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Incidence and Predictors of Osteoporotic Fractures in Barrett's Oesophagus Subjects: a Population-Based Nested Case Control Study

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Summary

BACKGROUND—Proton pump inhibitors (PPI) are inconsistently associated with osteoporotic fractures. Barrett's oesophagus patients are treated with high PPI doses for prolonged periods, but there is limited data on the incidence of osteoporosis and fractures in them.

AIM—In this study, we aimed to estimate the incidence of (and risk factors for) low bone mass (osteoporosis and/or osteopenia) related fractures in a population-based Barrett's oesophagus cohort.

METHODS—All subjects with Barrett's oesophagus and a diagnosis of osteoporosis and fractures were identified using Rochester Epidemiology Project (REP) resources. The incidence rates of all and osteoporotic fractures in these subjects were compared to an age- and gender similar population in Olmsted County to determine standardized incidence ratios (SIR). Predictors were assessed using Cox proportional hazards models.

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RESULTS—Five hundred and twenty-one patients were included [median (IQR) age 61(52, 72) years; three hundred ninety-eight (76%) men] of whom one hundred thirteen (21.7%) had fractures, and forty-six (8.8%) had osteoporotic fractures. The incidence of all fractures and osteoporotic fractures was comparable to that of an age- and gender- matched population (SIR 1.09; 95% CI 0.92–1.29; SIR 1.05; 95% CI 0.85–1.29). PPI use, dose or duration of use was not associated with osteoporotic fracture risk (HR 0.87; 95% CI 0.12–6.39). Independent risk factors for osteoporotic fractures included older age, female gender and higher co-morbidity index.

CONCLUSIONS—The incidence of osteoporotic fractures was not increased in Barrett's oesophagus patients compared to the general population. Additionally, PPI use was not associated with increased fracture risk regardless of the duration of therapy or dose.

Keywords

Barrett's oesophagus; osteopenia; osteoporosis; fracture; proton pump inhibitor

INTRODUCTION

Barrett's oesophagus (BE) is characterized by the replacement of squamous epithelium in the esophagus with specialized intestinal metaplasia and remains the strongest risk factor for esophageal adenocarcinoma (EAC).¹ Acid suppressive medications such as proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs) are commonly used medications to control gastro-esophageal reflux symptoms, with some recent data suggesting their use being associated with lower risk of progression to EAC.² Patients with Barrett's oesophagus are often treated with higher doses of proton pump inhibitors for more prolonged periods than other patients with gastro-oesophageal reflux disease (GERD) given the known greater severity of reflux in Barrett's oesophagus compared to erosive and non-erosive reflux disease and the need to ensure tight reflux control during and after ablative therapy.³

Although several studies examining the association between acid inhibition and hip fractures exist, the results have frequently been discordant.^{5–12} A case-control study using the UK General Practice Database found an increased fracture risk among persons taking acid inhibitors (both PPI and H2RA) for more than one year, even after adjustment for multiple confounders.⁴ However, a nested case-control study using the same database, restricted to persons without risk factors for hip fracture, found no association between proton pump inhibitor and fracture risk.⁵ Another study reported an increased risk of fracture with even short durations (< 1 year) of acid inhibitor (PPI or H2RA) use.⁶ A Canadian study, in contrast, found elevated risk only after more than six years of use.⁷ In contrast to other studies, which did not report an increased risk of fragility fractures with proton pump inhibitor use.^{8, 9} Finally, while some meta-analyses have reported an increased incidence of hip and vertebral fractures with proton pump inhibitor use, the absence of randomized controlled studies included in those analyses weakens conclusions that can be drawn.^{8–10}

Putative mechanisms by which proton pump inhibitor might affect skeletal integrity include altered bone remodeling by modulating the activity of acid-related enzymes at the level of the osteoclast, thereby affecting fracture risk.^{11, 12} Alternatively, it has been suggested that prolonged proton pump inhibitor use results in decreased intestinal calcium absorption and

negative overall body calcium balance, ultimately leading to secondary hyperparathyroidism, skeletal calcium losses, and increased fracture risk.^{13–15}

Patients with Barrett's oesophagus represent a unique population for studying the association between proton pump inhibitor use and osteoporosis-related fractures, due to their treatment with long-term and high dose acid suppressive therapy with proton pump inhibitors to control reflux. However, there are no data on the incidence of low bone mass (osteoporosis and/or osteopenia) related fractures in this population. We therefore performed a nested case-control study to determine the incidence of low bone mass and related fractures in patients with Barrett's oesophagus and to compare this incidence to that of the general population. We also performed additional analyses to assess predictors of osteoporotic fractures in this cohort.

MATERIALS AND METHODS

The Rochester Epidemiology Project

The Rochester Epidemiology Project (REP) is an initiative of Mayo Clinic, Olmsted Medical Center and the Rochester Family Medicine Clinic in Olmsted County, Minnesota, that contains a unique linked database of medical information for all individuals residing in Olmsted County, who obtain medical care through these facilities.¹⁶ The availability of a centralized index to access patient medical records makes this database well suited for conducting population-based disease observational studies.^{17, 18}

Subject identification and data abstraction

The Institutional Review Boards of Mayo Clinic and Olmsted Medical Center (OMC) approved this study.

Search strategies and characteristics of the Barrett's esophagus cohort

Patients who had Barrett's oesophagus diagnosed between 1989 and 2013 formed our study cohort. These subjects were identified using REP resources as previously described.¹⁹ This included an electronic search of the REP database followed by chart review of electronic and paper medical records of identified patients. We chose to include Barrett's oesophagus patients diagnosed from 1989 as this coincides approximately with the introduction of proton pump inhibitor therapy for the treatment of acid reflux disease.¹⁹

For the electronic medical records search, we utilized the International Classification of Diseases, 9th version (ICD-9)/Hospital Adaptation of the International Classification of Disease - A (HICDA) coding systems. The electronic search codes utilized for identifying Barrett's oesophagus, osteoporosis, osteopenia and fracture(s) are included in Appendix 1. Medical records of all identified subjects were then examined for confirmation of reported diagnoses and to obtain additional clinical data.

Electronic and paper medical records of all study subjects were reviewed for demographic details, office visit records, esophagogastroduodenoscopy (EGD) notes, and laboratory and pathology reports as available. The age and severity weighted Charlson comorbidity index was used to assess comorbidity.²⁰ Body mass index (BMI) was recorded at the time of

diagnosis of Barrett's oesophagus, with obesity defined as BMI > 30. Cigarette smoking and alcohol use were classified as following : ever used (current or past history) or never used. Data on type, dose, as well as number of years of proton pump inhibitor use were also determined from clinical records. Data on other medication use and comorbidities that may be associated with bone loss or osteoporosis/osteopenia pharmacotherapy were also recorded.

Osteoporosis and/or fracture diagnoses

Using the search strategies discussed above, we collected information on all patients in our study cohort for a diagnosis of osteoporosis, osteopenia and/or any fracture. Subjects with a diagnosis of osteoporosis, osteopenia and/or osteoporotic fracture prior to a diagnosis of Barrett's oesophagus were excluded.

Fractures were identified from review of clinical notes and radiology reports. For example, the diagnosis of a vertebral fracture, whether symptomatic or not, was made based on a radiology report of compression or collapse of one or more thoracic or lumbar vertebrae.²¹ All fractures were further classified according to the circumstances of injury as follows. Any fall from standing height or occurring during daily activities was considered mild or moderate trauma while falls from greater than standing height and motor vehicle accidents were determined to be due to severe trauma (see Appendix 2 for classification schema).²⁴ Fractures attributable to specific bone lesions, such as metastatic malignancies, were classified as pathologic fractures. Fractures discovered by radiographs in the course of routine clinical care for an unrelated problem were classified as incidental fractures.²⁵

Low bone mass was identified in patients who had an available bone mineral densitometry (DXA) test result. International Society for Clinical Densitometry (ISCD) 2007 guidelines were utilized for defining osteoporosis and osteopenia based on DXA measurements. In patients who did not have a DXA scan, but in whom, there was clinical suspicion for osteoporosis or osteopenia, the occurrence of a fragility fracture was deemed sufficient for a diagnosis of osteoporosis, consistent with World Health Organization (WHO) and ISCD guidelines.²⁶ An osteoporotic fracture (fragility fracture) was defined as a non-pathologic, non-incidental moderate trauma fracture at one or more sites where such a fracture would be frequently expected to occur (such as hip, thoracic or lumbar vertebrae, wrist or distal forearm).

Nested case: control study design

All patients with Barrett's oesophagus who were diagnosed with low bone mass and/or osteoporotic fracture after the Barrett's oesophagus diagnosis (cases) were compared with patients within the cohort who did not develop low bone mass and/or osteoporotic fracture (controls).

Statistical analyses

The primary analysis compared the number of fractures observed at each skeletal site (based on the first fracture of a given type per person) to the number expected in the cohort during follow-up in the community, i.e., standardized incidence ratios (SIRs). Expected numbers

were derived by applying local calendar year-, age-, and sex-specific incidence rates for fractures to the calendar year- and age-specific person-years of follow-up in the Barrett's oesophagus cohort and summing over the strata. This has been previously reported.^{22–25} Ninety-five percent confidence intervals (95% CI) for the SIRs were calculated assuming the expected rates are fixed and the observed fractures follow a Poisson distribution. Sub-group analyses for the risk of osteoporotic fractures were also performed. Univariate and multivariate associations of clinical characteristics that may influence the incidence of fractures in subjects with Barrett's oesophagus, such as age, gender, Charlson comorbidity index, corticosteroid use, smoking history and proton pump inhibitor use were assessed using Cox Proportional Hazard models.

RESULTS

Study cohort

Five hundred eighty-five patients were diagnosed with Barrett's oesophagus during the period from 1989 to 2013, of which fourteen patients were excluded as they had declined to authorize use of their medical records for research. Of the remaining five hundred seventy-one patients whose records were reviewed, fifty patients were excluded from further analyses due to either a diagnosis of low bone mass or an osteoporotic fracture prior to Barrett's oesophagus diagnosis. Hence, our final study cohort was composed of five hundred twenty-one patients.

Clinical characteristics

Clinical characteristics for Barrett's oesophagus patients (with and without low bone mass and fractures) are outlined in Table 1. The patient population was 88.3% Caucasian, reflective of the local community (85.7 % of Olmsted county residents were Caucasian in 2014). The majority (81%) of patients at the time of diagnosis had non-dysplastic Barrett's oesophagus (NDBE), while 9.6% had low-grade dysplasia (LGD), 3.6% had high-grade dysplasia (HGD) and 5.8% had esophageal adenocarcinoma. Almost all (94.8%) patients were on proton pump inhibitor therapy, with a median (IQR) duration of use of nine (4, 14) years. The most commonly used proton pump inhibitor was omeprazole (63.8%) followed by pantoprazole (29.6%). Most patients in the cohort (72%) were on a once daily dosing maintenance regimen while 22.8% patients were on twice a day dosing regimen. Of note, 29.2% patients on a proton pump inhibitor also reported use of other anti-reflux medications such as H2RA or antacids at least once while on acid suppressive therapy for Barrett's oesophagus. Amongst two hundred two (38.8%) patients with documented glucocorticoid use, 53 (26.2%) had a diagnoses of low bone mass, fifty (24.8%) had fractures and twenty-four (11.9%) had an osteoporotic fracture diagnosis.

Osteoporosis and/or fracture diagnoses

Ninety-seven (18.6%) patients in the cohort were diagnosed to have low bone mass after receiving a Barrett's oesophagus diagnosis. Osteoporotic fractures occurred in 46 (8.8%) patients in the cohort that was sufficient for a diagnosis of low bone mass (meeting diagnostic criteria for osteoporosis as stated earlier).

Following an initial diagnosis of Barrett's oesophagus, one hundred thirteen of five hundred twenty-one patients (21.7 %) experienced one hundred fifty-two distinct fractures. While seventy-six (67.3%) subjects experienced no subsequent fractures, thirty-one (27.4%) had one additional subsequent fracture and six (5.3%) had more than one subsequent fracture. Forty-six patients (of one hundred thirteen, 40.7 %) had osteoporotic fractures. This is further detailed in Figure 1. Fracture occurrence according to skeletal site as well as immediate cause is detailed in Table 2. Overall, forty-one fractures (of one hundred fifty-two; 27%) were the result of severe trauma (e.g., motor vehicle accident, fall from height exceeding 3m), whereas one hundred (65.8%) were attributed to mild/moderate trauma. The most common sites of fractures secondary to mild/moderate trauma were the thoracic/lumbar vertebrae (twenty-one fractures) and hip (twenty fractures) (detailed in Table 2). Eight fractures (5.2%) resulted from a specific pathologic lesion (in the axial skeleton due to metastatic malignancy). The etiology of the remaining three (2%) fractures was uncertain. Highest fracture occurrence rates were observed at the level of thoracic/lumbar vertebrae (17.8%) followed by other lower extremity (16.4%) and proximal femur (14.5%).

Incidence ratios of fractures and osteoporotic fractures

The relative risk (RR) of fracture occurrence by skeletal site and immediate cause is shown in Table 3. While statistically significant incidence ratios were not observed for fractures at any specific site (such as hip, vertebrae, wrist or ribs), the highest numerical risk was observed both for any fracture, as well as for osteoporotic fracture, at the axial skeleton (thoracic and/or lumbar vertebrae) [SIR 1.54; 95% CI 0.99–2.30; SIR 1.41; 95% CI 0.84–2.23]. The overall relative risk of any fracture in the BE cohort was also not statistically different when compared to the general population (SIR 1.09; 95% CI 0.92–1.29). The risk of an osteoporotic fracture following Barrett's oesophagus diagnosis was also not statistically significant when compared to the expected risk in the Olmsted County population (SIR 1.05; 95% CI 0.85–1.29).

Predictors of osteoporosis and/or fracture occurrence in the cohort

Potential risk factors for osteoporotic fracture occurrence are outlined in Table 4 and 5. Specifically, proton pump inhibitor use in our study cohort was not associated with a statistically significant risk for developing an osteoporotic fracture at any site (HR 0.89; 95% CI 0.12–6.55). The duration and dosing regimen of proton pump inhibitor use (once daily versus twice daily) were also found not to be associated with increased osteoporotic fracture risk [HR 0.96; 95% CI 0.89–1.02; HR 0.49; 95% CI 0.21–1.16]

Variables previously shown to be associated with osteoporotic fractures such as female gender and older age were significantly associated with the occurrence of these fractures (female gender $p = 0.005$; older age $p < 0.001$), while a history of corticosteroid use showed a trend toward statistical significance ($p = 0.05$). In addition, a higher Charlson comorbidity index at the time of diagnosis of Barrett's oesophagus was associated with increased fracture risk ($p < 0.001$). Reported p values were estimated from univariate Cox proportional Hazard models.

DISCUSSION

In this large population based cohort of patients of Barrett's oesophagus, we demonstrate that the overall risk of any fracture was not elevated when compared to the reference (age and gender matched) population in Olmsted County, Minnesota. Fractures were categorized as attributable to severe trauma (such as motor vehicle accident), osteoporosis-related, of pathologic origin, or incidentally detected on radiologic imaging. Additionally, osteoporotic fracture incidence was also not increased compared to the expected incidence (SIR 1.05; 95% CI 0.85–1.29).^{27–30} These findings suggest that patients with Barrett's oesophagus, who are on chronic proton pump inhibitor therapy are not at increased risk for the development of subsequent fractures (from any etiology or secondary to low bone mass) relative to the general population.

No specific skeletal site was associated with an increased risk of osteoporotic fracture in our patient cohort. However, numerically (but non-significantly) elevated fracture risks were observed at the thoracic/lumbar spine and hip, with SIRs of 1.41 (95% CI 0.84–2.23) and 1.21 (95% CI 0.72–1.92), respectively. These findings may represent the overall predisposition for osteoporotic fractures to occur at these sites in our patient cohort. In addition, the ascertainment of vertebral fractures by self-report or administrative data is a limitation of any observational study like ours. In our study, we had access to radiologic imaging reports on all subjects, documenting twenty-seven fractures of the thoracic/lumbar spine (five pathologic and one from severe trauma), making the clinical diagnosis of vertebral fractures more reliable.

The available evidence on the association between proton pump inhibitor use and fracture risk is conflicting; with most studies showing a moderately elevated risk of developing a subsequent fracture on PPI therapy. However, these associations have been reported in the presence of at least one other risk factor for osteoporosis.^{5–7} Indeed, in our study predictors of an osteoporotic fracture included some well-known risk factors such as older age, female gender and a higher co-morbidity score, which may reflect a more fragile medical state, as reported by other investigators.²⁶ In contrast to other studies, we did not observe an increased risk of osteoporotic fractures in Barrett's oesophagus patients treated with chronic proton pump inhibitors (HR 0.89; CI 0.12–6.55). Compared to studies from administrative databases, our study is not only population based, but allows both initial case ascertainment using diagnostic codes and subsequent verification by access to linked medical records to confirm or refute these diagnoses, due to the resources available via the REP, making the results of the study more robust. Additionally, given the availability of fracture rates in the general population of Olmsted County,^{27, 28} we were able to calculate SIRs, which are not available in other population-based studies given lack of expected incidence at a population level. The substantially longer and complete follow up available in the subjects of this study (almost eight years) is an additional strength of this study, which makes its results more reliable.

The duration of use of proton pump inhibitor also seemed to have some role in association with fracture occurrence with most studies generally demonstrating increased risk with longer durations of use.^{5–7} In our study, the duration of use of proton pump inhibitor was not

associated with increased osteoporotic fracture risk (HR 0.96; 95% CI 0.89–1.02) despite the median duration of PPI use being almost ten years. In addition, the dosing regimen (once daily versus twice a day maintenance therapy) was also not associated with an osteoporotic fracture risk (HR 0.49; 95% CI 0.21–1.16). The potential effect of confounders such as daily calcium supplementation (documented in 58% of our population) negating deleterious effects of proton pump inhibitor use must be considered when interpreting these findings.

An increased risk of osteoporotic fractures was identified in patients treated with bisphosphonates (HR 4.59, CI 2.47–8.52), despite data from large randomized clinical trials documenting the anti-fracture efficacy of these agents. This finding likely reflects the use of these skeletal anti-resorptive agents in patients identified clinically to be at sufficiently high risk for fracture development and likely reflects confounding by indication. Analogous findings have been previously observed in studies on patients with breast cancer treated with bisphosphonate therapy.²⁹

Our study has a number of strengths. This is the first study to assess the incidence of low bone mass related fractures in patients with Barrett's oesophagus, which is an important population to study, since nearly all these patients are maintained on long-term, high-dose proton pump inhibitor therapy. During chart review, fractures were confirmed in the medical records spanning each subject's entire period of residency in the community. Since most fractures come to medical attention, ascertainment should be nearly complete, with the possible exception of incidentally detected vertebral fractures.

There are also potential limitations to studies that use medical records. One potential limitation may be the generalizability of these data obtained in a predominantly Caucasian Midwestern community, although the incidence of fractures in Olmsted County has been shown to be comparable to that of the US Caucasian population generally.³² Additionally, Barrett's oesophagus affects Caucasians at a higher rate than other ethnic groups. In addition, since measurements of bone mineral density were not routinely performed in all patients, the contribution of bone loss to fracture risk could not be evaluated directly. However, this was somewhat mitigated by using an accepted clinical definition of osteoporotic fractures which allows fractures to be classified as osteoporotic even in the absence of documented reduced bone density by a DXA scan. Given that incidence rates for osteoporosis and osteopenia are not available for the Olmsted County population, we were unable to estimate SIRs for osteoporosis or osteopenia in our cohort. Further, osteoporosis and/or osteopenia may be clinically silent in individuals, thereby requiring a screening, DXA scan in everyone to be able to ascertain the true incidence rates of low bone mass in the general population. Finally, the presence of confounding factors, both identified and unidentified, limit the ability of an observational study such as this to determine causality.

In conclusion, while fractures (both osteoporotic and from any etiology) are not uncommon in subjects with Barrett's oesophagus, their incidence is not increased when compared to that of the general population. In addition, proton pump inhibitor use in patients with Barrett's oesophagus was not associated with an increased osteoporotic fracture risk when compared to the general population regardless of the duration of use and dosing strategy.

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Appendix 1

Diagnostic codes used for identification of patients with fracture and osteoporosis/osteopenia in Olmsted County (HIC: HICDA codes, I9: ICD9 codes)

07210140	HIC
07230110	HIC
07230120	HIC
07230130	HIC
07230131	HIC
07230132	HIC
07230140	HIC
07230150	HIC
07230151	HIC
07230152	HIC
07230153	HIC
07230154	HIC
07230155	HIC
07230156	HIC
07230160	HIC
07230170	HIC
07230210	HIC
07230230	HIC
07230310	HIC
07231120	HIC
07231121	HIC
07231140	HIC
07231141	HIC
07231142	HIC
07232150	HIC
733.0	I9
733.00	I9

733.01	I9
733.02	I9
733.03	I9
733.09	I9
733.1	I9
733.10	I9
733.11	I9
733.12	I9
733.13	I9
733.14	I9
733.15	I9
733.16	I9
733.19	I9

Appendix 2

Descriptive categories of Landin with modified trauma levels (adapted from *J Bone Miner Res* 2008 Feb; 23(2):173–9)

Descriptives indicating mild trauma

- Falling to the ground from standing height or less (<0.5 m)
- Falling to a resilient surface (rubber, glass or sand) from 0.5 to 3 m
- Falling from a bed or couch

Descriptives indicating moderate trauma ^a

- Falling to concrete or other non-resilient surface from 0.5 to 3 m
- Falling downstairs
- Falling from a bicycle or horseback
- Falls while moving on skis, rollerblades, or skates
- Moderate energy collisions with an object moving at fast speed

Descriptives indicating severe trauma

- Falling from greater than standing height exceeding 3 m
 - Traffic accidents
 - Being hit by a moving heavy object
-

^aIndividuals who sustained moderate trauma and had sustained fractures at such locations where an osteoporotic fracture would be expected to occur (hip, thoracic or lumbar vertebrae, wrist or distal forearm) received an osteoporotic fracture diagnosis

References

1. Nelsen EM, Hawes RH, Iyer PG. Diagnosis and management of Barrett's esophagus. *The Surgical clinics of North America*. 2012; 92(5):1135–54. [PubMed: 23026274]

2. Dunbar KB, Souza RF, Spechler SJ. The Effect of Proton Pump Inhibitors on Barrett's Esophagus. *Gastroenterology clinics of North America*. 2015; 44(2):415–24. [PubMed: 26021202]
3. Katzka DA, Castell DO. Successful elimination of reflux symptoms does not insure adequate control of acid reflux in patients with Barrett's esophagus. *Am J Gastroenterol*. 1994; 89(7):989–91. [PubMed: 8017396]
4. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. 2006; 296(24):2947–53. [PubMed: 17190895]
5. Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. *Pharmacotherapy*. 2008; 28(8):951–9. [PubMed: 18657011]
6. Corley DA, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology*. 2010; 139(1): 93–101. [PubMed: 20353792]
7. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2008; 179(4):319–26.
8. Eom C-SPS, Myung S-K, Yun MJ, Ahn J-S. Use of acid suppressive medication and risk of fracture: a meta-analysis of observational studies. *Ann Fam Med*. 2011; 9(3):257–267. [PubMed: 21555754]
9. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. *Am J Gastroenterol*. 2011; 106(7):1209–18. quiz 1219. [PubMed: 21483462]
10. Zhou B, Huang Y, Li H, Sun W, Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. *Osteoporos Int*. 2016; 27(1):339–47. [PubMed: 26462494]
11. Tuukkanen J, Vaananen HK. Omeprazole, a specific inhibitor of H⁺-K⁺-ATPase, inhibits bone resorption in vitro. *Calcified tissue international*. 1986; 38(2):123–5. [PubMed: 3006888]
12. Mizunashi K, Furukawa Y, Katano K, Abe K. Effect of omeprazole, an inhibitor of H⁺,K⁽⁺⁾-ATPase, on bone resorption in humans. *Calcified tissue international*. 1993; 53(1):21–5. [PubMed: 8102318]
13. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med*. 2005; 118(7):778–81. [PubMed: 15989913]
14. Yang YX. Proton pump inhibitor therapy and osteoporosis. *Current drug safety*. 2008; 3(3):204–9. [PubMed: 18691003]
15. Gagnemo-Persson R, Samuelsson A, Hakanson R, Persson P. Chicken parathyroid hormone gene expression in response to gastrin, omeprazole, ergocalciferol, and restricted food intake. *Calcified tissue international*. 1997; 61(3):210–5. [PubMed: 9262512]
16. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *American journal of epidemiology*. 2011; 173(9):1059–68. [PubMed: 21430193]
17. Jung KW, Talley NJ, Romero Y, et al. Epidemiology and natural history of intestinal metaplasia of the gastroesophageal junction and Barrett's esophagus: a population-based study. *The American journal of gastroenterology*. 2011; 106(8):1447–55. quiz 1456. [PubMed: 21483461]
18. Sami SS, Dunagan KT, Johnson ML, et al. A randomized comparative effectiveness trial of novel endoscopic techniques and approaches for Barrett's esophagus screening in the community. *Am J Gastroenterol*. 2015; 110(1):148–58. [PubMed: 25488897]
19. Lindberg P, Brandstrom A, Wallmark B, Mattsson H, Rikner L, Hoffmann KJ. Omeprazole: the first proton pump inhibitor. *Medicinal research reviews*. 1990; 10(1):1–54. [PubMed: 2404184]
20. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of clinical epidemiology*. 1992; 45(6):613–9. [PubMed: 1607900]
21. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. *J Bone Miner Res*. 1992; 7(2):221–7. [PubMed: 1570766]
22. Melton LJ 3rd, Sampson JM, Morrey BF, Ilstrup DM. Epidemiologic features of pelvic fractures. *Clin Orthop Relat Res*. 1981; (155):43–7.

23. Rose SH, Melton LJ 3rd, Morrey BF, Ilstrup DM, Riggs BL. Epidemiologic features of humeral fractures. *Clin Orthop Relat Res.* 1982; (168):24–30.
24. Melton LJ 3rd, Therneau TM, Larson DR. Long-term trends in hip fracture prevalence: the influence of hip fracture incidence and survival. *Osteoporos Int.* 1998; 8(1):68–74. [PubMed: 9692080]
25. Melton LJ 3rd, Amadio PC, Crowson CS, O’Fallon WM. Long-term trends in the incidence of distal forearm fractures. *Osteoporos Int.* 1998; 8(4):341–8. [PubMed: 10024904]
26. Targownik LE, Lix LM, Leung S, Leslie WD. Proton-pump inhibitor use is not associated with osteoporosis or accelerated bone mineral density loss. *Gastroenterology.* 2010; 138(3):896–904. [PubMed: 19931262]
27. Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ 3rd. Trends in fracture incidence: a population-based study over 20 years. *J Bone Miner Res.* 2014; 29(3):581–9. [PubMed: 23959594]
28. Melton LJ 3rd, Kearns AE, Atkinson EJ, et al. Secular trends in hip fracture incidence and recurrence. *Osteoporos Int.* 2009; 20(5):687–94. [PubMed: 18797813]
29. Melton LJ 3rd, Hartmann LC, Achenbach SJ, Atkinson EJ, Therneau TM, Khosla S. Fracture risk in women with breast cancer: a population-based study. *J Bone Miner Res.* 2012; 27(5):1196–205. [PubMed: 22258822]

Figure 1.
Flowsheet describing identification of patients with osteoporosis/osteopenia and fractures in the study

Table 1

Baseline characteristics of Barrett's oesophagus patients included in the study

Characteristics	Patients with low bone mass ^a (n = 97)	Patients with osteoporotic fractures (n=46)	Patients with fracture of any etiology (n=113)	Patients without low bone mass or a fracture (n = 366)
Mean (SD) age at diagnosis	65 (12)	68 (12)	65 (13)	60 (13)
Male gender (n, %)	52 (53.6%)	26 (56.5%)	75 (66.4%)	300 (82.0%)
Mean (SD) BMI ^b	28.6 (5)	29.6 (5)	30.6 (5)	30.8 (7.5)
Caucasian ethnicity (Caucasian) (%)	90 (92.8%)	44 (95.6%)	104 (92.0%)	318 (86.9%)
GERD symptoms (% yes) ^b	63 (65.0%)	29 (63.0%)	65 (57.5%)	239 (65.3%)
Smokers (% ever or current yes)	64 (66.0%)	34 (73.9%)	80 (70.8%)	204 (55.7%)
Alcohol use (% yes)	49 (50.5%)	21 (45.6%)	55 (48.7%)	205 (56.0%)
PPI use (% yes)	96 (99.0%)	45 (97.8%)	108 (95.6%)	343 (93.7%)
Used PPI twice daily (% yes)	16 (16.5%)	6 (13%)	30 (26.5%)	81 (22.1%)
Mean (SD) duration of PPI use (yrs.)	12.7 (5.4)	12.2 (5.9)	11.4 (5.7)	8.7 (5.6)
Used other acid suppressants (% yes)	22 (22.7%)	10 (21.7%)	35 (31.0%)	108 (29.5%)
Malignancy (% yes) ^c	51 (52.6%)	21 (45.6%)	55 (48.7%)	138 (37.7%)
Used glucocorticoids (% yes)	53 (54.6%)	24 (52.2%)	50 (44.2%)	129 (35.2%)
Used bisphosphonates (% yes)	34 (35.1%)	15 (32.6%)	26 (23.0%)	3 (0.8%)
Used calcium supplements ^d (% yes)	81 (83.5%)	34 (73.9%)	79 (69.9%)	185 (50.6%)
DXA testing (% Yes)	72 (74.2%)	22 (47.8%)	37 (32.7%)	33 (9.0%)
Mean (SD) T score at				
Hip	-2.0 (1.0)	-2.0 (1.2)	-1.9 (1.5)	-0.09 (0.9)
Wrist	-2.7 (3.1)	-1.8 (2.0)	-1.6 (3.4)	n/a
Spine	-1.4 (1.6)	-1.9 (1.2)	-1.7 (1.4)	0.7 (1.2)
Mean Z (SD) score at				
Hip	-0.7 (1.0)	-0.6 (1.1)	-0.6 (1.3)	0.5 (0.9)
Wrist	-1.0 (2.6)	0.2 (0.1)	-0.4 (2.6)	n/a
Spine	-0.4 (1.5)	-0.7 (1.3)	-0.6 (1.4)	0.9 (1.3)
Mean (SD) BMD in g cm ⁻² at ^b				
Hip	0.76 (0.15)	0.77 (0.15)	0.76 (0.19)	1.00 (0.11)
Wrist	0.48 (0.18)	0.52 (0.08)	0.59 (0.26)	n/a
Spine	1.01 (0.18)	0.96 (0.15)	0.99 (0.16)	1.26 (0.14)

Characteristics	Patients with low bone mass ^a (n = 97)	Patients with osteoporotic fractures (n=46)	Patients with fracture of any etiology (n=113)	Patients without low bone mass or a fracture (n = 366)
Any risk factor for secondary osteoporosis (% yes) ^e	65 (67.0%)	31 (67.4%)	71 (62.8%)	179 (48.9%)
Any risk factor for falls (% yes) ^f	77 (79.4%)	40 (87.0%)	91 (80.5%)	188(51.4%)

^aPatients with low bone mass were diagnosed on the basis of DXA testing and/or occurrence of an osteoporotic fracture

^bBMI – Body mass index; GERD – Gastro-esophageal reflux disease; BMD – Bone mineral density

^cMalignancies reported include solid tumors (prostate, liver, lung, colon, breast, and thyroid) as well as leukemia/lymphomas.

^dCalcium supplement use was recorded from review of pharmacy claims in inpatient medical records and from REP database

^eIf yes to any of the following: increased thyroid function, peptic ulcer disease, gastric resection, resection of large or small bowel, renal failure/uremia, rheumatoid arthritis, decreased or increased adrenal function, increased parathyroid function, pancreatitis, liver cirrhosis, malabsorption syndrome, pernicious anemia, emphysema, chronic bronchitis, or treatment with thyroid medication.³¹

^fIf yes to any of the following: stroke, hemiparesis, hemiplegia, transient ischemic attack, dementia, vertebral-basilar insufficiency, vertigo, cataracts, blindness, other vision problems, heart arrhythmia, postural/orthostatic hypotension, syncopal attacks, Parkinsonism, polio sequelae, multiple sclerosis, seizure, or paraplegia.³¹

Table 2

Sites and immediate cause of fractures in Barrett's oesophagus subjects

Site of Fracture	Cause of fracture									
	Severe trauma		Moderate trauma		Pathologic cause		Uncertain			
	N	%	N	%	N	%	N	%		
Skull/face	5	71.4	2	28.6	0	0	0	0		
Hands/fingers	6	85.7	1	14.3	0	0	0	0		
Distal forearm	2	18.2	8	72.7	1	9.1	0	0		
Other arm	8	47	8	47	1	5.9	0	0		
Clavicle/scapula/sternum	1	16.7	4	66.7	1	16.7	0	0		
Ribs	7	41.2	10	58.8	0	0	0	0		
Thoracic/lumbar vertebrae	1	3.7	21	77.8	5	18.5	0	0		
Cervical vertebrae	1	50	1	50	0	0	0	0		
Pelvis	0	0	7	100	0	0	0	0		
Proximal femur	2	9.1	20	90.9	0	0	0	0		
Other lower extremity	7	28	15	60	0	0	3	12		
Feet/toes	1	25	3	75	0	0	0	0		
All sites [*]	41 (34)	27	100 (69)	65.8	8 (8)	5.2	3 (2)	2		

^{*} Number of patients is in last row in ().

Table 3

Observed and expected numbers of all fractures and osteoporotic fractures in Barrett's oesophagus subjects and respective standardized incidence ratios (SIR)

Fracture Site	All fractures (any etiology)			Non-pathologic, non-incidental fractures due to moderate trauma ^a		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Skull/face	7	5.05	1.39 (0.56, 2.85)	2	2.13	0.94 (0.11, 3.38)
Hands/fingers	7	12.42	0.56 (0.23, 1.16)	1	4.91	0.20 (0.01, 1.13)
Distal forearm	11	10.71	1.03 (0.51, 1.84)	8	7.83	1.02 (0.44, 2.01)
Other arm	15	12.54	1.20 (0.67, 1.97)	6	9.28	0.65 (0.24, 1.41)
Clavicle/scapula/sternum	6	6.03	0.99 (0.36, 2.16)	4	3.01	1.33 (0.36, 3.41)
Ribs	14	22.66	0.62 (0.34, 1.04)	10	15.06	0.66 (0.32, 1.22)
Thoracic/lumbar/vertebrae	24	15.56	1.54 (0.99, 2.30)	18	12.76	1.41 (0.84, 2.23)
Cervical vertebrae	2	2.05	0.98 (0.12, 3.52)	1	0.80	1.24 (0.03, 6.90)
Pelvis	7	6.90	1.01 (0.41, 2.09)	7	5.24	1.34 (0.54, 2.75)
Proximal femur	19	16.64	1.14 (0.69, 1.78)	18	14.82	1.21 (0.72, 1.92)
Other leg	25	18.10	1.38 (0.89, 2.04)	15	11.46	1.31 (0.73, 2.16)
Feet/toes	4	11.89	0.34 (0.09, 0.86)	3	3.08	0.97 (0.20, 2.84)
Any site ^b	141	129.10	1.09 (0.92, 1.29)	93	88.38	1.05 (0.85, 1.29)

^a osteoporotic fracture

^b The number of fractures observed at specific skeletal sites may differ from those reported in Table 3 because only the first fracture of each type per patient was counted in this analysis.

Table 4

Univariate Cox Proportional Hazards models for risk of osteoporotic fractures in Barrett's oesophagus patients (n=46 patients)

Risk factors	HR (95% CI)	p-value
Univariate Cox Models		
Female (vs Male)	2.32 (1.29,4.15)	0.005
Age at Barrett's diagnosis (per 1 year)	1.07 (1.04,1.10)	< 0.001
Charlson Index pre Barrett's diagnosis (per 1 unit)	1.18 (1.08,1.29)	< 0.001
Smoking (vs never smoked)	1.73 (0.90,3.34)	0.10
Alcohol use (vs no alcohol use)	0.66 (0.37,1.18)	0.16
Malignancy (vs no malignancy)	1.10 (0.61,1.96)	0.75
PPI use (vs no PPI use)	0.87 (0.12,6.39)	0.89
Twice a day dosing regimen of PPI (vs once daily)+	0.49 (0.21,1.16)	0.10
Duration of PPI therapy(per 1 year)+	0.96 (0.89,1.02)	0.18
Bisphosphonates (vs no Bisphosphonates)	4.59 (2.47,8.52)	< 0.001
Corticosteroids (vs no steroids)	1.79 (1.00,3.19)	0.05

HR: Hazard ratio; CI: Confidence Interval; PPI: Proton Pump Inhibitor; + in subset of patients who used PPI

Table 5

Multivariate Cox Proportional Hazards models for risk of osteoporotic fractures in Barrett's oesophagus patients (n=46 patients)

Risk factors	HR (95% CI)	p-value
Multivariate Cox Models		
Female (vs Male)	2.01 (1.08,3.72)	0.03
Age at Barrett's diagnosis (per 1 year)	1.06 (1.03,1.09)	<0.001
Charlson Index pre Barrett's diagnosis (per 1 unit)	1.12 (1.02,1.23)	0.02
Bisphosphonates (vs no Bisphosphonates)	2.58 (1.32,5.02)	0.005
Corticosteroids (vs no steroids)	1.19 (0.65,2.19)	0.57

HR: Hazard ratio; CI: Confidence Interval