potential as a cyclooxygenase-2 (COX-2) inhibitor compared to meclofenamic acid. (Diyah, NW, *et al*., 2020)

However, at the gene level, COX-2 inhibitors can reduce inflammatory factors thereby regulating macrophage recruitment to activate the antitumor immune microenvironment; downregulates vascular endothelial growth factor (VEGF) to inhibit tumor angiogenesis. In cancer treatment of various antineoplastic drugs combined with COX-2 inhibitors, this combination shows a synergistic anti-tumor effect (Li, *et al*., 2020)

The role of the use of selective COX-2 inhibitors can reduce non-metastatic breast cancer in Single University hospitals, inhibit cell proliferation and angiogenesis through decreased prostaglandin synthesis. Phase II trials revealed that the combination of celecoxib and capecitabine provided a clinical benefit rate of 42.1% -47.5% in breast cancer patients (Gharib, *et al*, 2020).

Referring to the findings of this research, the researchers are proudly to present this result of this research since some similar or previous researches are fewer and the researchers can say that this research is really new and can be as a reference to other researchers. But the researchers here would like to present a previous study from Tsuji, *et al*., (2013). Their research was about Celecoxib, a selective cyclooxygenase-2 inhibitor, reduces level

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of a bone resorption marker in postmenopausal women with rheumatoid arthritis. Although no clinical data have been reported, celecoxib (CEL), a selective cyclooxygenase-2 (COX-2) inhibitor, has been shown to inhibit osteoclastogenesis in vitro, lower levels of bone resorption markers in ovariectomized (OVX) mice, and prevent bone destruction in rheumatoid arthritis (RA) model mice. Here, in order to investigate the effects of a selective COX-2 inhibitor on bone metabolism, we prospectively assessed the changes in bone turnover indicators in RA patients who transitioned from NSAIDs to CEL. Patients with RA who had been on NSAIDs for more than 12 weeks were switched to CEL (400 mg/day) without making any further adjustments to their pre-existing prescription drugs. Before switching to CEL and 16 weeks later, the levels of urine type I collagen cross-linked N-telopeptide (uNTX), serum bone alkaline phosphatase (BAP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3 (MMP-3) were assessed. In 60 female patients, there were significant decreases in the bone resorption marker uNTX (P = 0.042), particularly in 52 postmenopausal women (P = 0.033). However, neither premenopausal males nor females experienced a substantial change in uNTX levels. The bone formation marker BAP did not change significantly. ESR and MMP-3 remained steady, while CRP dramatically dropped (P = 0.007). In postmenopausal RA patients, CEL decreased levels of a bone resorption marker, indicating that this medication may lessen the increased osteoclastic bone resorption linked to menopause.

CONCLUSION

There is a significant difference in the measurement of BMD (Bone Mineral Density) between postmenopausal women using COX-2 Inhibitors and menopause women who do not use COX-2 Inhibitors. It is necessary to supervise postmenopausal women regarding the long-term use of COX-2 inhibitors.

Non-steroidal anti-inflammatory drugs (NSAIDs) indications for use of more than one month can treat various diseases, can reduce inflammatory factors and have a synergistic antitumor effect. However, if it is not used rationally, it can cause adverse side effects.

This research is still far of being good or perfect since the limitation of this research. Further research about Cox-2 inhibitors and bone mass of menopause women should be conducted to enhance our understanding and give more references to other researches in conducting more about this topic.

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