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Literature Review: The Long-Term Use Effect of Proton Pump Inhibitors and The Risk of Fractures

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ABSTRACT

Proton Pump Inhibitors (PPIs) are a group of drugs widely used to treat gastrointestinal disorders. Long-term use of PPIs has a risk of several side effects, one of them is fractures. The aims of this study is to examine the relationship between long-term PPIs use and the risk of fractures. The method in this literature review was literature study by searching for research article through Google Scholar and Pubmed Central by using the keywords "Proton pump inhibitors, Long-term use, Risk, Fracture". An analysis of 10 selected journals was conducted and concluded that the long-term use of PPIs has a risk of fracture.

1. INTRODUCTION

Proton pump inhibitors are a class of drugs widely used for treating gastrointestinal diseases, including peptic ulcers, gastroesophageal ulcers, Zollinger-Ellison syndrome, ulcers due to NSAIDs, and treatment of infections caused by Helicobacter pylori. [1]

In 2011 the FDA warned that long-term use of PPI could increase the risk of hip, wrist, and spinal fractures. [2] The use of PPI is increasing in many countries. [3] The widespread use of PPI is widely prescribed for stomach acid therapy in the world. [4] In America, the third rank of drugs that are widely sold is PPI. [5] In Indonesia, PPI is a class of drugs that are widely used in inpatients in hospitals, which is around 26.90% [6] and in prescribing in clinics as much as 51.79%. [7]

From its widespread and effective use against gastrointestinal disorders, but in long-term use PPI has several risks of side effects, including lowering the microbiome in the intestines, vitamin B12 deficiency, hypomagnesemia, fractures, pneumonia, up to stomach and bowel cancer. [4] From the description above, this review was written to see the relationship between long-term PPI use and the risk of fractures.

2. METHOD

This study was done by literature study looking for research journals through google scholar and pubmed central using some keywords "Proton pump inhibitors, Long-term use, Risk, Fractures". The data obtained were selected on inclusion criteria and exclusion criteria. The inclusion criteria set include national and international journals regarding the use of long-term PPI against the risk of fractures, published in the range of 2012-2022, accessible in full text. Meanwhile, the exclusion criteria set include review articles, published under 2012, and not available in full text form. A total of 12 articles was found and after analysis 10 articles were selected for reviewed.

3. RESULTS AND DISCUSSION

Based on the literature study that has been carried out long-term use of PPI and the risk of fractures can be described on the table below.

Table 1. Result of Literature Study Long-term Use Effect of PPI and The Risk of Fractures

Design Study	Duration PPI Therapy	Group of Ages	Part of Fractures	PPI Relationship with The Risk of Fractures	Research
Prospective Cohort Study	1 years	>65 years (average 80 years)	Hip	OR: 2.17 (95% CI: 1.25–3.77)	[8]
Nationwide Cohort study	>90 days	>40 years (average 54 years)	Hip	RR: 1.78 (95% CI: 1.26-2.53)	[9]
Nested Case-control Study	>1 years	>50 years	Hip	OR: 1.42, (95% CI: 1.32–1.52)	[10]
Nationwide Cohort Study	1 years	<18 years (average 12 years)	Upper-limb, under-limb, and other fractures	Upper-limb HR: 1.08 (95% CI: 1.03-1.13), Under-limb HR: 1.19 (95% CI: 1.10-1.29), Other fractures HR: 1.11 (95% CI: 1.06-1.15)	[11]
Nested Case-control Study	3 years	Women >65 years (average 74 years)	Wrist, spine, hip	OR: 1.15 (95% CI: 1.11-1.20)	[12]
Cohort Study	2 years	6 months – 15.5 years (average 4 years)	Inferior, ribs, spine	OR: 1.2 (95% CI: 1.0-1.4)	[13]
Retrospective Cohort Study	5 years	>18 years	Hip	HR 1.41 (95% CI: 1.29–1.54)	[14]
Prospective Cohort Study	10 - 28 months	Average 63 years	Hip	SHR 1.35 (95% CI: 1.13-1.62)	[15]
Retrospective Case-control Study	3 years	Average 71 years	Hip	OR: 1.19 (95% CI: 1.11-1.28)	[16]
Case-control study	1 years	>50 years	Hip, spine, arm, pelvis, femur	OR: 2.4 (95% CI: 1.6-3.5)	[17]

Based on table 1, it has been found that long-term PPI use has an effect on the risk of fractures. The population taken ranges from pediatrics, geriatrics, and special populations, including type 2 diabetes patients, patients undergoing hemodialysis, and patients undergoing kidney transplants.

A number of mechanisms may be involved as a result of the use of PPIs on the risk of fractures, namely impaired absorption of several components, such as calcium, vitamin B12, and magnesium.

The mechanism of PPI for the occurrence of calcium malabsorption, which is related to the function of PPI as an antiulcer. PPI works as an antiulcer by inhibiting the production of acid or H+ in the H+/K+ATPase proton pump. Under acidic conditions, the stomach helps release calcium ions from their insoluble salt form. Active PPIs work by suppressing acid from the stomach resulting in an increase in gastric pH, resulting in inhibition of the dissolution of calcium salts and later can inhibit the absorption of calcium. Furthermore, a deficit in the amount of calcium in the bones results in a risk of fractures. [10], [13]

The process of bone remodelling requires a balanced condition, namely the processes of resorption and deposition that go hand in hand. Low calcium levels in the body can trigger the parathyroid glands to release parathyroid hormone which can affect the process of accelerating bone

resorption. Bone resorption is related to bone density. Meanwhile, bone deposition is related to the breakdown of the matrix in the bones. [18] If the bone remodelling process is not balanced, it can cause a risk of decreased bone density. [14]

Acidic stomach conditions are optimal conditions for the absorption of vitamin B12. Acid suppression by PPIs results in impaired absorption of vitamin B12 and results in vitamin B12 deficiency. [10] B12 deficiency results in increased homocysteine. Homocysteine plays a role in the formation of cross linking as a regulatory factor. Homocysteine inhibits the action of lysyl oxidase, an enzyme that plays a role in the process of forming bone tissue. As a result, there is a disruption of the bone remodelling process by weakening the mechanism of collagen cross linking. The largest component of the bone matrix is collagen so that disruption of this process can affect a decrease in bone density and result in a risk of fractures. [19], [20] Reduced levels of vitamin B12 in the body can also be at risk of falling. This occurs due to muscle weakness due to neurological disorders and is associated with gait disturbances or an abnormal gait. [16]

Another mechanism for the occurrence of fractures risk can result from magnesium deficiency. Magnesium is a group of minerals that play a role in metabolism and bone mineralization. [21], [22] Magnesium initiates the activation of osteoblasts and phosphate enzymes which play a role in the process of bone formation. [22] The mechanism that might occur due to magnesium deficiency on the risk of fractures occurs directly by the formation of crystals in bone cells and indirectly by interfering with the work of parathyroid hormone which can result in increased osteoclast activity and interfere with vitamin D synthesis. [8], [16] The association of PPIs with active magnesium transport can also contribute to fractures. [16]

In Wang (2020) and Fleishman (2020) studies it was found that pediatrics treated with PPI have a risk of fractures occurrence. In geriatrics, both men and women are also at risk for fractures due to long-term PPI use. [10] Moreover, in the population of menopausal women who are at higher risk due to the internal factor of the hormone estrogen where the decrease in bone mass can be influenced by this hormone. [23]

Special populations need to pay more attention to the use of PPIs because they are associated with a higher risk of fractures that can result in death. The population with type 2-diabetes is at higher risk of fractures than the general population. This is related to changes in microarchitecture which have an effect on decreasing bone strength and quality and also having disturbances in calcium metabolism so that they are at risk for fractures. [14]Based on a study in Fusaro research (2019) a relationship between fractures and mortality, seen by an increase in the potential for mortality by 20% one year after a hip fractures. Moreover, in patients receiving hemodialysis therapy the risk of death is higher. [15] Kidney transplant patients on PPI use are at increased risk for major fractures, such as fractures of the hip, spine, arm, pelvis, thigh, or femur. Fractures in kidney transplant patients after transplantation have a 60% higher risk of death. [17]

As an effort to prevent fractures or osteoporosis, therapy with bisphosphonates (BP) can be used. BP works by increasing bone density by suppressing osteoclasts. However, its use has side effects causing esophageal inflammation, ulcers, and dyspepsia so BP is usually combined with PPI to overcome these side effects. However, the use of PPI as an antiulcer is at risk for the occurrence of osteoporotic fractures with the mechanism of interfering with the bone remodelling process so that the bones that are formed are prone to fractures. Seeing the relationship between PPI therapy and BP, it is necessary to choose the right antifractures and ensure the safety of using PPI. [11]

4. CONCLUSION

Long-term use of PPIs carries a risk of fractures and this risk of fractures can be happened not only in adult, but also childrens are at risk of fractures. Moreover patient with Their prescribing needs to be considered by considering the possible risks. Alternatives to minimize the risk of fractures in patient with gastrointestinal disease can be done with lifestyle changes to reduce the degree of disease factors or therapy using other class of medicine, namely H2 inhibitors.

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