ESOPHAGUS

Oral Bisphosphonates and the Risk of Barrett's Esophagus: Case–Control Analysis of US Veterans

Derek Lin, MD[1], Jennifer R. Kramer, PhD[2], David Ramsey, PhD[2], Abeer Alsarraj, BS[2], Gordana Verstovsek, MD[3,4], Massimo Rugge, MD[5], Paola Parente, MD[6], David Y. Graham, MD[1,7] and Hashem B. El-Serag, MD, MPH[1,2,7]

OBJECTIVES: **This study examined Barrett's esophagus (BE) risk factors in veterans to determine the association between risk of BE and use of oral bisphosphonates.**

METHODS: **We conducted a case–control study among eligible patients scheduled for an elective esophagogastroduodenoscopy (EGD) and a sample of patients eligible for screening colonoscopy recruited from primary care clinics from a single VA Medical Center. Cases with definitive BE were compared with controls; all underwent study EGD. Use of oral bisphosphonates was ascertained by reviewing filled prescriptions in electronic pharmacy records. We calculated odds ratios (ORs) and 95% confidence intervals (95% CIs), using multivariate logistic regression modeling while adjusting for sex, age, race, proton-pump inhibitor use, hiatal hernia, waist-to-hip ratio, *Helicobacter pylori* infection, and gastroesophageal reflux disorder (GERD) symptoms.**

RESULTS: **There were 285 BE cases, 1,122 endoscopy controls, and 496 primary care controls. Alendronate and risedronate were the only oral bisphosphonates prescribed. The proportion of BE cases with filled prescription of oral bisphosphonates (4.6%) was greater than in endoscopy controls (1.6%) or primary care controls (2.9%). In the adjusted analysis, oral bisphosphonate use was significantly associated with BE risk (OR = 2.33; 95% CI: 1.11–4.88) compared with the combined control groups. This association remained significant when BE cases were compared with endoscopy controls only (OR = 2.74; 95% CI: 1.28–5.87) but was attenuated when compared with primary care controls only (OR = 2.60; 95% CI: 0.99–6.84). The association was observed in patients with GERD symptoms (OR = 3.29; 95% CI: 1.36–7.97) but not in those without GERD symptoms.**

CONCLUSIONS: **Oral bisphosphonate use may increase the risk for BE, especially among patients with GERD.**

Am J Gastroenterol 2013; 108:1576–1583; doi:10.1038/ajg.2013.222; published online 16 July 2013

INTRODUCTION

Bisphosphonates are selective inhibitors of osteoclast-mediated bone resorption that are used for the treatment and prevention of osteoporosis. The use of oral bisphosphonates has increased dramatically in recent years, despite its association with adverse gastrointestinal effects, including an increased risk of esophagitis, esophageal erosions, and esophageal ulcers (1,2).

Barrett's esophagus (BE) is a known premalignant precursor lesion in most cases of esophageal adenocarcinoma and is a relatively common problem, thought to affect 1–2% of the general population (3,4). The risk of esophageal adenocarcinoma in patients with BE is 30–125 times greater than the general population (5). The US Food and Drug Administration (FDA) reported on several cases of esophageal adenocarcinoma in bisphosphonate users (6,7). Some of these patients also carried a diagnosis of BE. The author of that FDA report cautioned physicians to avoid prescribing oral bisphosphonates to patients with BE (7). However, recent population-based studies examining the association between bisphosphonate use and esophageal adenocarcinoma have arrived at conflicting results (8–11). Moreover, to assess the safety of oral bisphosphonates, it is important to examine its association with BE. To our knowledge, there are no published studies on this subject.

[1]Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA; [2]Houston VA HSR&D Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA; [3]Department of Pathology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA; [4]Department of Pathology, Baylor College of Medicine, Houston, Texas, USA; [5]Surgical Pathology and Cytopathology Unit, Department of Medicine (DIMED), University of Padova, Padova, Italy; [6]Casa Sollievo della Sofferenza, Department of Pathology, San Giovanni Rotondo, Italy; [7]Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA. **Correspondence:** Hashem B. El-Serag, MD, MPH, Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd. (152), Houston, Texas 77030, USA. E-mail: hasheme@bcm.edu
Received 19 March 2013; accepted 11 June 2013

We conducted a case–control study to examine BE risk factors in a large population of US veterans. Here we report the association between the risk of BE with oral bisphosphonate use, ascertained by pharmacy records.

METHODS

Study population

We used data from a case–control study of BE risk factors conducted at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) in Houston, Texas. Details of this study population have been previously described (12). Briefly, participants were recruited at MEDVAMC either before an elective esophagogastroduodenoscopy (EGD) for any indication from 1 September 2008 to 20 March 2012 or from among patients eligible for screening colonoscopy who attended one of seven selected MEDVAMC primary care clinics from 1 September 2008 to 31 December 2010. No primary care patients were primarily referred for EGD; if they agreed to participate in the study, they underwent the study EGD at the same time as their colonoscopy. The minimum age limit for the EGD group (40 years) was lower than that for the primary care group (50 years). Patients with a previous history of gastroesophageal surgery or diagnosis of cancer, currently taking anticoagulants, with significant liver disease (as indicated by platelet count <70,000, ascites, or known gastroesophageal varices), or with a history of major stroke or mental disorder were ineligible for the study.

Cases were patients with both endoscopically suspected and histologically confirmed BE (i.e., specialized intestinal metaplasia on targeted biopsy from suspected BE areas). We excluded patients with only endoscopically suspected BE from the analysis; however, if they had histologically confirmed BE on a follow-up EGD they were included as BE cases. We compared the BE cases with two control groups: participants without endoscopically suspected BE who underwent an elective EGD ("endoscopy controls") and those recruited from primary care without endoscopically suspected BE on their study EGD ("primary care controls"). Waist and hip circumferences were measured, and waist-to-hip ratios were calculated. Height in inches was also obtained, and body mass index was calculated using the Quetlet index formula.

All participants completed a computer-assisted survey with guidance from a trained research assistant. The survey elicited information about race and ethnicity, social background, frequency and severity of gastroesophageal reflux disorder (GERD) symptoms, cigarette smoking, alcohol use, medical history, ever use of proton-pump inhibitors (PPIs), and use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) in the past year.

For this study, information on oral bisphosphonate use was primarily obtained through manual searches of the Computerized Patient Record System, the VA electronic medical record system, for all filled (dispensed) prescriptions of the following oral bisphosphonates: alendronate (Fosamax), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Atelvia), and tiludronate (Skelid). These prescriptions could have been either mailed or picked up at the window pharmacy. The self-reported survey also included questions about bisphosphonate use.

Statistical analysis

Bisphosphonate use was defined based on the findings of chart reviews of VA pharmacy data. We calculated the proportions of cases and controls with dispensed bisphosphonate prescriptions. We fitted logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between oral bisphosphonates and the risk of BE, using combined control groups and each control group separately. In multivariate analyses, we adjusted for age, sex, race (White, Other), smoking status (nonsmoker, ex-smoker, current smoker), GERD symptoms (never, <10 years, 10+ years), PPI use (never, ever), *H. pylori* infection (positive, negative), waist-to-hip ratio (high and low risk), and hiatal hernia (None, <3 cm, ≥3 cm). Stratified analyses were performed, based on the presence of GERD symptoms, PPI use or both, or NSAID use. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Statistical significance was determined at $\alpha = 0.05$, and all tests for statistical significance were two sided.

RESULTS

Among the 2,226 eligible patients who arrived at their elective EGD appointment and were contacted by our study staff, 1,912 met the study criteria, and 1,489 were enrolled in the study. Among 1,309 eligible primary care patients who were invited to participate, 603 were enrolled in the study. We subsequently excluded 22 patients who withdrew consent, 48 patients without a complete study EGD, and 119 patients with BE only endoscopically suspected but not confirmed (i.e., specialized intestinal metaplasia was absent on biopsy). Of the patients who were screened and found eligible on or before 20 March 2012, a greater percentage of women (33.8% vs. 28.1%, $P = 0.009$), whites (30.4 vs. 26.9% (black) vs. 14.4% (other), $P < 0.001$), and endoscopy patients (34.5% vs. 19.6% (primary care), $P < 0.001$) were enrolled than their counterparts.

We, therefore, had 1,903 patients analyzed in this study: 285 cases of denitive BE, 1,122 endoscopy controls, and 496 primary care controls. The mean age of the study cohort was 60.5 years (s.d. 7.9), and 92.3% were men. Most were white (64.5%) or black (32.5%). Comparisons of demographic, anthropometric, and specific clinical characteristics of the BE cases and the combined control groups are shown in **Table 1**. Patients with definite BE were more likely to be male (97.2% vs. 91.5%, $P < 0.001$) and white (86.3% vs. 61.1%, $P < 0.001$) and an average 1.2 years older than controls ($P = 0.009$). The presence of GERD symptoms (61.6% vs. 46.0%, $P < 0.001$), as well as a long history of GERD symptoms (11.6 vs. 7.4 years, $P < 0.001$), was significantly more common in BE cases than in the combined control groups. PPI use was significantly more common in BE cases (70.4% vs. 51.6%, $P < 0.001$). There was no significant difference in self-reported NSAID use in the past year between BE cases and combined control groups (47.4% vs. 50.0%, $P = 0.45$).

Filled prescriptions for oral bisphosphonates before study endoscopy were ascertained in 54 (2.8%) study participants in a

Table 1. Demographic, anthropometric, and clinical characteristics of BE cases and control groups for the 1,903 study participants

Variable	BE (*N*=285)	Endo Control (*N*=1,121)	PCP Control (*N*=485)	*P* value	
				Endo	PCP
Sex					
Male	277 (97.2%)	1,001 (89.2%)	470 (96.9%)	<0.001	0.778
Female	8 (2.8%)	121 (10.8%)	15 (3.1%)		
Race					
Black	36 (12.6%)	370 (33.0%)	206 (42.5%)	<0.001	<0.001
White	246 (86.3%)	715 (63.7%)	269 (55.5%)		
Other	3 (1.1%)	37 (3.3%)	10 (2.0)		
Mean age (s.d.)	61.5 (7.0)	59.7 (8.6)	62.0 (6.6)	<0.001	0.391
Oral bisphosphonate use					
Yes	13 (4.6%)	33 (2.9%)	8 (1.6%)	0.140	0.008
No	272 (95.4%)	1,089 (97.1%)	477 (98.4%)		
Oral alendronate use					
Yes	12 (4.2%)	31 (2.8%)	5 (1.0%)	0.172	0.002
No	273 (95.8%)	1,091 (97.2%)	480 (99.0%)		
Mean months prescribed (s.d.)	23.08 (36.89)	29.3 (23.88)	31.63 (28.49)	0.499	0.583
<1 year	6 (46.2%)	6 (18.2%)	2 (25.0%)	0.070	0.400
1 year	7 (53.8%)	27 (81.8%)	6 (75.0%)		
Mean BMI (s.d.)	30.09 (5.61)	29.81 (6.88)	30.65 (6.16)	0.375	0.352
Mean WHR (s.d.)	0.98 (0.06)	0.95 (0.07)	0.97 (0.21)	<0.001	0.422
H. pylori infection					
Negative	223 (78.2%)	789 (71.1%)	301 (63.2%)	0.001	<0.001
Positive	55 (19.3%)	319 (28.9%)	175 (36.8%)		
Missing	7 (2.5%)				
GERD symptoms					
None	103 (36.1%)	472 (42.1%)	337 (69.5%)	0.010	<0.001
<10 years	41 (14.4%)	206 (18.4%)	45 (9.3%)		
10+ years	124 (43.5%)	371 (33.1%)	68 (14.0%)		
Missing	17 (6.0%)	73 (6.5%)	35 (7.2%)		
PPI use					
Yes	188 (66.0%)	368 (35.5%)	100 (22.3%)	0.025	<0.001
No	79 (27.7%)	670 (64.5%)	348 (77.7%)		
Missing	18 (6.3%)				
NSAID use					
Yes	131 (46.0%)	457 (48.3%)	233 (53.6%)	0.241	0.955
No	118 (41.4%)	490 (51.7%)	202 (46.4%)		
Missing	36 (12.6%)				
H2RA use					
Yes	25 (8.8%)	135 (13.0%)	25 (5.6%)	0.141	0.071
No	241 (84.6%)	902 (87.0%)	423 (94.4%)		
Missing	19 (6.6%)				

Table 1 continued on following page

Table 1. Continued

Variable	BE (*N*=285)	Endo Control (*N*=1,121)	PCP Control (*N*=485)	*P* value	
				Endo	PCP
Hiatal hernia					
No	47 (16.5%)	398 (35.7%)	220 (45.5%)	<0.001	<0.001
<3	111 (38.9%)	460 (41.3%)	174 (36.1%)		
3+	125 (43.9%)	257 (23.0%)	89 (18.4%)		
Missing	2 (0.7%)				
Smoking status					
Never	61 (21.4%)	284 (27.6%)	108 (24.4%)	0.172	0.627
Former	124 (43.5%)	406 (39.5%)	217 (49.0%)		
Current	80 (28.1%)	338 (32.9%)	118 (26.6%)		
Missing	20 (7.0%)				
Alcohol status					
Never drank	19 (6.7%)	104 (10.0%)	28 (6.3%)	0.313	0.711
Former drinker	144 (50.5%)	511 (49.1%)	255 (57.2%)		
Current drinker	104 (36.5%)	425 (40.9%)	163 (36.5%)		
Missing	18 (6.3%)				

BE, Barrett's esophagus; BMI, body mass index; Endo, endoscopy controls GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; H2RA, histamine 2 receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PCP, primary care patients; PPI, proton-pump inhibitor; WHR, waist-to-hip ratio.

systematic review of electronic pharmacy records for all participants. Only 6 of these 54 patients reported taking alendronate on the self-reported survey. On the other hand, no study participants who did not have oral bisphosphonate prescriptions in their medical records self-reported bisphosphonate use. The only two oral bisphosphonates prescribed in this study were alendronate ($n=48$) and risedronate ($n=6$). Oral bisphosphonates were significantly more commonly prescribed for older, white, and female participants than for their counterparts (**Table 2**). Greater proportions of patients on bisphosphonates were also prescribed PPIs and had GERD symptoms than those not on bisphosphonates, although the differences in GERD symptoms were not statistically significant (**Table 2**).

A greater proportion of BE cases had filled prescriptions for any oral bisphosphonate than the combined groups of controls (4.6% vs. 2.5%; $P=0.078$), and significantly greater proportions of BE cases had alendronate than controls (4.2% vs. 2.2%, $P=0.045$). To examine if increased healthcare contacts may make patients more likely to receive a bisphosphonate prescription, we excluded the 68 prevalent BE cases from the analysis and only included newly diagnosed BE cases. There was an even higher proportion of BE cases with any filled oral bisphosphonate or alendronate prescriptions (4.9% vs. 4.4%, respectively) than those in the combined controls (2.5% vs. 2.2%, respectively). The *P*- value for the χ^2 test for any bisphosphonate increased from 0.078 to 0.041, and that for oral alendronate use changed only slightly from 0.045 to 0.040.

There were no significant differences in the duration of prescriptions between cases and the combined controls (23.1 vs. 29.8 months, $P=0.45$) or in the mean cumulative dose (3,473 mg (s.d. 4,164) vs. 5,691 mg (s.d. 6,013), $P=0.22$). The proportions of patients with 5 mg and ≥10 mg weekly doses were slightly greater in cases than controls (2.1% vs. 0.9% and 2.5% vs. 1.7%, respectively; $P=0.106$). This analysis was limited by the small numbers in the dose groups.

We also compared the distribution of bisphosphonate prescriptions between cases and each control group separately and found significantly higher usage in cases than in primary care controls (1.6%, $P=0.02$), but not endoscopy controls (2.9%, $P=0.19$). Alendronate accounted for most of the oral bisphosphonate prescriptions in BE cases, primary care controls, and endoscopic controls, 31 (93.9%), 5 (62.5%), and 12 (92.3%), whereas risedronate accounted for only 2, 3, and 1 patients in the three groups, respectively.

In the multiple regression model, oral bisphosphonates were significantly associated with a greater than twofold increased risk of BE (OR=2.33; 95% CI: 1.11–4.88) compared with the combined control groups after adjustment for sex, age, race, PPI use, hiatal hernia, waist-to-hip ratio, *H. pylori* infection, and GERD symptoms (**Table 3**). Removing the prevalent 68 BE cases from the analysis and examining only newly diagnosed BE cases slightly changed the OR from 2.33 to 2.45, with the *P* value being unchanged ($P=0.025$).

The risk of BE with bisphosphonate use was slightly higher when we examined BE cases compared with endoscopy control patients only (OR=2.74; 95% CI: 1.28–5.87), but the association was of borderline significance (OR=2.60; 95% CI: 0.99–6.84) when

Table 2. Demographic and clinical characteristics of oral bisphosphonate cases and those not taking oral bisphosphonates

Variable	No oral bisphosphonate	Oral bisphosphonate	*P* value
Sex			
Male	1,834 (93.6%)	38 (61.3%)	<0.001
Female	126 (6.4%)	24 (38.7%)	
Age group			
40s	194 (9.9%)	1 (1.6%)	0.010
50s	612 (31.2%)	12 (19.4%)	
60s	919 (46.9%)	38 (61.3%)	
70s	235 (12.0%)	11 (17.7%)	
Race			
Black	631 (32.2%)	12 (19.4%)	0.023
White	1,281 (65.4%)	46 (74.2%)	
Other	48 (2.4%)	4 (6.5%)	
GERD symptoms			
None	942 (48.1%)	21 (33.9%)	0.071
<10 years	301 (15.4%)	13 (21.0%)	
10+ years	586 (29.9%)	24 (38.7%)	
Missing	131 (6.6%)	4 (6.4%)	
PPI use			
Yes	981 (50.1%)	39 (62.9%)	0.042
No	835 (42.6%)	18 (29.0%)	
Missing	144 (7.3%)	5 (8.1%)	

GERD, gastroesophageal reflux disease; PPI, proton-pump inhibitor.

we compared BE cases with primary care control patients only. However, this analysis was limited by a small number of bisphosphonate users in the primary care control group ($n=8$).

We examined the association between bisphosphonates and BE in several stratified analyses (**Table 3**). The association between oral bisphosphonates and BE increased when limited to patients with GERD symptoms (OR=3.29; 95% CI: 1.36–7.97). However, no association was observed in patients without GERD symptoms (OR=0.86; 95% CI: 0.19–3.93). A similar relationship was also present when examining PPI use; we observed an association between oral bisphosphonates and BE among those using PPIs (OR=2.71; 95% CI: 1.15–6.41) but no significant association in patients without PPI use (OR=1.56; 95% CI: 0.32–7.52). Finally, among NSAID users, there was no significant association between bisphosphonates and BE (OR=1.23; 95% CI: 0.38–3.95), whereas among participants with no reported NSAID use, the OR increased to 4.51 (95% CI: 1.49–13.65).

We also compared 119 patients endoscopic only (without specialized intestinal metaplasia) BE cases, and found no significant differences from patients with definitive BE in filled bisphosphonate prescriptions (4.6% vs. 6.7%, $P=0.37$). Similar to the findings with definitive BE, endoscopic only BE cases were significantly more likely to take bisphosphonate (6.7% vs. 2.2% $P=0.003$) than combined controls. Significantly more bisphosphonate users had esophageal erosions (22.6% vs. 11.0% of nonusers, $P=0.005$); most erosion were grade A (9.5%) followed by grade B (5.3%) and grade C (2.0%).

DISCUSSION

In this large, single-center, case–control study, mostly of male veterans, we found a significant association between previous or current use of oral bisphosphonates and the presence of BE. The use of oral bisphosphonates was associated with a greater than twofold increase in risk of BE than in control patients after adjustment for sex, age, race, PPI use, hiatal hernia, waist-to-hip ratio, *H. pylori* infection, and GERD symptoms. The association between oral bisphosphonates and BE was seen only among patients with frequent GERD symptoms, PPI use, or both.

BE is thought to develop from an inflammatory process caused by chronic gastroesophageal reflux contents leading to mucosal injury and DNA damage (13). Mediators of inflammation such as nuclear factor-κB have been linked to the induction of CDX genes that play an important role in the initiation of BE (14,15). Similarly, evidence suggests that bisphosphonate users develop esophagitis, esophageal erosions, and esophageal ulcers through direct topical injury, as esophageal biopsies have revealed foreign material consistent with the appearance of alendronate tablets (16). It is plausible that, through a common inflammatory process, oral bisphosphonates could be associated with BE.

The mechanisms underlying the association between BE and bisphosphonates are unknown. The nitrogen-containing bisphosphonates including alendronate and risedronate, which were used by subjects in this study, act by inhibiting the mevalonate pathway through farnesyl diphosphate synthase (17). The *in vitro* models of human epidermal keratinocytes exposed to alendronate or risedronate revealed suppression of epithelial cell growth via inhibition of farnesyl diphosphate synthase in the mevalonate to cholesterol pathway; the resulting reduction in cholesterol synthesis and geranylgeranylation suppresses cell growth by interfering with progression through the cell cycle (18). The inhibition of esophageal epithelial stem cells could potentiate the damage of gastroesophageal reflux and lead to inactivation of squamous differentiation and activation of columnar differentiation.

We observed that the association between bisphosphonate use and BE was modified by the presence of GERD symptoms, PPI use, and NSAID use. These factors could facilitate or inhibit the way oral bisphosphonates affect BE development. For example, there could be a potentiating effect for GERD, which is the most common risk factor for BE. PPIs are the primary antisecretory treatment for patients with GERD-related syndromes (19), and therefore they could a marker of GERD. NSAIDs have been studied in observational studies for a potentially protective effect against BE (20,21).

Bisphosphonates have come under the scrutiny of the FDA Advisory Committee for Reproductive Health Drugs and Drug Safety

Table 3. Multivariate odds ratios for association of oral bisphosphonate use with BE cases vs. controls

	N	Odds ratio	95% Confidence interval	*P* value
BE cases vs. all controls	265/1,488	2.33	1.110–4.875	0.025
BE cases vs. endoscopy controls only	264/1,007	2.74	1.280–5.874	0.009
BE cases vs. primary care controls only	260/464	2.60	0.989–6.839	0.053
Stratified analyses: BE cases vs. all controls	285/1,618			
GERD symptoms				
Present	159/678	3.29	1.358–7.966	0.008
Absent	99/776	0.862	0.189–3.927	0.848
PPI use				
Yes	186/767	2.71	1.146–6.414	0.023
No	79/721	1.56	0.323–7.524	0.581
GERD symptoms or PPI use				
Yes	209/951	2.61	1.178–5.768	0.018
No	49/524	1.41	0.153–12.986	0.761
NSAID use				
Yes	131/692	1.23	0.384–3.948	0.726
No	116/674	4.51	1.488–13.651	0.008
Gender				
Male	256/1,324	2.07	0.890–4.806	0.091
Female	8/135	15.45	1.259–189.728	0.032

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.
Models adjusted for sex, age, race, PPI use, hiatal hernia, waist-to-hip ratio, *Helicobacter pylori* infection, and GERD symptoms.

and Risk Management Committee in response to postmarketing reports of rare but serious adverse events, including esophageal cancer (22). A total of 34 cases were submitted to the FDA Adverse Event Reporting System of esophageal cancer of unspecified histological type in bisphosphonate users during 1998–2009. Histological analysis showed adenocarcinoma in 7 patients and squamous cell carcinoma in 1 patient. An additional 34 cases of esophageal cancer among bisphosphonate users were also reported from Europe and Japan. Histological analysis showed adenocarcinoma in six patients and squamous cell carcinoma in five patients. One patient from the United States and three patients from Europe and Japan concomitantly carried a diagnosis of BE (3). All cases reported in the United States and most cases in Europe and Japan involved alendronate as the suspect bisphosphonate. The bisphosphonate use in our study was predominantly alendronate (89%) rather than risedronate (11%). Animal models have shown that risedronate, a pyridinyl bisphosphonate, induces less gastric damage compared with the primary amino bisphosphonates including pamidronates (23,24).

Subsequently, population-based studies conducted in the United Kingdom, Denmark, and Taiwan have arrived at conflicting results regarding the use of bisphosphonates and esophageal cancer (8–11). Green *et al.* (8) showed an increased risk between oral bisphosphonates and esophageal cancer, whereas the other three studies concluded that oral bisphosphonates were not likely risk factors for esophageal cancer. Only one study by Cardwell *et al.* (9), conducted among 46,036 bisphosphonate users, reported on prior BE diagnosis, but rates of BE were low, accounting for 0.5% of the study participants, with only 1 patient developing cancer.

It is unknown how bisphosphonate use influences adenocarcinoma risk in BE. A recent study conducted of a national VA cohort of patients with BE found that oral bisphosphonates were not associated with an increased risk of esophageal adenocarcinoma, but this study was limited by only 2 cases (of 116 total cases) being exposed to oral bisphosphonates (25). This is further complicated by growing evidence that bisphosphonates demonstrate antitumor activity through inhibition of the mevalonate pathway that has been implicated in various aspects of tumor development and progression (26–28).

The strengths of our study include a large sample size and the accurate endoscopic and histologic definition of cases and controls. All patients completed a comprehensive survey before the EGD to capture several potential confounders. Oral bisphosphonate use was ascertained by filled prescriptions in the electronic pharmacy records and supplemented by self-report information in all cases and controls. Exposure to the medication was based on prescriptions that were actually filled. Finally, corroborating

the known associations between BE and older age, male sex, white race, GERD symptoms, and waist-to-hip ratio confers internal validity to the new observation related to bisphosphonates.

However, our study has several limitations. It was conducted at a single-center VA medical center, where patients are likely to be older men, which may limit the generalizability of the results. Patients who were enrolled in this study may have received bisphosphonates from non-VA pharmacies, although studies have shown that veterans who use the VA healthcare system tend to disproportionately or exclusively use VA pharmacy services (29). There are no data as to whether oral bisphosphonates were taken according to directions, which require patients to remain upright for at least 30 min after ingestion, or as to the actual ingestion of medications, given that compliance with oral bisphosphonates is already known to be suboptimal (30). Of the 54 patients with a filled bisphosphonate prescription, only 6 reported taking alendronate on the self-reported survey. This could indicate a high percentage of noncompliance, although we believe that using the electronic pharmacy data for filled (dispensed) prescription is a more accurate and complete method for ascertaining medications use than self-report. Polypharmacy, which is quiet high among older veteran patients, likely contributed to the inaccuracy of self-report information in this study. Although we conducted a survey with an extensive questionnaire to document potential confounders, we cannot rule out other residual confounding from unmeasured or poorly measured variables. For example, the BE cases in this study were more likely than controls to have a long history of GERD symptoms. Oral bisphosphonate use may have worsened existing symptoms, leading to presentation to a physician and subsequent recruitment for a research endoscopy and the possible introduction of a selection bias.

In conclusion, among 285 veterans with denitive BE and 1,618 controls, we found a significant association between oral bisphosphonate use and an increased risk of BE, especially among patients with GERD symptoms, those on PPI treatment, or those not taking NSAIDs. This is the first published study on this association. Additional studies are needed to further examine this association, as it could suggest an increased risk of esophageal cancer in oral bisphosphonate users.

CONFLICT OF INTEREST

Guarantor of the article: Hashem B. El-Serag, MD, MPH.

Specific author contributions: H.B.E.-S. conceived the study and participated in its design, acquired the funding, and drafted and revised the manuscript; D.L. conducted the medical chart reviews, assisted with the data analysis, interpreted the data, and drafted the manuscript; J.R.K. contributed to study design, monitored data collection, wrote the statistical analysis plan, and interpreted the data; D.R. contributed to the data analysis plan, cleaned and analyzed data, and assisted with data interpretation; A.A. designed data collection tools, enrolled subjects, and participated in study design and coordination; G.V., M.R., P.P., and D.Y.G. participated in study design, monitoring data collection, determining BE status, and interpretation of data. All authors read, revised, and approved the final manuscript.

Financial support: This work is funded in part by NIH grant NCI R01 116845, the Houston VA HSR&D Center of Excellence (HFP90-020), and the Texas Digestive Disease Center NIH DK58338. Hashem B. El-Serag is also supported by NIDDK K24-04-107.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government.

Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The link between oral bisphosphonates and esophageal cancer is controversial.
- ✓ Barrett's esophagus is the precursor lesion to esophageal adenocarcinoma.
- ✓ The association between oral bisphosphonates and Barrett's esophagus is unknown.

WHAT IS NEW HERE

- ✓ The use of oral bisphosphonates was significantly but modestly associated with an increased risk of Barrett's esophagus.
- ✓ This association was observed only in those with frequent gastroesophageal reflux symptoms and/or proton-pump inhibitor use.

REFERENCES

1. Udell JA, Fischer MA, Brookhart MA *et al.* Effect of the Women's Health Initiative on osteoporosis therapy and expenditure in Medicaid. J Bone Miner Res 2006;21:765–71.
2. Graham DY. What the gastroenterologist should know about the gastrointestinal safety profiles of bisphosphonates. Dig Dis Sci 2002;47:1665–78.
3. Ronkainen J, Aro P, Storskrubb T *et al.* Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology 2005;129:1825–31.
4. Hamilton SR, Smith RR, Cameron JL. Prevalence and characteristics of Barrett esophagus in patients with adenocarcinoma of the esophagus or esophagogastric junction. Hum Pathol 1988;19:942–8.
5. Pera M. Trends in incidence and prevalence of specialized intestinal metaplasia, Barrett's esophagus, and adenocarcinoma of the gastroesophageal junction. World J Surg 2003;27:999–1008.
6. Wysowski DK. Oral bisphosphonates and oesophageal cancer. BMJ 2010;341:c4506.
7. Wysowski DK. Reports of esophageal cancer with oral bisphosphonate use. N Engl J Med 2009;360:89–90.
8. Green J, Czanner G, Reeves G *et al.* Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ 2010;341:c4444.
9. Cardwell CR, Abnet CC, Cantwell MM *et al.* Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA 2010;304:657–63.
10. Ho YF, Lin JT, Wu CY. Oral bisphosphonates and risk of esophageal cancer: a dose-intensity analysis in a nationwide population. Cancer Epidemiol Biomarkers Prev 2012;21:993–5.
11. Abrahamsen B, Pazianas M, Eiken P *et al.* Esophageal and gastric cancer incidence and mortality in alendronate users. J Bone Miner Res 2012;27:679–86.
12. Kramer JR, Fischbach LA, Richardson P *et al.* Waist to hip ratio but not body mass index is associated with increased risk of Barrett's esophagus in white men. Clin Gastroenterol Hepatol 2013;11:373 .
13. Olliver JR, Hardie LJ, Gong Y *et al.* Risk factors, DNA damage, and disease progression in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev 2005;14:620–5.
14. Colleypriest BJ, Ward SG, Tosh D. How does inflammation cause Barrett's metaplasia? Curr Opin Pharmacol 2009;9:721–6.

15. Chen H, Fang Y, Tevebaugh W *et al.* Molecular mechanisms of Barrett's esophagus. Dig Dis Sci 2011;56:3405–20.
16. Ribeiro A, DeVault KR, Wolfe JT III *et al.* Alendronate-associated esophagitis: endoscopic and pathologic features. Gastrointest Endosc 1998;47:525–8.
17. Rogers MJ, Crockett JC, Coxon FP *et al.* Biochemical and molecular mechanisms of action of bisphosphonates. Bone 2011;49:34–41.
18. Reszka AA, Halasy-Nagy J, Rodan GA. Nitrogen-bisphosphonates block retinoblastoma phosphorylation and cell growth by inhibiting the cholesterol biosynthetic pathway in a keratinocyte model for esophageal irritation. Mol Pharmacol 2001;59:193–202.
19. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology 2008;135:1383–91.
20. Thrift AP, Pandeya N, Smith KJ *et al.* The use of nonsteroidal anti-inflammatory drugs and the risk of Barrett's oesophagus. Aliment Pharmacol Ther 2011;34:1235–44.
21. Anderson LA, Johnston BT, Watson RG *et al.* Nonsteroidal anti-inflammatory drugs and the esophageal inflammation-metaplasia-adenocarcinoma sequence. Cancer Res 2006;66:4975–82.
22. US Food and Drug Administration. Background document for meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. September 2011 Available at http://www.nice.org.uk/media/91D/04/MedicinesAwarenessWeekly310812.pdf.
23. Blank MA, Ems BL, Gibson GW *et al.* Nonclinical model for assessing gastric effects of bisphosphonates. Dig Dis Sci 1997;42:281–8.
24. Blank MA, Gibson GW, Myers WR *et al.* Gastric damage in the rat with nitrogen-containing bisphosphonates depends on pH. Aliment Pharmacol Ther 2000;14:1215–23.
25. Nguyen DM, Schwartz J, Richardson P *et al.* Oral bisphosphonate prescriptions and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Dig Dis Sci 2010;55:3404–7.
26. Thurnher M, Nussbaumer O, Gruenbacher G. Novel aspects of mevalonate pathway inhibitors as antitumor agents. Clin Cancer Res 2012;18:3524–31.
27. Santini D, Schiavon G, Angeletti S *et al.* Last generation of amino-bisphosphonates (N-BPs) and cancer angio-genesis: a new role for these drugs? Recent Pat Anticancer Drug Discov 2006;1:383–96.
28. Green JR. Bisphosphonates in cancer therapy. Curr Opin Oncol 2002;14:609–15.
29. Morgan RO, Petersen LA, Hasche JC *et al.* VHA pharmacy use in veterans with Medicare drug coverage. Am J Manag Care 2009;15:e1–8.
30. Cramer JA, Gold DT, Silverman SL *et al.* A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int 2007;18:1023–31.