Executive Summary

Proton pump inhibitor use and risk of osteoporotic fracture in Korean adults with peptic ulcer disease and gastroesophageal reflux disease

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▢ Background

With the high morbidity rate of peptic ulcer disease (PUD) and gastro-esophageal reflux disease (GERD) around the world, currently there is an increase in the use of digestive disease medications. Commonly used medications for the diseases include H2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). PPIs are known to inhibit acid secretion more effectively compared to H2RAs in terms of their underlying mechanism. In Korea, there is a dramatic increase in the frequency of use of the medication.

Recent studies have indicated that the long-term use of PPIs may have an effect on increasing bone fracture. However, few studies have investigated the risk of bone fracture by long-term use of PPIs in Korea. Accordingly, it is required to examine the association between PPI use and bone fracture using large-scale data collected in clinical settings.

▢ Objective

In the present study, we explore the association between PPI use and

osteoporotic bone fracture. Specifically, we investigate any use, cumulative use, dose, recent use, and regular use of PPIs are associated with a increased risk of bone fracture.

▢ Methods

The nested case-control study was conducted using insurance claims data, qualification data, and national health examination data provided in the Korea National Health Insurance Service.

People treated with PPIs or H2RAs under the diagnosis codes of PUD and GERD (ICD-10 code: K21, K25, K26, K27, and K28) from 1 January 2006 to 31 December 2015, were eligible for subjects in the cohort.

The cohort entry date is the day of the first drug administration (PPIs or H2RAs). We excluded patients who: (1) were aged less than 50 years based on the cohort entry date; (2) were treated with PPIs or H2RAs during the year before cohort entry date; or (3) had a diagnosis (or treatment) of cancer, AIDS, osteoporosis/bone fracture during the same period. People without the record of national health examination during the year before or after cohort entry date were also excluded due to data loss.

Cases were defined as patients who experienced osteoporotic fracture for the first time (index date: fracture occurrence date) in the period from the cohort entry date to 2015. For each case, up to five controls were matched on sex, age (±5 year), bisphosphonate use, cohort entry date and follow-up duration.

Drug exposures include any PPI use, cumulative number of days of PPI use, low dose use/ high dose use of PPI during the follow-up period, recent use of PPI (PPI use during one year before fracture), and recent regular use of PPI (the number of quarters when PPIs were administered for more than 28 days during one year before fracture).

Conditional logistic regression models were employed to estimate odds ratio (OR), and provide 95% confidence interval (CI) and significance probability (p-value). Covariates include sociodemographic factors (such as

sex, age, residential district, and income quintile), variables for medical examination and medical examination by interview (such as height, weight, BMI, drinking, smoking, and locomotion), and comorbidities (defined by specific drug use, or several diagnosis codes) that may have a direct or indirect effect on fracture.

To examine additionally the factors affecting the occurrence of osteoporotic fracture by PPI use, we analyzed subgroups using matching variables such as sex, age, and bisphosphonate use.

▢ Results

The number of patients treated with medications for PUD or GERD for the past ten years were 35,520,188 persons. After applying the exclusion criteria, osteoporotic fracture was found in 78,465 subjects (3.3%) among 2,388,137 during the study period. Subjects were 59,240 matched cases and 296,200 matched controls. 78.0% of total subjects were female.

During the follow-up period, subjects administered with any PPI showed higher risk of fracture (OR 1.11; 95% CI: 1.08 - 1.13) compared to those who didn't take it. This result was statistically significant. Moreover, there was a higher risk of fracture in the greater cumulative number of days of PPI administration (p for trend <.0001). In particular, patients treated with PPIs for one year or more showed higher risk of fracture (OR 1.42; 95% CI: 1.32 - 1.52) compared to those who didn't take it. Both low dose taker or high dose taker showed higher risk of fracture compared to those who didn't take it.

Subjects administered with PPIs during one year before fracture showed higher risk of fracture (OR 1.30; 95% CI: 1.27 - 1.33) than those who didn't take it. Dividing the one year period by 4 quarters, subjects administered with PPI for four weeks or more in all quarters showed higher risk of fracture (OR 1.37; 95% CI: 1.26 - 1.50).

In addition, there was an increased risk of osteoporotic fracture by PPI use in both male and female subjects. The risk of fracture by PPI use

tended to increase in highly aged subjects. Subjects who were treated, as well as not treated, with bisphosphonates showed also a high fracture risk by PPI use.

▢ Conclusions

A great number of Korean people have been treated with medication for PUD and GERD. However, PPI administration in older age groups increased the risk of bone fracture. Moreover, it was found that continued PPI administration had a greater effect on increasing the risk. Therefore, it is required to check medical histories of patients before PPI administration. Especially, for elderly patients requiring long-term PPI administration, the risk of PPI use should be informed and needless administration should be limited. Also, for those who have been administered with PPIs for a long time, we should make an effort to prevent bone fracture and manage osteoporosis.

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Key words

Peptic ulcer disease, gastro-esophageal reflux disease, proton pump inhibitors, H2 receptor antagonists, osteoporotic fracture