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## Clinicians should be aware of proton pump inhibitor–related changes in the gastric mucosa

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See “Association between occurrence of multiple white and flat elevated gastric lesions and oral proton pump inhibitor intake” by Rino Hasegawa, Kenshi Yao, Takao Kanemitsu, et al., *Endosc* 2024;57:65–72.

Since the clinical introduction of omeprazole in the early 1990s, proton pump inhibitors (PPIs) have been used worldwide to prevent gastroduodenal mucosal injuries caused by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as to treat acid-related diseases such as peptic ulcers and gastroesophageal reflux disease (GERD). In particular, many patients with GERD (especially those with Barrett’s esophagus) and individuals who use NSAIDs require long-term PPI therapy.<sup>1-3</sup> An important problem associated with long-term PPI therapy is hypergastrinemia secondary to the homeostatic response of antral G cells to decreased gastric acidity. Histopathologically, long-term PPI therapy induces protrusion of parietal cells into the lumen of glands, cystic dilatation of the fundic glands of the stomach, and hyperplasia of foveolar epithelial cells.<sup>4</sup> Long-term PPI therapy has been associated with the formation of gastric mucosal lesions, including fundic gland polyps, hyperplastic polyps, multiple white and flat elevated lesions (MWFELs),

cobblestone-like mucosa, and black spots (Table 1).<sup>4</sup> Fundic gland polyps, cobblestone-like mucosa, and black spots are attributed to parietal cell protrusion and cystic dilatation of the fundic glands, whereas hyperplastic polyps and MWFELs result from foveolar epithelial hyperplasia.

MWFELs are defined as circumscribed, white, flat, protruding mucosal lesions with serrated borders on endoscopy.<sup>5</sup> These are usually detected in the upper gastric corpus and fundus, and regular tubular structures can be seen on their surface on close observation. Recently, image-enhanced endoscopy techniques, such as narrow-band imaging (NBI), have increased the detection rate of MWFELs, with a reported incidence of 14% to 26% in PPI users.<sup>4</sup> Several observational studies have reported that MWFELs are significantly associated with PPI use (odds ratio [OR], 3.58), moderate to severe atrophic gastritis (OR, 2.63), *Helicobacter pylori* eradication therapy (OR, 2.11), female sex (OR, 1.92), and aging (OR, 1.05).<sup>4,6,7</sup> In the current issue of *Clinical Endoscopy*, Hasegawa et al.<sup>8</sup> reported a significantly higher incidence of MWFELs in PPI users than in non-PPI users (49.3% vs. 10.9%,  $p < 0.01$ ; OR, 5.78 in multivariable analysis) and an association between MWFELs and hypergastrinemia. These results confirm the strong association between PPI use and MWFELs suggested in previous studies.

In practice, MWFELs can be misdiagnosed as intestinal metaplasia, especially by endoscopists who lack knowledge about MWFELs. The main differentiating features are as follows: MWFELs are detected in the upper corpus and fundus;

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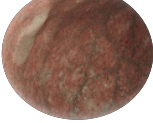
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**Table 1.** Histopathological and endoscopic features of proton pump inhibitor-related changes in the gastric mucosa

Histopathological features	Endoscopic findings
Parietal cell protrusion and cystic dilatation of fundic glands	Fundic gland polyps 
	Cobblestone-like mucosa 
	Black spots 
Foveolar epithelial hyperplasia	Hyperplastic polyps 
	Multiple white and flat elevated lesions 

intestinal metaplasia in the antrum usually appears as whitish elevated patches, whereas intestinal metaplasia in the corpus is usually seen as flat areas. In addition, MWFELs exhibit a ridged or papillary surface structure that lacks the light-blue crest sign on magnifying endoscopy with NBI.<sup>4,9</sup>

Because long-term PPI use has increased in response to the increasing prevalence of chronic disorders in aging societies, endoscopic identification of PPI-related gastric mucosal lesions is essential. Therefore, endoscopists should be aware of the occurrence of these lesions among PPI users and avoid providing unnecessary or worrisome information to patients. In addition, when these lesions are observed during endoscopy, the clinician should ask the patient about the use of PPIs.

**Conflicts of Interest**

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**REFERENCES**

- Nocon M, Labenz J, Jaspersen D, et al. Long-term treatment of patients with gastro-oesophageal reflux disease in routine care: results from the ProGERD study. *Aliment Pharmacol Ther* 2007;25:715–722.
- Joel A, Konjengbam A, Viswanath Y, et al. Endoscopic radiofrequency Stretta therapy reduces proton pump inhibitor dependency and the need for anti-reflux surgery for refractory gastroesophageal reflux disease. *Clin Endosc* 2024;57:58–64.
- Welsch L, May A, Blasberg T, et al. Bile acid sequestrants in poor healing after endoscopic therapy of Barrett's esophagus. *Clin Endosc* 2023;56:194–202.
- Kim GH. Proton pump inhibitor-related gastric mucosal changes. *Gut Liver* 2021;15:646–652.
- Haruma K, Kato M, Inoue K, et al. *Kyoto classification of gastritis*. 2nd ed. Tokyo: Nihon Medical Center; 2019.
- Hatano Y, Haruma K, Kamada T, et al. Factors associated with gastric black spot, white flat elevated mucosa, and cobblestone-like mucosa: a cross-sectional study. *Digestion* 2018;98:185–193.
- Majima K, Muraki Y, Shimamoto T. Multiple white and flat elevated lesions observed in the stomach: a prospective study of clinical characteristics and risk factors. *Intern Med* 2018;57:2613–2619.
- Hasegawa R, Yao K, Kanemitsu T, et al. Association between occurrence of multiple white and flat elevated gastric lesions and oral proton pump inhibitor intake. *Clin Endosc* 2024;57:65–72.
- Uedo N, Yamaoka R, Yao K. Multiple white flat lesions in the gastric corpus are not intestinal metaplasia. *Endoscopy* 2017;49:615–616.