

The effect of proton pump inhibitors and vonoprazan on the development of ‘gastric mucosal redness’

SATOSHI SHINOZAKI^{1,2}, HIROYUKI OSAWA², YOSHIMASA MIURA², YOSHIKAZU HAYASHI², HIROTSUGU SAKAMOTO², TOMONORI YANO², ALAN KAWARAI LEFOR³ and HIRONORI YAMAMOTO²

¹Shinozaki Medical Clinic, Utsunomiya, Tochigi 321-3223; ²Department of Medicine, Division of Gastroenterology;

³Department of Surgery, Jichi Medical University, Shimotsuke, Tochigi 329-0498, Japan

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Abstract. The safety of long-term proton pump inhibitor (PPI) and vonoprazan (VPZ) use is a relatively recent concern. Gastric mucosal redness was reported as a VPZ-associated lesion in a previous study. The aim of this study was to investigate the prevalence and risk factors for gastric mucosal redness. Between December 2020 and November 2021, 1,101 patients who underwent esophagogastroduodenoscopy were reviewed. The cohort was divided into four groups: Control (n=580), histamine-2 receptor antagonist (H2RA) (n=65), PPI (n=146) and VPZ groups (n=310). Gastric mucosal redness was present in 48/1,101 patients (4%). The prevalence in controls, H2RA, PPI and VPZ groups was 1.9% (11/580), 1.5% (1/65), 6.2% (9/146) and 8.7% (27/310), respectively. Both the PPI and VPZ groups had a significantly higher prevalence of gastric mucosal redness compared with the control group ($P < 0.001$). In the multivariate analysis, PPI and VPZ use were significantly associated with gastric mucosal redness. Fundic gland polyps, gastric hyperplastic polyps, multiple white and flat elevated lesions, cobblestone-like mucosa, and stardust gastric mucosa were also significantly associated with PPI and VPZ use in the multivariate analysis. Back-to-back analysis showed that gastric mucosal redness was not seen before starting PPI/VPZ in most patients. The duration of treatment with VPZ was investigated to determine if it affected the prevalence of gastric mucosal redness. There were no significant differences in treatment duration among patients with and without gastric mucosal redness (mean \pm standard deviation: 3.0 ± 1.5 vs. 2.5 ± 1.4 years, $P = 0.077$). In conclusion, the prevalence of gastric mucosal redness was low but was associated with PPI and VPZ use.

Introduction

The long-term safety of acid blockers is a relatively recent concern for general practitioners as well as gastroenterologists. Vonoprazan (VPZ), a potassium-competitive acid blocker, was made available in 2015 and has a stronger acid-suppressing effect than proton pump inhibitors (PPI) (1). VPZ is widely used in Japan for the long-term treatment of gastroesophageal reflux disease as well as *Helicobacter pylori* (*H. pylori*) eradication therapy. We previously reported the long-term effects of PPI and VPZ on gastric morphological changes including fundic gland polyps, gastric hyperplastic polyps, multiple white and flat elevated lesions, and cobblestone-like gastric mucosa (2). Recently, a new morphological change referred to as ‘stardust gastric mucosa’ was reported, which is strongly related to long-term VPZ therapy (3).

In 2020, Kubo *et al* (4) reported a novel lesion which they termed ‘gastric mucosal redness’ in patients undergoing VPZ therapy in a case series. Gastric mucosal redness was characterized by linear or spotty red areas along the greater curvature of the gastric body. The pathology was characterized by inflammatory cell infiltration, oxyntic gland dilatation, and parietal cell protrusion (5). However, the prevalence of this finding and its association with acid blockers were not reported. The aim of the present study was to investigate the prevalence and risk factors for the development of gastric mucosal redness.

Patients and methods

Study population. This study was a retrospective observational study based on the medical records and endoscopic reports of patients who underwent esophagogastroduodenoscopy (EGD). Patients who underwent EGD at the Shinozaki Medical Clinic (Utsunomiya, Tochigi, Japan) between December 2020 and November 2021 were included. The medications taken by each patient were verified before EGD by checking the personal ‘medicine notebook’ issued by the Japan Pharmaceutical Association and scrupulously maintained by each patient that documents all prescriptions regardless of the medical facility that prescribed it. When multiple EGDs were performed on one patient during the study period, only the first EGD was included. At least 1-year of continuous administration of VPZ, PPI, and H2RA was confirmed using the medicine notebook.

Correspondence to: Professor Hiroyuki Osawa, Department of Medicine, Division of Gastroenterology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan
E-mail: osawa@jichi.ac.jp

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Patients with current *H. pylori* infection status (n=58), acid suppression therapy for <1-year despite being currently treated with acid-suppressing drugs (n=41), previous esophageal or gastric surgery (n=27), and gastric residue (n=7) were excluded. Consequently, 1,101 patients were finally enrolled. We retrospectively reviewed their medical records and abstracted all pertinent information regarding acid blockers including H2RA, PPI, and VPZ. The present study was approved by the Institutional Review Board of the Shinozaki Medical Clinic (approval no. ID#31-R001). The need for written informed consent was waived due to the retrospective design of the study.

Endoscopic evaluation. All EGDs were performed by the first author and recorded on video. In the case of unclear findings or lack of data, the video was immediately checked. An ultra-thin endoscope (EG-L580NW7, Fujifilm Corporation) was used and endoscopic observation was performed using linked color imaging throughout the procedure (6). The standard endoscopic report included the grade of gastric atrophy classified by the Kimura-Takemoto system (7), the presence/absence of fundic gland polyps, gastric hyperplastic polyps, multiple white and flat elevated lesions (8), cobblestone-like mucosa (9), stardust gastric mucosa (3) and gastric mucosal redness (4) as compulsory items. ‘Gastric mucosal redness’ was defined as multiple spotty and/or linear areas of redness along the greater curvature of the gastric body or fundus in *H. pylori*-negative individuals (Figs. 1 and 2). The first author assessed these compulsory items during EGD and completed the standardized endoscopic report form just after finishing the EGD. The *H. pylori* infection status was evaluated by serum IgG, ¹³C-urea breath test, and/or a stool antigen test. *H. pylori* eradication history was confirmed by an interview with the patients and/or review of the medical record.

Statistical analysis. The frequency of gastric mucosal changes was compared among the four groups in this study using a χ^2 test. Univariate analysis was performed using a logistic regression model. To diminish the influence of confounding factors, multivariate logistic regression analysis was used. Factors for multivariate analysis were selected based on clinical significance. To compare continuous data between two groups, a Student's t-test was used. Statflex version 7.0 software (Artech Co. Ltd.) was used for all statistical analyses. P<0.05 was considered to indicate a statistically significant difference.

Results

Prevalence of gastric mucosal redness. Almost half of the patients (47%) were treated with acid blockers (Table I). Gastric atrophy was present in 57% of patients (631/1,101), and 46% (502/1,101) previously underwent successful *H. pylori* eradication. None of the patients were treated with any combination of H2RA, PPI, or VPZ. The overall prevalence of gastric mucosal redness was 4% (48/1,101).

The 1,101 included patients were divided into four groups: Controls, H2RA, PPI, and VPZ groups (Fig. 3). Even in patients receiving PPI or VPZ, the prevalence of gastric mucosal redness was not high (6-9%). Both the PPI and VPZ groups had a significantly higher prevalence of gastric mucosal redness

Table I. Baseline characteristics and endoscopic findings of the recruited cohort.

Characteristic	Value
Age, years, mean \pm standard deviation	62.9 \pm 14.8
Sex, n (%)	
Male	492 (45%)
Female	609 (55%)
Acid suppression drug, n (%)	
None	580 (53%)
Histamine-2 receptor antagonist	65 (6%)
Proton pump inhibitor	146 (13%)
Vonoprazan	310 (28%)
Degree of gastric atrophy, n (%)	
None	470 (43%)
Closed type	296 (27%)
Open type	335 (30%)
Fundic gland polyps, n (%)	366 (33%)
Gastric hyperplastic polyps, n (%)	48 (4%)
Multiple white and flat elevated lesions, n (%)	235 (21%)
Cobblestone-like mucosa, n (%)	52 (5%)
Stardust gastric mucosa, n (%)	168 (15%)
Gastric mucosal redness, n (%)	48 (4%)

than the control group (both P<0.001). The VPZ group also had a significantly higher prevalence of mucosal redness than the H2RA group (P=0.028). The reddish finding associated with portal hypertensive gastropathy should be differentiated from gastric mucosal redness, but 8 patients with cirrhosis had neither gastric mucosal redness nor portal hypertensive gastropathy.

Additionally, the prevalence of five representative changes associated with acid blockers including fundic gland polyps, gastric hyperplastic polyps, multiple white and flat elevated lesions, cobblestone-like mucosa, and stardust gastric mucosa were compared (Fig. 4). Both the PPI and VPZ groups had a significantly higher prevalence of all five representative changes compared with the control group.

Factors associated with gastric mucosal redness. Risk factors for gastric mucosal redness were investigated (Table II). In the multivariate analysis, PPI and VPZ use were significantly associated with the prevalence of gastric mucosal redness. The VPZ group had a slightly stronger association with the development of gastric mucosal redness compared with the PPI group (odds ratio: 3.415 vs. 2.665). VPZ was not the only risk factor for gastric mucosal redness; PPI use was also identified as a risk factor.

We previously reported four representative gastric mucosal changes associated with acid blocker use (2). In the current study, multivariate analyses were performed on the five gastric mucosal changes. Consequently, all five changes including fundic gland polyps (Table III), gastric hyperplastic polyps (Table IV), multiple white and flat elevated lesions (Table V), cobblestone-like mucosa (Table VI) and stardust gastric

Table II. Factors associated with gastric mucosal redness.

Factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age ≥ 60 y	2.102	1.035-4.266	0.039 ^a	1.327	0.616-2.861	0.470
Male sex	1.146	0.642-2.044	0.645			
Histamine-2 receptor antagonist use	0.329	0.045-2.422	0.274			
Proton pump inhibitor use	1.530	0.725-3.228	0.264	2.665	1.061-6.692	0.036 ^a
Vonoprazan use	3.498	1.946-6.288	<0.001 ^c	3.415	1.477-7.899	0.004 ^b
Open type gastric atrophy	1.673	0.929-3.015	0.086	1.553	0.825-2.924	0.172
Fundic gland polyps	1.596	0.890-2.864	0.116			
Gastric hyperplastic polyps	4.214	1.783-9.961	0.001 ^b	2.384	0.975-5.828	0.056
Multiple white and flat elevated lesions	0.968	0.475-1.974	0.929			
Cobblestone-like mucosa	1.903	0.657-5.514	0.235			
Stardust gastric mucosa	3.612	1.964-6.643	<0.001 ^c	1.650	0.781-3.485	0.189

^aP \leq 0.05, ^bP \leq 0.01, ^cP \leq 0.001.

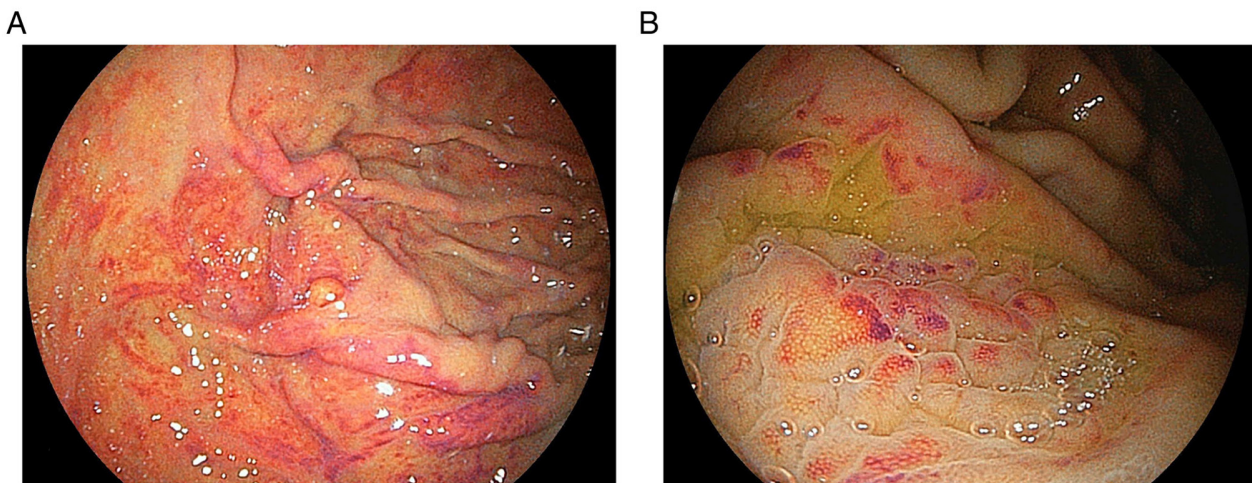


Figure 1. Endoscopic images of gastric mucosal redness using linked color imaging. (A) Distant view of spotty and linear areas of redness along the greater curvature of the upper body and fundus of the stomach in a patient undergoing vonoprazan therapy; (B) near view showing multiple small round pits surrounded by redness on bump-like mucosa.

mucosa (Table VII) were significantly associated with PPI and VPZ use.

Presence of gastric mucosal redness before starting PPI or VPZ. Among the 48 patients who had gastric mucosal redness, 9 and 27 patients were undergoing PPI and VPZ therapy, respectively. EGD data existed for 7/9 patients in the PPI group and in 26/27 patients in the VPZ group [naïve (n=15) and changed from PPI (n=11)] before starting their respective therapy. EGD data were reviewed to determine the presence or absence of gastric mucosal redness before starting PPI or VPZ to perform back-to-back analyses (Fig. 5). Of the 7 patients in the PPI group, 1 patient (14%) presented with gastric mucosal redness before starting PPI (Fig. 5A). In the VPZ group, gastric mucosal redness was present in 3 (20%) of the 15 naïve patients (Fig. 5B) and in 1 (9%) of the 11 patients (Fig. 5C)

who were changed from PPI therapy before starting VPZ. In most patients, gastric mucosal redness developed *de novo* after starting PPI or VPZ.

Prevalence of gastric mucosal redness and duration of treatment with VPZ. The duration of treatment with VPZ was investigated to determine if it affected the prevalence of gastric mucosal redness. The mean VPZ treatment duration was 2.6 years (n=310). There were no significant differences in treatment duration among patients with and without gastric mucosal redness (mean \pm standard deviation: 3.0 \pm 1.5 vs. 2.5 \pm 1.4 years, P=0.077). The treatment duration with VPZ did not affect the prevalence of gastric mucosal redness. Regarding the H2RA and PPI groups, formal evaluation could not be performed due to the lack of a sufficient number of patients in these groups.

Table III. Factors associated with fundic gland polyps.

Factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age ≥60 y	0.807	0.622-1.048	0.107			
Male sex	0.598	0.462-0.773	<0.001 ^c	0.669	0.498-0.898	0.007 ^b
Histamine-2 receptor antagonist use	1.029	0.606-1.748	0.915	2.161	1.169-3.995	0.013 ^a
Proton pump inhibitor use	2.976	2.089-4.240	<0.001 ^c	5.932	3.744-9.401	<0.001 ^c
Vonoprazan use	1.800	1.371-2.362	<0.001 ^c	2.817	2.019-3.931	<0.001 ^c
Open type gastric atrophy	0.086	0.055-0.136	<0.001 ^c	0.069	0.043-0.112	<0.001 ^c
Gastric mucosal redness	1.596	0.890-2.864	0.116			
Gastric hyperplastic polyps	1.460	0.811-2.628	0.207			
Multiple white and flat elevated lesions	1.749	1.301-2.351	<0.001 ^c	1.389	0.965-1.999	0.077
Cobblestone-like mucosa	2.085	1.193-3.646	0.009 ^b			
Stardust gastric mucosa	1.449	1.034-2.030	0.031 ^a			

^aP≤0.05, ^bP≤0.01, ^cP<0.001.

Table IV. Factors associated with gastric hyperplastic polyps.

Factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age ≥60 y	2.788	1.292-6.019	0.009 ^b			
Male sex	0.879	0.489-1.581	0.667			
Histamine-2 receptor antagonist use ^d						
Proton pump inhibitor use	3.894	2.096-7.233	<0.001 ^c	15.886	5.742-43.952	<0.001 ^c
Vonoprazan use	3.200	1.785-5.737	<0.001 ^c	10.725	4.050-28.402	<0.001 ^c
Open type gastric atrophy	1.393	0.765-2.536	0.278			
Gastric mucosal redness	4.214	1.783-9.961	0.001 ^c	2.551	1.050-6.194	0.038 ^a
Fundic gland polyps	1.460	0.811-2.628	0.207			
Multiple white and flat elevated lesions	1.100	0.552-2.192	0.785			
Cobblestone-like mucosa	2.489	0.942-6.573	0.065			
Stardust gastric mucosa	2.964	1.588-5.533	<0.001 ^c			

^aP≤0.05, ^bP≤0.01, ^cP<0.001. ^dNo gastric hyperplastic polyp in the histamine-2 receptor antagonist group.

Discussion

The present study demonstrated the influence of acid blockers on the prevalence of gastric mucosal redness. The overall prevalence of gastric mucosal redness is low (4%), even in patients treated with PPI or VPZ (6-9%). Both PPI and VPZ use were identified as significant factors contributing to the development of gastric mucosal redness. Most instances of gastric mucosal redness occurred after starting PPI or VPZ. Treatment duration with VPZ was not associated with the prevalence of gastric mucosal redness. To the best of our knowledge, this is the first study reporting the prevalence and risk factors for the development of gastric mucosal redness.

Few studies are available regarding the development of gastric mucosal redness secondary to the use of acid blockers and its pathogenesis is unknown (4,5). The endoscopic characteristics have been described in a previous study (4) and included spotty and linear areas of redness along the greater curvature in the gastric body, which is consistent with the endoscopic images shown in the present study. Endoscopic images from the previous study and the present study show hypertrophic and bump-like gastric mucosa accompanying gastric mucosal redness. Laser endoscopic imaging systems allow clearer visualization of vascular and structural patterns on the mucosal surface at a near view than white light imaging (6). In the present study, linked color imaging showed

Table V. Factors associated with multiple white and flat elevated lesions.

Factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age ≥ 60 y	3.466	2.387-5.033	$<0.001^c$	2.767	1.869-4.096	$<0.001^c$
Male sex	0.481	0.354-0.653	$<0.001^c$	0.507	0.365-0.704	$<0.001^c$
Histamine-2 receptor antagonist use	0.655	0.329-1.306	0.229			
Proton pump inhibitor use	2.964	2.051-4.283	$<0.001^c$	3.070	1.962-4.804	$<0.001^c$
Vonoprazan use	1.959	1.446-2.653	$<0.001^c$	1.768	1.140-2.741	0.010 ^b
Open type gastric atrophy	1.237	0.910-1.681	0.174			
Gastric mucosal redness	0.968	0.475-1.974	0.929			
Fundic gland polyps	1.749	1.301-2.351	$<0.001^c$	1.361	0.978-1.893	0.067
Gastric hyperplastic polyps	1.100	0.552-2.192	0.785	0.542	0.262-1.122	0.098
Cobblestone-like mucosa	3.131	1.775-5.524	$<0.001^c$	2.036	1.093-3.793	0.025 ^a
Stardust gastric mucosa	2.832	1.992-4.028	$<0.001^c$	1.846	1.167-2.920	0.008 ^b

^aP \leq 0.05, ^bP \leq 0.01, ^cP \leq 0.001.

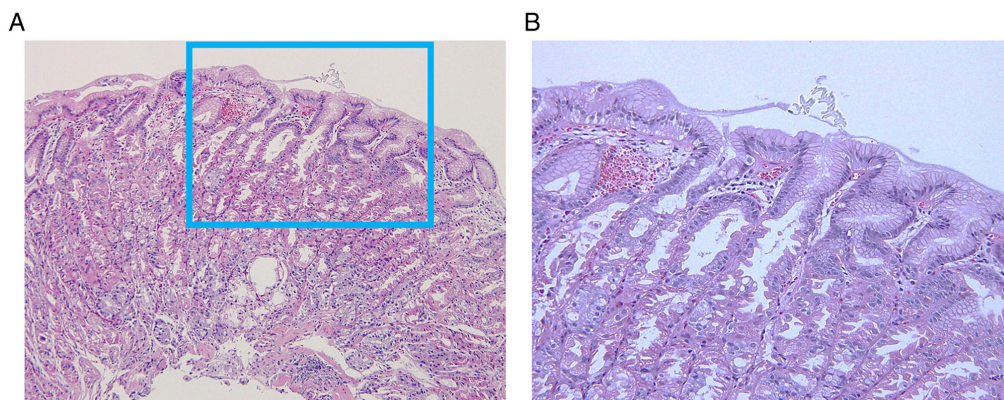


Figure 2. Microscopic images of areas of gastric mucosal redness. (A) Slight lymphatic infiltration and dilated oxyntic glands (magnification, x100); (B) high power field within the blue box. Increased numbers of parietal cells are evident with protrusion. Congestion and dilated vessels underneath the surface epithelium (magnification, x200).

that slightly dilated vessels surrounded white marginal crypt epithelium diffusely and equally on the mucosal surface, which corresponded to the fine network pattern visualized in the magnified imaging. These endoscopic findings were similar in patients with gastric mucosal redness regardless of the acid blocker prescribed. Pathological findings in the present study showed not only oxyntic gland dilation with parietal cell protrusions, but also congestion and dilated vessels underneath the surface epithelium in the intervening portion (Fig. 2). These endoscopic and pathological findings suggested that increased intramucosal blood perfusion may be the cause of mucosal redness. Kubo *et al* (4) first reported the pathological characteristics as ‘inflammatory cell infiltration’ and the disappearance of these inflammatory changes after discontinuation of VPZ without changes in parietal cell protrusions. In the present study, the presence of gastric hyperplastic polyps had a weak association with gastric mucosal redness. Gastric hyperplastic polyps

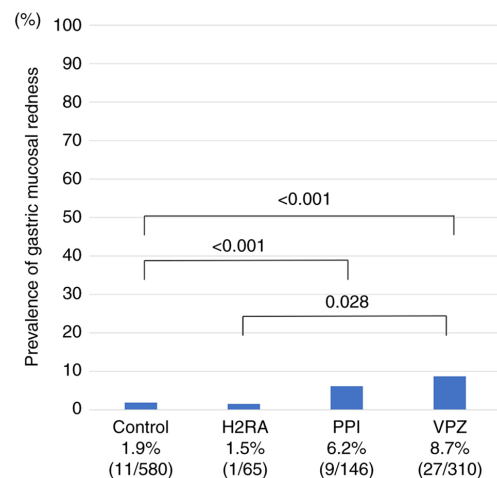


Figure 3. The prevalence of gastric mucosal redness in each group. All differences among groups were evaluated, but only statistically significant results are described. H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor, VPZ, vonoprazan.

Table VI. Factors associated with cobblestone-like mucosa.

Factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age \geq 60 y	2.669	1.287-5.536	0.008 ^b			
Male sex	1.596	0.911-2.796	0.102	1.955	1.084-3.526	0.025 ^a
Histamine-2 receptor antagonist use	0.626	0.149-2.632	0.522	4.778	0.855-26.714	0.074
Proton pump inhibitor use	3.776	2.072-6.882	<0.001 ^c	16.826	5.500-51.473	<0.001 ^c
Vonoprazan use	3.173	1.809-5.567	<0.001 ^c	12.683	4.367-36.833	<0.001 ^c
Open type gastric atrophy	1.017	0.556-1.860	0.956			
Gastric mucosal redness	1.903	0.657-5.514	0.235			
Fundic gland polyps	2.085	1.193-3.646	0.009 ^b			
Gastric hyperplastic polyps	2.489	0.942-6.573	0.065			
Multiple white and flat elevated lesions	3.131	1.775-5.524	<0.001 ^c	2.107	1.151-3.856	0.015 ^a
Stardust gastric mucosa	2.141	1.133-4.045	0.019 ^a			

^aP \leq 0.05, ^bP \leq 0.01, ^cP $<$ 0.001.

Table VII. Factors associated with stardust gastric mucosa.

Factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age \geq 60 y	2.026	1.378-2.977	<0.001 ^c			
Male sex	0.684	0.488-0.960	0.028 ^a	0.613	0.401-0.937	0.023 ^a
Histamine-2 receptor antagonist use ^d						
Proton pump inhibitor use	0.664	0.373-1.114	0.115	23.192	6.553-82.080	<0.001 ^c
Vonoprazan use	37.603	22.654-62.417	<0.001 ^c	192.686	60.197-616.771	<0.001 ^c
Open type gastric atrophy	1.099	0.772-1.564	0.599			
Gastric mucosal redness	3.612	1.964-6.643	<0.001 ^c	2.032	0.957-4.315	0.064
Fundic gland polyps	1.449	1.034-2.030	0.031 ^a	0.714	0.468-1.088	0.116
Gastric hyperplastic polyps	2.964	1.588-5.533	<0.001 ^c			
Multiple white and flat elevated lesions	2.832	1.992-4.028	<0.001 ^c	1.930	1.229-3.031	0.004 ^b
Cobblestone-like mucosa	2.141	1.133-4.045	0.019 ^a			

^aP \leq 0.05, ^bP \leq 0.01, ^cP $<$ 0.001. ^dNo gastric hyperplastic polyp in the histamine-2 receptor antagonist group.

are generally caused by excessive proliferation of foveolar cells due to longstanding inflammation. We suggest that increased intramucosal perfusion due to sustained inflammation results in gastric mucosal redness and hyperplastic polyp formation. We previously reported an association of gastric hyperplastic polyps with PPI/VPZ use (2). Further studies are necessary to clarify why acid blockers lead to persistent inflammation and increased perfusion in a limited population of patients.

Estimation of the malignant potential of gastric mucosal redness is important. According to previous reports, gastric mucosal redness disappears after cessation of VPZ (4,5). We hypothesize that gastric mucosal redness is not a premalignant

lesion. To clarify this issue, a long-term observational study is necessary regardless of the cessation of PPI/VPZ.

In the multivariate analysis, the VPZ group had a slightly stronger association with the development of gastric mucosal redness compared to the PPI group. The degree of acid inhibition may contribute to the prevalence of gastric mucosal redness. A case series reported 'VPZ-associated gastric mucosal redness' and changing therapy to PPI results in the disappearance of the lesion (5). However, the present study demonstrated that certain patients in the PPI group also had gastric mucosal redness similar to the VPZ group, despite no findings of mucosal changes before starting PPI. Therefore, gastric mucosal redness is not a specific change associated with VPZ therapy. Further,

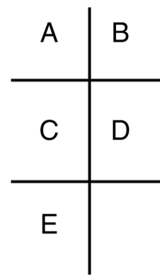
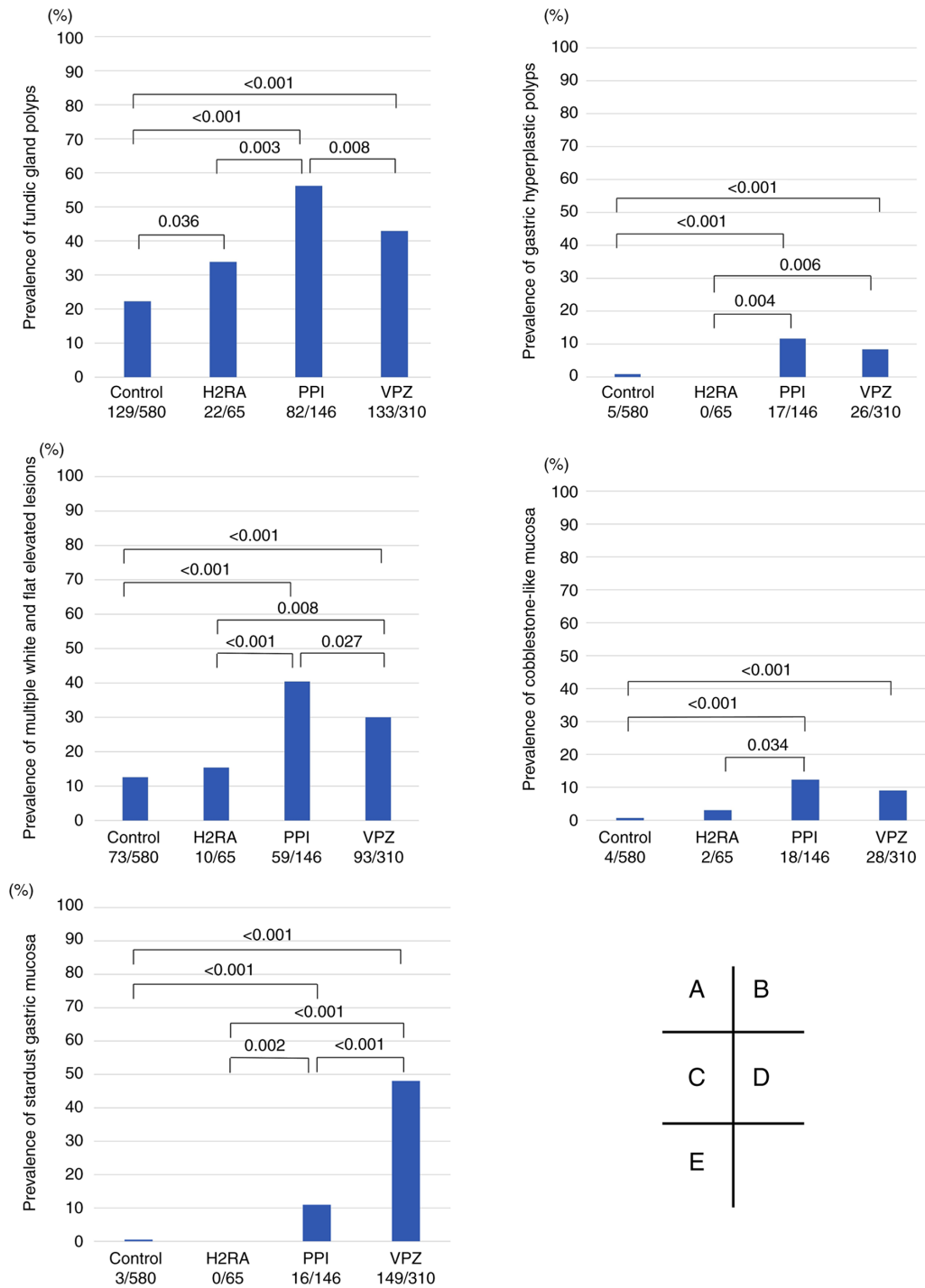


Figure 4. The prevalence of five representative gastric lesions associated with acid blockers in each group. (A) Fundic gland polyps, (B) gastric hyperplastic polyps, (C) multiple white and flat elevated lesions, (D) cobblestone-like mucosa and (E) stardust gastric mucosa. All differences among groups were evaluated, but only statistically significant results are described. H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; VPZ, vonoprazan.

five other gastric mucosal changes are also associated with PPI and VPZ use. According to a previous study, stardust gastric mucosa was only associated with VPZ use, but not PPI (3). We first demonstrated the association between stardust gastric mucosa and PPI as well as VPZ, although the association with VPZ was stronger than PPI.

The treatment duration with VPZ in the present study (median: 2.6 years) was long, and patients treated with acid blockers for <1 year were excluded. Treatment duration with VPZ was not associated with the prevalence of gastric

mucosal redness. Past case series reported that gastric mucosal redness presented 2-6 months after starting VPZ (4). Based on the results of the present study, it is hypothesized that the majority of cases of gastric mucosal redness develop within a few months after initiation of VPZ therapy.

There are some limitations to this study. First, this is a retrospective observational study, but gastric mucosal redness was managed as a compulsory item in the endoscopic report and all EGD procedures were recorded on video. Second, the data after cessation of PPI/VPZ were not assessed. It is

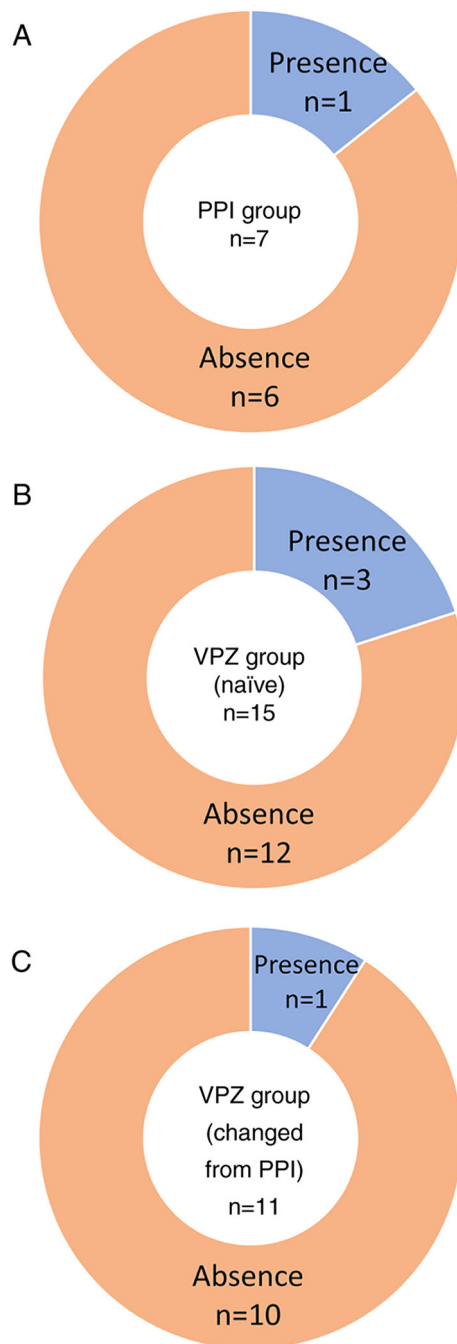


Figure 5. Presence or absence of gastric mucosal redness before initiation of PPI or VPZ therapy (A) PPI group; (B) VPZ group (naïve); (C) VPZ group (changed from PPI). PPI, proton pump inhibitor; VPZ, vonoprazan.

hypothesized that the development of gastric mucosal redness does not necessitate cessation of PPI/VPZ unless it is considered to be a source of hemorrhage. This mucosal finding may be a phenotype of persistent inflammatory changes and increased intramucosal blood flow with hyperplastic glands, but not neoplastic changes. Third, the diagnosis of gastric mucosal redness was determined only based on endoscopic findings without pathological evaluation. Gastric mucosal redness may be similar to diffuse redness caused by a current *H. pylori* infection, but the present study excluded patients with current *H. pylori* infections. Fourth, gastric mucosal redness is not always a PPI/VPZ-specific change. This mucosal change

was identified in the control group, although the frequency was significantly higher in PPI/VPZ groups. Fifth, the H2RA group (n=65) may not have sufficient power to evaluate differences among these groups.

In conclusion, the prevalence of gastric mucosal redness was low. Gastric mucosal redness is associated with PPI use as well as VPZ use and is not influenced by the treatment duration with VPZ. Due to the inflammatory nature of this lesion, the presence of gastric mucosal redness does not necessitate the cessation of acid blocker therapy. To the best of our knowledge, this is the first original report investigating the influence of PPI or VPZ on gastric mucosal redness.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SS and HO conceived and designed the study, collected, analyzed and interpreted the data, and drafted the manuscript. YM, HY, HS were involved in conception and design of the study, and in the drafting of the manuscript. TY was involved in conception and design of the study, drafting of the manuscript, and in the data analysis and interpretation. AKL and HY were involved in the drafting of the manuscript, and in data analysis and interpretation. SS and HO confirm the authenticity of all the raw data. All authors have read and reviewed the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Shinozaki Medical Clinic (approval no. ID#31-R001). The need for written informed consent was waived due to the retrospective design of the study.

Patient consent for publication

Not applicable.

Competing interests

SS has received honoraria from Takeda and Otsuka Pharmaceuticals. HO has received honoraria from AstraZeneca, Daiichi Sankyo, Takeda and Otsuka Pharmaceuticals. YM has received honoraria from AstraZeneca, Daiichi Sankyo, Takeda, Otsuka and EA Pharmaceuticals. HY has received honoraria from Takeda Pharmaceutical. All other authors declare no conflicts of interest regarding this study.

References

1. Sakurai Y, Mori Y, Okamoto H, Nishimura A, Komura E, Araki T and Shiramoto M: Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—a randomised open-label cross-over study. *Aliment Pharmacol Ther* 42: 719-730, 2015.
2. Shinozaki S, Osawa H, Hayashi Y, *et al*: Changes in gastric morphology during long-term use of vonoprazan compared to proton pump inhibitors. *Singapor Med J* (in press): Accepted on April 24, 2021.
3. Yoshizaki T, Morisawa T, Fujinami M, Matsuda T, Katayama N, Inoue K, Matsumoto M, Ikeoka S, Takagi M, Sako T, *et al*: Propensity score matching analysis: Incidence and risk factors for 'stardust' gastric mucosa, a novel gastric finding potentially induced by vonoprazan. *Aliment Pharmacol Ther* 53: 94-102, 2021.
4. Kubo K, Kimura N, Matsuda S, Tsuda M, Mabe K and Kato M: Vonoprazan-associated gastric mucosal redness: A report of four cases. *Intern Med* 59: 507-511, 2020.
5. Kubo K, Kimura N, Watanabe R, Higashino M, Tsuda M and Kato M: Vonoprazan-associated gastric mucosal redness in non-*Helicobacter pylori*-infected and *Helicobacter pylori*-eradicated stomach. *Case Rep Gastroenterol* 15: 751-758, 2021.
6. Shinozaki S, Osawa H, Hayashi Y, Lefor AK and Yamamoto H: Linked color imaging for the detection of early gastrointestinal neoplasms. *Therap Adv Gastroenterol* 12: 1756284819885246, 2019.
7. Kimura K and Takemoto T: An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* 1: 87-97, 1969.
8. Hasegawa R, Yao K, Ihara S, Miyaoka M, Kanemitsu T, Chuman K, Ikezono G, Hirano A, Ueki T, Tanabe H, *et al*: Magnified endoscopic findings of multiple white flat lesions: A new subtype of gastric hyperplastic polyps in the stomach. *Clin Endosc* 51: 558-562, 2018.
9. Miyamoto S, Kato M, Tsuda M, Matsuda K, Muranaka T, Abiko S, Ono M, Mizushima T, Omori S, Yamamoto K, *et al*: Gastric mucosal cracked and cobblestone-like changes resulting from proton pump inhibitor use. *Dig Endosc* 29: 307-313, 2017.



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