Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Association of medications for lifestyle-related diseases with reflux esophagitis

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
4 October 2016
Number of times this article has been viewed

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Background: Because of a change in lifestyle, especially adoption of westernized eating habits, lifestyle-related diseases have become increasingly prevalent. The aim of this study was to investigate the association of medications for lifestyle-related diseases with reflux esophagitis (RE).

Methods: We conducted a hospital-based, cross-sectional retrospective study of consecutive outpatients who received an upper gastrointestinal endoscopy in our department from February 2008 to November 2014, which was performed by one specialist who was a member of the Japan Gastroenterological Endoscopy Society. We investigated the patient profile, *Helicobacter pylori* (*H. pylori*) infection status, medications for lifestyle-related diseases (including calcium channel blockers, statins, and bisphosphonates), and upper gastrointestinal endoscopic findings (RE, hiatal hernia, Barrett's mucosa, and endoscopic gastric mucosal atrophy [EGA]). Patients with gastrectomy, peptic ulcer disease, gastric or esophageal malignant disease, and those who used proton pump inhibitors or histamine-2 receptor antagonists were excluded. We divided the subjects into a group without RE (RE(−)) and a RE (RE(+)) group as judged by endoscopy, and investigated the risk factors for RE.

Results: Of 1,744 consecutive cases, 590 cases (300 males and 290 females; mean age 60.5±13.2 years) were eligible. RE(−) and RE(+) cases numbered 507 and 83, respectively. Bivariate analysis showed significant positive associations of RE with male sex, body mass index (BMI), calcium channel blockers, Barrett's mucosa, hiatal hernia and negative associations of RE with *H. pylori* positivity, EGA. Multivariate analysis showed significant positive associations of RE with BMI (odds ratio [OR]: 1.20, 95% confidence interval [95% CI]: 1.10–1.29), use of calcium channel blockers (OR: 2.12, 95% CI: 1.16–3.87), Barrett's mucosa (OR: 2.97, 95% CI: 01.64–5.38), hiatal hernia (OR: 3.13, 95% CI: 1.79–5.47) and negative associations of RE with *H. pylori* positivity (OR: 0.20, 95% CI: 0.07–0.57), use of statins (OR: 0.42, 95% CI: 0.18–0.96), and EGA (OR: 0.83, 95% CI: 0.70–0.98).

Conclusion: Calcium channel blockers were positively associated with RE and statins were negatively associated with RE, while bisphosphonates were not associated with RE.

Keywords: reflux esophagitis, calcium channel blockers, statins, bisphosphonates, *H. pylori*, hiatal hernia, Barrett's mucosa, endoscopic gastric mucosal atrophy

Introduction

Because of a change in lifestyle, especially adoption of westernized eating habits, metabolic syndrome and lifestyle-related diseases such as hypertension, dyslipidemia, diabetes, and osteoporosis have become a significant public health problem in Japan. These diseases are closely associated with reflux esophagitis (RE).[1–3] These lifestyle-related diseases increase the risk of death and reduce the quality of life and life expectancy. Consequently, there is an increase in national cost of medical care, which highlights that preventive therapy for lifestyle-related diseases are very important.[4]

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Dovepress
http://dx.doi.org/10.2147/TCRM.S114709

With regard to the association between RE and medications for lifestyle-related diseases, calcium channel blocker use might affect lower esophageal sphincter pressure, while bisphosphonate use has been associated with esophagitis in Western countries.[5,6] The pleiotropic effects and therapeutic potential of statins in gastrointestinal tract disorders have also been reported.[7] However, there are few reports relating to the association between RE and medications for lifestyle-related diseases in Japan.[8] Furthermore, most previous reports concerning the risk factors for RE have included subjects who were taking gastric acid secretion inhibitors such as proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA) that may affect the development of RE. Therefore, the risk factors for RE should be investigated in patients who are not taking PPI or H2RA. The aim of this study was to investigate the association of medications for lifestyle-related diseases with RE.

Methods

We conducted a hospital-based, cross-sectional retrospective study of consecutive outpatients who received an upper gastrointestinal endoscopy in our department from February 2008 to November 2014, which was performed by one specialist (DA) who was a member of the Japan Gastroenterological Endoscopy Society. Subjects were included if information on all of the following aspects were available in the medical records: patient profile (age, sex, body mass index [BMI], cumulative alcohol intake [kg], and Brinkman index); *Helicobacter pylori* (*H. pylori*) infection status (negative, positive, or negative after eradication therapy); medications for lifestyle-related diseases (including calcium channel blockers, statins, and bisphosphonates); and findings of upper gastrointestinal endoscopy (RE, hiatal hernia, Barrett's mucosa, and endoscopic gastric mucosal atrophy [EGA]). BMI was calculated as body weight divided by the square of body height in meters (kg/m^2). The Brinkman index score was determined by the number of cigarettes smoked per day multiplied by the number of years of smoking.[9] Cumulative alcohol intake was defined as the cumulative intake of ethanol (kg). *H. pylori* infection status was assessed by the 13C-urea breath test[10] and/or serum antibodies to *H. pylori*. We defined a positive result for any of these tests as being positive for *H. pylori* infection. We also defined a negative after eradication result by the 13C-urea breath test as negative for *H. pylori* infection, 4–8 weeks after eradication therapy. We defined cases as users of a specific therapy who were taking a typical dose of calcium channel blockers, statins, or bisphosphonates for more than half a year. We investigated findings from upper gastrointestinal endoscopy (RE, Barrett's mucosa, hiatal hernia, and EGA). We defined RE as grade A, B, C, and D according to the Los Angeles Classification. Barrett's mucosa is defined as the area between the squamocolumnar junction and the esophagogastric junction. The esophagogastric junction was defined as the end of the inferior palisade vessel. When we could not detect the palisade vessel, we defined it as the proximal margin of the gastric fold. The squamocolumnar junction is recognized as the area that demarcates the "reddish" gastric epithelium from the "whitish" esophageal epithelium. Hiatal hernia was defined as an apparent separation of the esophagogastric junction and diaphragm impression by more than 2 cm at endoscopy. EGA was classified as C-0 (normal), C-1, C-2, C-3, O-1, O-2, or O-3 using the Kimura–Takemoto classification system,[11] which identifies the location of the endoscopic atrophic border. Overall, the EGA was scored as 0 for C-0 type, 1 for C-1 type, 2 for C-2 type, 3 for C-3 type, 4 for O-1 type, 5 for O-2 type, and 6 for O-3 type.

We excluded patients with the following: those who had gastrectomy, peptic ulcer disease, and gastric or esophageal malignant disease. Additionally, we also excluded patients who were currently or previously treated with agents affecting RE, including PPI or H2RA, in bivariate and multivariate analysis. This study was conducted in accordance with the tenets of the Declaration of Helsinki. The Juntendo University Ethics Committee approved the study and the study protocol (reference number 15–114). In regard to the informed consent of participants, the Juntendo University Ethics Committee made a decision based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects that states that non-intervention studies are deemed exempt from patient's consent and instead researchers must notify the study subjects of the information about study contents on a homepage and guarantee the opportunity when the study subjects could refuse it. According to the decision of the Juntendo University Ethics Committee, we notified the study subjects of the information about our study contents on a homepage of our hospital and guaranteed the opportunity when the study subjects could refuse it.

Statistical analysis

We divided the subjects into a group without RE (RE[–]) and a group with RE (RE[+]), as judged by endoscopy. We then investigated the risk factors for RE, especially the association between RE and medications for lifestyle-related diseases, using bivariate and multivariate analysis. Multivariate logistic regression analysis was performed using a backward selection method (likelihood ratio). The odds ratio (OR) and 95% confidence intervals (CIs) were also used to identify the presence and strength of any associations. Standard techniques for

model checking, including the model square test, Hosmer–Lemeshow goodness of fit test, Nagelkerke R^2, and discriminant hit ratio, were used to determine the adequacy of the multivariate logistic regression model. All statistical analyses were performed using Statistical Package for the Social Sciences, version 19 software (IBM Corporation, Armonk, NY, USA). Statistical significance was inferred at $P<0.05$.

Results

Clinical characteristics

Of the 1,744 consecutive investigated cases, 562 were excluded because of unknown status for *H. pylori* (379 cases), evidence of gastrectomy (97 cases), peptic ulcer disease (58 cases), and gastric or esophageal malignant disease (28 cases). The clinical characteristics of the 1,182 eligible cases, including users of gastric acid secretion inhibitors (598 males [50.6%] and 584 females [49.4%]), are summarized in Table 1. Mean age of the patients was 61.8±13.2, and mean BMI was 22.7±3.5.

After excluding users of gastric acid secretion inhibitors, the clinical characteristics of the 590 eligible cases (300 males [50.8%] and 290 females [49.2%]) are summarized in Table 2. The mean age was 60.5±13.2 (19–87) years, and mean BMI was 22.7±3.5. Cases who were *H. pylori* negative, *H. pylori* positive, and *H. pylori* negative after eradication therapy numbered 349 (59.1%), 149 (25.3%), and 92 (15.6%), respectively. Calcium channel blockers, statins, and bisphosphonates were being taken by 115 (19.5%), 91 (15.4%), and 24 (4.1%) cases, respectively. Of the 590 eligible cases, there were 507 (85.9%) and 83 (14.1%) cases of RE(−) and RE(+), respectively. Sixty-three, 18, 2, and 0 cases of RE had Los Angeles grade A, B, C, and D, respectively. Barrett's mucosa and hiatal hernia were observed in 129 (21.9%) and 267 (45.3%) cases, respectively. Mean EGA was 2±2. The number of cases of EGA for C-0, C-1, C-2, C-3, O-1, O-2, and O-3 were 173, 145, 63, 29, 91, 58, and 31 cases, respectively.

Table 1 Clinical characteristics of patients (including users of gastric acid secretion inhibitors; n=1,182)

Patient profile	
Age (years)	61.8 (±13.2)[a]
Sex	
Female	584 (49.4)[b]
Male	598 (50.6)[b]
BMI (kg/m^2)	22.7 (±3.5)[a]
Cumulative alcohol intake (kg)	235 (±541)[a]
Brinkman index	217 (±406)[a]
***H. pylori* infection status**	
H. pylori infection	
Negative	678 (57.4)[b]
Positive	283 (23.9)[b]
Negative after eradication	221 (18.7)[b]
Gastric acid secretion inhibitors	
PPI	
Nonuser	703 (59.5)[b]
User	479 (40.5)[b]
H2RA	
Nonuser	1,069 (90.4)[b]
User	113 (9.6)[b]
Medications for lifestyle-related diseases	
Calcium channel blockers	
Nonuser	931 (78.8)[b]
User	251 (21.2)[b]
Statins	
Nonuser	938 (79.4)[b]
User	244 (20.6)[b]
Bisphosphonates	
Nonuser	1,091 (92.3)[b]
User	91 (7.7)[b]
Upper GI findings	
RE	
No	1,055 (89.3)[b]
Yes	127 (10.7)[b]
LA-grade A	86 (67.7)[b]
Grade B	35 (27.6)[b]
Grade C	2 (1.6)[b]
Grade D	4 (3.1)[b]
Barrett's mucosa	
No	889 (75.2)[b]
Yes	293 (24.8)[b]
Hiatal hernia	
No	612 (51.8)[b]
Yes	570 (48.2)[b]
EGA	2.1 (±1.9)[a]
C-0	312 (26.4)[b]
C-I	296 (25.0)[b]
C-2	147 (12.4)[b]
C-3	77 (6.5)[b]
O-1	191 (16.2)[b]
O-2	106 (9.0)[b]
O-3	31 (5.3)[b]

Note: [a]Median (± SD), [b]number (%).

Abbreviations: BMI, body mass index; PPI, proton pump inhibitors; H2RA, histamine-2 receptor antagonists; GI, gastrointestinal; RE, reflux esophagitis; EGA, endoscopic gastric mucosal atrophy; SD, standard deviation; *H. pylori*, *Helicobacter pylori*.

Bivariate analysis

Risk factors for RE (including users of gastric acid secretion inhibitors) in bivariate analysis are listed in Table 3. Approximately 42.5% (448/1,055) of patients in the RE(−) group used PPI versus 24.4% (31/127) in the RE (+) group.

After excluding users of gastric acid secretion inhibitors, results of the bivariate analysis are listed in Table 4. In the RE(−) and RE(+) groups, the mean age was 60.7±13.2 versus 59.4±13 years (P=0.415); the proportion of males was 48.3% (245/507) versus 66.3% (55/83) (P=0.003); BMI was 22.3±3.3 versus 24.8±4.3 ($P<0.001$); cumulative alcohol intake was 209±503 versus 264±497 kg (P=0.352); and Brinkman index was 197±386 versus 236±379 (P=0.396). Those who were *H. pylori* positive comprised 28.4% (144/507) versus 6% (5/83) ($P<0.001$); those in whom *H. pylori* was negative after eradication therapy comprised

Table 2 Clinical characteristics (excluding users of gastric acid secretion inhibitors; n=590)

Patient profile	
Age (years)	60.5 (±13.2)[a]
Sex	
Female	290 (49.2)[b]
Male	300 (50.8)[b]
BMI (kg/m^2)	22.7 (±3.5)[a]
Cumulative alcohol intake (kg)	217 (±502)[a]
Brinkman index	203 (±385)[a]
***H. pylori* infection status**	
H. pylori infection	
Negative	349 (59.1)[b]
Positive	149 (25.3)[b]
Negative after eradication	92 (15.6)[b]
Medications for lifestyle-related diseases	
Calcium channel blockers	
Nonuser	475 (80.5)[b]
User	115 (19.5)[b]
Statins	
Nonuser	499 (84.6)[b]
User	91 (15.4)[b]
Bisphosphonates	
Nonuser	566 (95.9)[b]
User	24 (4.1)[b]
Upper GI findings	
RE	
No	507 (85.9)[b]
Yes	83 (14.1)[b]
LA-grade A	63 (75.9)[b]
Grade B	18 (21.7)[b]
Grade C	2 (2.4)[b]
Grade D	0 (0.0)[b]
Barrett's mucosa	
No	461 (78.1)[b]
Yes	129 (21.9)[b]
Hiatal hernia	
No	323 (54.7)[b]
Yes	267 (45.3)[b]
EGA	2.0 (±2.0)[a]
C-0	173 (29.3)[b]
C-I	145 (24.6)[b]
C-2	63 (10.7)[b]
C-3	29 (4.9)[b]
O-1	91 (15.4)[b]
O-2	58 (9.8)[b]
O-3	31 (5.3)[b]

Note: [a]Median (± SD), [b]number (%).
Abbreviations: BMI, body mass index; GI, gastrointestinal; RE, reflux esophagitis; LA, Los Angeles classification system; EGA, endoscopic gastric mucosal atrophy; SD, standard deviation; *H. pylori*, *Helicobacter pylori*.

15.6% (79/507) versus 15.7% (13/83) (P=0.985); calcium channel blockers users comprised 17.6% (89/507) versus 31.3% (26/83) (P=0.004); statin users comprised 16.2% (82/507) versus 10.8% (9/83) (P=0.216); and bisphosphonates users comprised 4.7% (24/507) versus 0% (0/83) (P=0.998). Comparing upper gastrointestinal findings between the RE(−) and RE(+) groups, Barrett's mucosa was present in 19.7% (100/507) versus 34.9% (29/83) (P=0.002), hiatal hernia in 40.8% (207/507) versus 72.3% (60/83) (P<0.001), and the mean EGA score was 2.1±2 versus 1.3±1.7 (P<0.001), respectively.

Multivariate logistic regression analysis

Models were adjusted for the parameters of sex, BMI, *H. pylori* infection status, calcium channel blockers, statins, Barrett's mucosa, hiatal hernia, and EGA. Multivariate logistic regression showed that BMI (OR: 1.20, 95% CI: 1.10–1.29, P<0.001), *H. pylori* positivity (OR: 0.20, 95% CI: 0.07–0.57, P=0.002), calcium channel blockers (OR: 2.12, 95% CI: 1.16–3.87, P=0.014), statins (OR: 0.42, 95% CI: 0.18–0.96, P=0.040), Barrett's mucosa (OR: 2.97, 95% CI: 1.64–5.38, P<0.001), hiatal hernia (OR: 3.13, 95% CI: 1.79–5.47, P<0.001), and EGA (OR: 0.83, 95% CI: 0.70–0.98, P=0.030) were associated with RE (Table 5). None of the other factors examined were associated with RE. Statistical compatibility in the multivariate analysis was as follows: model square test, P<0.01; Hosmer–Lemeshow goodness of fit test, P=0.276; Nagelkerke R^2=0.293; and the discriminant hit ratio =86.9%.

Discussion

This study showed that calcium channel blockers and statins as medications for lifestyle-related diseases were associated with the presence of RE, while bisphosphonates were not associated with the presence of RE. Furthermore, consistent with previous reports assessing the Japanese population, *H. pylori* infection, EGA, hiatal hernia, and Barrett's mucosa were also associated with RE.[1,2,36,42]

Previously, Hongo et al[5] reported that nifedipine significantly decreased lower esophageal sphincter pressure and contraction amplitude in the esophageal body; thus, it has been reported that calcium channel blockers may be useful as therapy for achalasia.[12] In patients with RE, Ishikawa et al[13] reported that duration of esophageal acid exposure after the administration of nifedipine was significantly longer compared with placebo. In this study, calcium channel blocker use was associated with the presence of RE, and a decrease in lower esophageal sphincter pressure might cause gastric acid reflux up the esophagus, resulting in a possible increase in RE. In those subjects who visited a medical center for their annual medical check-up, Niigaki et al[1] reported that subjects undergoing treatment for hypertension showed an increased risk of RE, while those with untreated hypertension were not statistically associated with prevalence of RE,

Table 3 Risk factors for RE (including users of gastric acid secretion inhibitors; n=1,182; bivariate analysis)

Covariates	RE(−) group 1,055 (89.3%)[b]	RE(+) group 127 (10.7%)[b]	Bivariate		
			Standardized coefficient	OR (95% CI)	*P*-value
Patient profile					
Age (years)	62.2 (±13.2)[a]	58.9 (±13.3)[a]	−0.0180	0.98 (0.97–0.99)	0.008
Sex					
Female	539 (51.1)[b]	45 (35.4)[b]		1.00 (reference)	
Male	516 (48.9)[b]	82 (64.6)[b]	0.6437	1.90 (1.30–2.79)	0.001
BMI (kg/m^2)	22.5 (±3.3)[a]	24.6 (±3.9)[a]	0.1603	1.17 (1.12–1.24)	<0.001
Cumulative alcohol intake (kg)	231 (±539)[a]	266 (±555)[a]	0.0001	1.00 (1.00–1.00)	0.503
Brinkman index	215 (±411)[a]	227 (±364)[a]	0.0001	1.00 (1.00–1.00)	0.756
***H. pylori* infection status**					
H. pylori infection					
Negative	582 (55.1)[b]	96 (75.6)[b]		1.00 (reference)	
Positive	276 (26.2)[b]	7 (5.5)[b]	−1.8040	0.17 (0.08–0.36)	<0.001
Negative after eradication	197 (18.7)[b]	24 (18.9)[b]	0.0147	1.02 (0.63–1.62)	0.951
Gastric acid secretion inhibitors					
PPI					
Nonuser	607 (57.5)[b]	103 (75.6)[b]		1.00 (reference)	
User	448 (42.5)[b]	31 (24.4)[b]	−0.8266	0.44 (0.29–0.67)	<0.001
H2RA					
Nonuser	955 (90.5)[b]	114 (89.8)[b]		1.00 (reference)	
User	100 (9.5)[b]	13 (10.2)[b]	0.0853	1.09 (0.59–2.00)	0.784
Medications for lifestyle-related diseases					
Calcium channel blockers					
Nonuser	838 (79.4)[b]	93 (73.2)[b]		1.00 (reference)	
User	217 (20.6)[b]	34 (26.8)[b]	0.3449	1.41 (0.93–2.15)	0.108
Statins					
Nonuser	831 (78.8)[b]	107 (84.3)[b]		1.00 (reference)	
User	224 (21.2)[b]	20 (15.7)[b]	−0.3661	0.69 (0.42–1.14)	0.151
Bisphosphonates					
Nonuser	968 (91.8)[b]	123 (96.9)[b]		1.00 (reference)	
User	87 (8.2)[b]	4 (3.1)[b]	−1.0166	0.36 (0.13–1.00)	0.051
Upper GI findings					
Barrett's mucosa					
No	811 (76.9)[b]	78 (61.4)[b]		1.00 (reference)	
Yes	244 (23.1)[b]	49 (38.6)[b]	0.7362	2.09 (1.42–3.07)	<0.001
Hiatal hernia					
No	581 (55.1)[b]	31 (24.4)[b]		1.00 (reference)	
Yes	474 (44.9)[b]	96 (75.6)[b]	1.3390	3.80 (2.49–5.79)	<0.001
EGA	2.2 (±1.9)[a]	1.3 (±1.6)[a]	−0.3040	0.74 (0.65–0.83)	<0.001
C-0	260 (24.6)[b]	52 (40.9)[b]			
C-I	257 (24.4)[b]	39 (30.7)[b]			
C-2	131 (12.4)[b]	16 (12.6)[b]			
C-3	73 (6.9)[b]	4 (3.1)[b]			
O-1	183 (17.3)[b]	8 (6.3)[b]			
O-2	102 (9.7)[b]	4 (3.1)[b]			
O-3	49 (4.6)[b]	4 (3.1)[b]			

Note: [a]Median (± SD), [b]number (%).

Abbreviations: BMI, body mass index; PPI, proton pump inhibitors; H2RA, histamine-2 receptor antagonists; GI, gastrointestinal; RE, reflux esophagitis; EGA, endoscopic gastric mucosal atrophy; SD, standard deviation; *H. pylori*, *Helicobacter pylori*; OR, odds ratio; CI, confidence interval.

although the details of their medical treatment could not be investigated.

However, it has been reported that several antihypertensive drugs have healing effects on the esophageal mucosa.[14] Miwa et al[15] reported that angiotensin II receptor blockers may act to promote healing of the esophageal mucosa. Further prospective studies are needed to elucidate the association between antihypertensive drugs (except calcium channel blockers) and the prevalence of RE.

In 1996, de Groen et al[6] demonstrated the association between esophagitis and the use of bisphosphonate. Although the pathogenesis of bisphosphonate-induced esophageal

Table 4 Risk factors for RE (excluding users of gastric acid secretion inhibitors; n=590; bivariate analysis)

Covariates	RE(−) group 507 (85.9%)[b]	RE(+) group 83 (14.1%)[b]	Bivariate		
			Standardized coefficient	OR (95% CI)	*P*-value
Patient profile					
Age (years)	60.7 (±13.2)[a]	59.4 (±13.0)[a]	−0.0072	0.99 (0.98–1.01)	0.415
Sex					
Female	262 (51.7)[b]	28 (33.7)[b]		1.00 (reference)	
Male	245 (48.3)[b]	55 (66.3)[b]	0.7422	2.10 (1.29–3.42)	0.003
BMI (kg/m^2)	22.3 (±3.3)[a]	24.8 (±4.3)[a]	0.1838	1.20 (1.12–1.29)	<0.001
Cumulative alcohol intake (kg)	209 (±503)[a]	264 (±497)[a]	0.0002	1.00 (1.00–1.00)	0.352
Brinkman index	197 (±386)[a]	236 (±379)[a]	0.0002	1.00 (1.00–1.00)	0.396
***H. pylori* infection status**					
H. pylori infection					
Negative	284 (56.0)[b]	65 (78.3)[b]		1.00 (reference)	
Positive	144 (28.4)[b]	5 (6.0)[b]	−1.8227	0.16 (0.06–041)	<0.001
Negative after eradication	79 (15.6)[b]	13 (15.7)[b]	0.0061	1.01 (0.53–1.91)	0.985
Medications for lifestyle-related diseases					
Calcium channel blockers					
Nonuser	418 (82.4)[b]	57 (68.7)[b]		1.00 (reference)	
User	89 (17.6)[b]	26 (31.3)[b]	0.7619	2.14 (1.28–3.59)	0.004
Statins					
Nonuser	425 (83.8)[b]	74 (89.2)[b]		1.00 (reference)	
User	82 (16.2)[b]	9 (10.8)[b]	−0.4615	0.63 (0.30–1.31)	0.216
Bisphosphonates					
Nonuser	483 (95.3)[b]	83 (100.0)[b]		1.00 (reference)	
User	24 (4.7)[b]	0 (0.0)[b]	−19.4417	0.00 (0.00)	0.998
Upper GI findings					
Barrett's mucosa					
No	407 (80.3)[b]	54 (65.1)[b]		1.00 (reference)	
Yes	100 (19.7)[b]	29 (34.9)[b]	0.7820	2.19 (1.32–3.61)	0.002
Hiatal hernia					
No	300 (59.2)[b]	23 (27.7)[b]		1.00 (reference)	
Yes	207 (40.8)[b]	60 (72.3)[b]	1.3299	3.78 (2.27–6.31)	<0.001
EGA	2.1 (±2.0)[a]	1.3 (±1.7)[a]	−0.2583	0.77 (0.67–0.89)	<0.001
C-0	137 (27.0)[b]	36 (43.4)[b]			
C-I	121 (23.9)[b]	24 (28.9)[b]			
C-2	54 (10.7)[b]	9 (10.8)[b]			
C-3	28 (5.5)[b]	1 (1.2)[b]			
O-1	85 (16.8)[b]	6 (7.2)[b]			
O-2	55 (10.8)[b]	3 (3.6)[b]			
O-3	27 (5.3)[b]	4 (4.8)[b]			

Note: [a]Median (± SD), [b]number (%).

Abbreviations: BMI, body mass index; GI, gastrointestinal; RE, reflux esophagitis; EGA, endoscopic gastric mucosal atrophy; SD, standard deviation; *H. pylori*, *Helicobacter pylori*; OR, odds ratio; CI, confidence interval.

mucosal damage has not been clearly demonstrated, direct chemical esophageal damage with prolonged local mucosal exposure to a drug with gastric acid might be the most plausible biological mechanism as suggested by the literature.[16] However, the highest level of evidence, randomized controlled trials, suggests little or no increase in risk of upper gastrointestinal tract problems if bisphosphonates are administered properly.[16,17] While pharmacists carefully instruct patients on the appropriate dosing regimen (taking a tablet with enough water and remaining upright for at least 30 minutes before the first food of the day) and patients tend to properly observe an internal use method in Japan, bisphosphonate use might be not associated with RE in this study. However, recognition of bisphosphonate-associated erosive or ulcerative esophagitis, and communication of this possibility to the clinician, may be important.

Recently, the pleiotropic effects of statins have been shown, with a demonstration of cholesterol-reducing effects, as well as anti-inflammatory action, antioxidative function, and ability to increase eNOS expression. According to recent reports, statins induce anti-inflammatory effects and demonstrate antioxidative function via inhibition of activation of

Table 5 Risk factors for RE (excluding users of gastric acid secretion inhibitors) (n=590) (multivariate analysis)

Covariates	Multivariate		
	Standardized coefficient	OR (95% CI)	*P*-value
Patient profile			
Sex			
Female		1.00 (reference)	
Male	0.282	1.33 (0.75–2.35)	0.334
BMI (kg/m^2)	0.176	1.20 (1.10–1.29)	<0.001
***H. pylori* infection status**			
H. pylori infection			
Negative		1.00 (reference)	
Positive	−1.589	0.20 (0.07–0.57)	0.002
Medications for lifestyle-related diseases			
Calcium channel blockers			
Nonuser		1.00 (reference)	
User	0.752	2.12 (1.16–3.87)	0.014
Statins			
Nonuser		1.00 (reference)	
User	−0.879	0.42 (0.18–0.96)	0.040
Upper GI findings			
Barrett's mucosa			
No		1.00 (reference)	
Yes	1.089	2.97 (1.64–5.38)	<0.001
Hiatal hernia			
No		1.00 (reference)	
Yes	1.141	3.13 (1.79–5.47)	<0.001
EGA	−0.185	0.83 (0.70–0.98)	0.030

Abbreviations: BMI, body mass index; GI, gastrointestinal; RE, reflux esophagitis; EGA, endoscopic gastric mucosal atrophy; SD, standard deviation; *H. pylori*, *Helicobacter pylori*; OR, odds ratio; CI, confidence interval.

NADPH oxidase, as well as upregulation of eNOS expression through the PI3K-Akt pathway.[18–21] In subjects who visited a medical center for their annual medical check-up, Niigaki et al[1] reported that the risk for subjects undergoing treatment for dyslipidemia was lower than those for subjects not undergoing such therapy, although the details of their medical treatment could not be investigated. It was reported that inflammatory cytokines, oxidative stress, and an eNOS expression decrease were associated with the pathophysiology of RE.[22–25] Thus, the pleiotropic effects such as eNOS upregulation, antioxidative function, and anti-inflammatory action may play a crucial role in prevention of RE. On the other hand, previous studies have indicated that lower serum adiponectin levels are associated with various inflammatory diseases of the digestive system,[26–30] and it was reported that statins possess an adiponectin-increasing effect.[31] Thus, the adiponectin-increasing effect of statins may be associated with the preventive effect of RE.

Consistent with previous studies on the Japanese population, BMI was associated with the development of RE in this study. Gastric acid reflux due to increased abdominal pressure through obesity is the most plausible biological mechanism for the development of RE. Although we did not investigate the waist circumference and visceral fat area, it has been reported that the abdominal visceral adipose tissues can secrete some substances such as adipokines that are associated with the development of RE.[28] Male sex has also been reported to be an important predictive factor for RE.[32,33] In this study, male sex was associated with the presence of RE in bivariate analysis, but was not associated with RE after multivariate analysis was performed. Since the number of study subjects was relatively small in this study, the inclusion of more cases may be necessary to truly ascertain whether there is a significant association between male sex and RE. Smoking affects esophageal defense mechanisms and decreases lower esophageal sphincter pressure.[34] Alcoholic beverages are associated with impairment of primary peristalsis and a decrease in lower esophageal sphincter (LES) pressure.[35] In this study, cumulative alcohol intake and the Brinkman index were not associated with the development of RE. Current alcohol intake and smoking might be more important for risk of RE than the quantity of alcohol and the Brinkman index, although we did not investigate current alcohol intake and smoking in this study.

H. pylori positivity and EGA had an inverse association with RE in our study. Generally, reflux of increased acid contents is associated with the development of RE.[36,37] The potential mechanisms behind the inverse association with RE may be due to neutralization of acid by ammonia generated by *H. pylori* organisms and decreased acid secretion as a consequence of corpus atrophy.[38] Consistent with previous studies of the Japanese population, hiatal hernia and Barrett's mucosa were associated with RE in this study.[32,39–42]

This study had several limitations. It was a hospital-based, single-center, cross-sectional retrospective study of consecutive outpatients who received an upper gastrointestinal endoscopy in our department. Furthermore, this procedure was conducted by one specialist who was a member of the Japan Gastroenterological Endoscopy Society; therefore, the data might not represent the general population. Furthermore, it might not be possible to fully evaluate the cause and effect association between RE and medications for lifestyle-related diseases. The sample size of this study was relatively small; therefore, further larger, multicenter prospective studies will be needed to clarify the true association between RE and prescribed medications for lifestyle-related diseases. Second, we could not evaluate the details of prescribed therapeutic drugs for diabetes mellitus,

nonsteroidal anti-inflammatory drugs, or other antihypertensive drugs except for a calcium channel blocker, which may have influenced the prevalence of RE. Finally, we could not investigate dietary intake, beverages, waist circumference, visceral fat area, exercise, eating habits, or sleeping, which can all affect the prevalence of RE.

Conclusion

We identified that calcium channel blockers and statins as medications for lifestyle-related diseases were associated with the presence of RE, while bisphosphonates were not associated with the presence of RE. As eating habits become more westernized, the prevalence of lifestyle-related diseases has increased in Japan, resulting in a significant public health problem. It may be useful to clarify the association of medications for lifestyle-related diseases with RE, as well to further elucidate the best medical treatment for RE.

Disclosure

The authors report no conflicts of interests in this work.

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