

## Validity of endoscopic classification of nonerosive reflux disease

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**Background.** Minimal changes, such as erythema without sharp demarcation or whitish turbidity of the lower esophageal mucosa, have recently been used for endoscopic classification of nonerosive reflux disease (NERD) in Japan. This study examined the usefulness of such changes in characterizing the pathophysiology of NERD. **Methods.** Physicians specializing in esophageal endoscopy performed endoscopy on 115 patients with NERD. Based on the presence or absence of minimal changes, patients were categorized as displaying NERD with minimal changes (grade M,  $n = 49$ ) or with no minimal changes or mucosal breaks (grade N,  $n = 66$ ). Clinical features, quality of life (QOL) scores, and ambulatory 24-h esophageal pH values were compared between groups. Ambulatory 24-h esophageal pH values were monitored in 31 patients (14 grade M and 17 grade N patients) who gave consent out of 115 patients. **Results.** In ambulatory 24-h esophageal pH monitoring, 57.1% (8/14) of grade M patients had pH < 4 more than 4% of the time (abnormal acid reflux) compared with 11.8% (2/17) in the grade N group, a significant difference ( $P = 0.018$ ). QOL scores did not differ significantly between grades and were significantly lower in both groups compared with the general Japanese population. No significant differences were observed in patient background between the grade M and grade N groups. **Conclusions.** Frequency of abnormal acid reflux with NERD is higher in patients with minimal changes than in patients without such changes. Minimal changes are most likely attributable to gastric acid reflux.

**Key words:** ambulatory 24-h esophageal pH monitoring, endoscopy, minimal change, nonerosive reflux disease, GERD, QOL score

### Introduction

Nonerosive reflux disease (NERD) is defined as “the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy” according to the Montreal definition.<sup>1</sup> Recent studies demonstrate that it is a chronic disease with a significant impact on quality of life, and very common in primary care settings.<sup>2</sup> NERD accounts for >50% of cases involving gastroesophageal reflux disease (GERD).<sup>1,3,4</sup> Although NERD clearly represents an important clinical entity, the pathophysiology underlying it remains unclear.<sup>5–7</sup> Esophageal erosions in most GERD patients are caused by pathological reflux of gastric acid, and most symptoms and esophageal lesions can thus be treated by pharmacotherapeutic suppression of gastric acid secretion. However, the involvement of gastric acid may be reduced in NERD, and proton-pump inhibitors (PPIs) are much less effective in NERD than in erosive GERD.<sup>8,9</sup> Numerous factors thus contribute to NERD, not simply acid reflux.

The diverse characteristics of NERD are also apparent on endoscopy. Erosions are absent in these patients, but changes such as reddish or whitish discoloration are sometimes seen in areas of the esophageal mucosa. Others patients may display normal esophageal mucosa without such changes. Some studies have employed a modified Los Angeles (LA) classification system, in which two grades, grade M (minimal changes such as erythema without sharp demarcation, whitish turbidity, and/or invisibility of vessels due to these findings), and grade N (esophagus without any such minimal changes or mucosal breaks) are added to the usual LA grades A, B, C, and D.<sup>10–12</sup> Identifying minimal endoscopic changes can prove difficult for endoscopists with standard knowledge, and thus represents one obstacle for the utilization of minimal changes in classifications of GERD.

The present study was conducted through 11 institutions in Japan with considerable experience in endoscopic diagnosis of GERD. NERD patients were endoscopically assessed by endoscopists specializing in GERD and were classified into groups displaying either grade M NERD (with minimal changes) or grade N NERD (without lesions). Clinical features, heartburn, quality of life (QOL), extent of esophageal acid exposure, and timing of symptom onset based on ambulatory 24-h esophageal pH monitoring were then compared between groups.

## Methods

### *Subjects*

Subjects comprised patients with heartburn who visited one of the 11 medical institutions between July 2003 and October 2004. Numerous clinical studies on GERD have been conducted at these institutions, and endoscopists specializing in GERD were available. Heartburn was defined as a burning sensation arising from the stomach or lower chest and appearing frequently or becoming aggravated after the patient ate or bent forward, or after pressure was placed on the abdomen. Patients presenting with a history of heartburn at least twice weekly over the previous month were enrolled in the study. Written informed consent was obtained from each subject after the objectives and significance of the study were thoroughly explained. All study protocols were approved by the ethical review board at each participating institution. Endoscopy was performed on each subject.

The following exclusion criteria were applied: age < 20 years; endoscopic diagnosis of erosive esophagitis (grades A–D); present or previous angina pectoris; history of upper gastrointestinal surgery; consumption of a PPI  $\leq 1$  month before the study; gastroduodenal ulceration; or malignant tumor.

### *Endoscopy*

Endoscopy was performed using a high-resolution video endoscope, and the lower esophagus was closely examined after it was rinsed with water. According to the LA classification system, esophageal erosions were classified into grades A–D.<sup>13</sup> When esophageal erosions were absent, cases were classified as either grade M (minimal changes such as erythema or whitish turbidity present) or grade N (no minimal changes).<sup>10–12</sup> The presence or absence of esophageal hiatal hernia was also evaluated. Subjects in the present study were patients who were endoscopically diagnosed with grade M or grade N NERD.

### *Clinical features and QOL score*

Height, body weight, and body mass index (BMI) were measured, and information regarding smoking and drinking history was gathered. Frequency of heartburn was carefully ascertained. Presence or absence of *Helicobacter pylori* infection was determined by either serum immunoglobulin (Ig)G antibody, the rapid urease test, or the urea breath test.

QOL was assessed prior to endoscopy, using the Japanese version 1.2 of the SF-36 scoring system and each of the following eight scales: physical functioning; role limitation-physical; bodily pain; general health; vitality; social functioning; role limitation-emotional; and mental health.<sup>14</sup>

### *Ambulatory 24-h esophageal pH monitoring*

Ambulatory 24-h esophageal pH values were monitored in those subjects who consented to the monitoring to assess the severity of acid reflux in the esophagus. Either a PH101ZG recorder (Chemical Instrument, Tokyo, Japan) or Digrapper Mark III recorder (Synectics Medical, Stockholm, Sweden) was used. The electrode was inserted intranasally and positioned 5 cm above the lower esophageal sphincter. Data were analyzed by computer to calculate the following: time with esophageal pH < 4.0(%); total number of acid reflux episodes/day; number of acid reflux episodes lasting >5 min; longest duration of a single acid reflux episode; esophageal clearance; and symptom index (SI). SI was calculated using the following formula: (number of symptoms with esophageal pH < 4/total number of symptoms)  $\times 100$ .<sup>15</sup> A symptom with esophageal pH < 4 was defined as one that occurred within 5 min before or after an acid reflux event (pH < 4).

### *Statistical analysis*

Clinical features were statistically compared between grades M and N using the  $\chi$ -squared test for categorical variables and the two-sample Wilcoxon test for continuous variables ( $P < 0.05$ , two-sided). QOL and esophageal acid reflux were assessed using two-sample Wilcoxon test ( $P < 0.05$ , two-sided). In addition, Fisher's exact test was used to compare between grades M and N the proportion of cases with pH < 4 (abnormal reflux)  $\geq 4\%$  of the time ( $P < 0.05$ , two-sided).

## Results

### *Clinical features*

Of the 115 patients with no esophageal erosions apparent on endoscopy and a history of heartburn >2 days/

**Table 1.** Clinical features of grade M and N patients

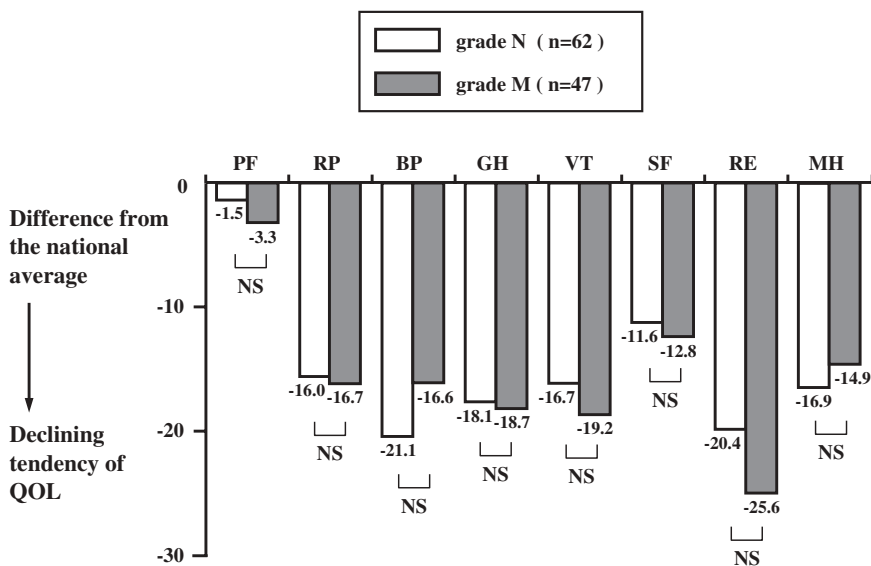
|  | Grade N ( <i>n</i> = 66) | Grade M ( <i>n</i> = 49) | <i>P</i>           |
|--|--------------------------|--------------------------|--------------------|
| Sex (men/women)                          | 29/37                    | 18/31                    | 0.437 <sup>a</sup> |
| Age (years)                              | 53 ± 16                  | 51 ± 18                  | 0.573 <sup>b</sup> |
| Height (cm)                              | 160 ± 10                 | 159 ± 10                 | 0.768 <sup>b</sup> |
| Body weight (kg)                         | 56.4 ± 12                | 56.6 ± 10                | 0.834 <sup>b</sup> |
| BMI (kg/m <sup>2</sup> )                 | 22.1 ± 3.3               | 22.3 ± 3.0               | 0.569 <sup>b</sup> |
| Heartburn (episodes/week)                | 4.4 ± 2.1                | 4.5 ± 2.2                | 0.898 <sup>b</sup> |
| Esophageal hiatal hernia (+)             | 26%                      | 39%                      | 0.167 <sup>a</sup> |
| <i>Helicobacter pylori</i> infection (+) | 38%                      | 29%                      | 0.185 <sup>a</sup> |
| Smoking (+)                              | 14%                      | 12%                      | 0.827 <sup>a</sup> |
| Drinking (+)                             | 44%                      | 41%                      | 0.738 <sup>a</sup> |

Values are means ± standard deviation

BMI, body mass index

<sup>a</sup>χ-squared test

<sup>b</sup>Two-sample Wilcoxon test



**Fig. 1.** Quality of life (QOL) assessment using the SF-36 system for grade M and N nonerosive reflux disease (NERD) patients. QOL scores for both grade M and N patients were significantly lower than the national average. No significant differences in QOL scores were apparent between grade M and N patients (two-sample Wilcoxon test). *PF*, physical functioning; *RP*, role limitation-physical; *BP*, bodily pain; *GH*, general health; *VT* vitality; *SF*, social functioning; *RE*, role limitation-emotional; *MH*, mental health

week for the last month, 49 displayed minimal changes in the lower esophagus and were diagnosed with grade M NERD. The remaining 66 patients did not exhibit minimal changes and were diagnosed with grade N NERD.

Table 1 shows clinical features of grade M and N patients. No significant intergroup differences were apparent in sex, age, height, body weight, BMI, frequency of heartburn, esophageal hiatal hernia, *H. pylori* infection, smoking, or alcohol consumption.

### QOL score

Figure 1 shows QOL scores for grade M and N patients as assessed using the Japanese version 1.2 of the SF-36 scoring system, compared with the average for the general Japanese population. Questionnaires were returned by 109 of the 115 patients surveyed (94.8%). QOL scores for the 109 NERD patients were significantly

lower than the national average in seven of the eight domains, with the exception of physical functioning. No significant differences were detected between grade M and N patients in any of the eight domains.

### Ambulatory 24-h esophageal pH monitoring

Of the 115 subjects, 14 grade M patients and 17 grade N patients consented to and underwent ambulatory 24-h esophageal pH monitoring to assess acid reflux in the esophagus. The total number of esophageal acid reflux episodes was significantly higher in grade M patients than in grade N patients ( $P = 0.049$ ) (Table 2).

While six grade M patients and ten grade N patients experienced heartburn during ambulatory 24-h esophageal pH monitoring, SI tended to be greater in grade M patients than in grade N patients. While no significant differences in median percentage time with pH < 4.0 were observed between the groups, grade M patients

**Table 2.** Results of pH monitoring for grade M and N patients

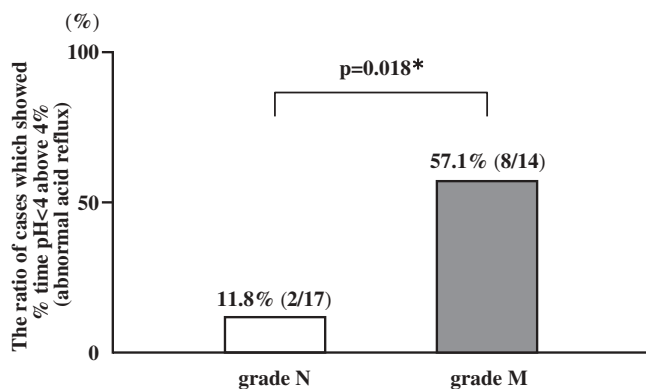
|   | Grade N ( <i>n</i> = 17)             | Grade M ( <i>n</i> = 14)            | <i>P</i> <sup>a</sup> |
|---|--------------------------------------|-------------------------------------|-----------------------|
| Time with pH <4.0 (%)                         | 1.5 (0.0–11.1)                       | 6.4 (0.3–14.9)                      | 0.080                 |
| Total number of acid reflux episodes          | 29 (0–497)                           | 108 (9–399)                         | 0.049**               |
| Number of acid reflux episodes lasting >5 min | 1 (0–5)                              | 1 (0–10)                            | 0.459                 |
| Longest duration of acid reflux episode (min) | 5.0 (0.0–53.0)                       | 5.0 (0.0–32.0)                      | 0.436                 |
| Esophageal clearance (min/episode)            | 1.1 (0.1–3.3)                        | 0.6 (0.2–1.5)                       | 0.306                 |
| SI (%)  | 70.9 (0.0–100.0)<br>[ <i>n</i> = 10] | 75.0 (0.0–100.0)<br>[ <i>n</i> = 6] | 0.819                 |

Values are median (range)

SI, symptom index

<sup>a</sup>Two-sample Wilcoxon test

\*Significant: *P* < 0.05



**Fig. 2.** Esophageal acid reflux in NERD patients as assessed by ambulatory 24-h esophageal pH monitoring. The proportion of patients with pH < 4 (abnormal acid reflux)  $\geq 4\%$  of the time was significantly higher in grade M (57.1%, 8/14) than in grade N (11.8%, 2/17) patients (Fisher's exact test)

tended to experience a higher degree of esophageal acid exposure. Values  $\geq 4\%$  for percentage time with pH < 4.0 are considered pathological. Esophageal pH was <4.0 for  $\geq 4\%$  of the time in eight of the 14 grade M patients (57.1%) and two of the 17 grade N patients (11.8%) (Fig. 2). Frequency of pathological reflux was thus significantly higher in the grade M group than in the grade N group (*P* = 0.018). Moreover, median percentage time with pH < 4.0 was 6.4% in grade M and 1.5% in grade N patients.

## Discussion

NERD is a multifactorial disease influenced by such factors as reflux of food materials, reflux of duodenal contents, reflux of neutral gastric juice, abnormal esophageal motor function, and visceral hypersensitivity, in addition to acid reflux into the esophagus.<sup>3</sup> The efficacy of PPI therapy is thus lower in NERD than in reflux esophagitis, with only 40%–60% of NERD patients responding to PPI therapy.<sup>5,8,9,16,17</sup> Identifying NERD pa-

tients who are responsive to this form of therapy is thus clinically important.

Frequent regurgitation and retention of acidic gastric juice in the esophagus for extended periods of time leads to inflammation of the esophageal squamous mucosa. Microscopically, this inflammation is accompanied by infiltration of inflammatory cells (predominantly eosinophils) into squamous epithelia, elongation of epithelial papillae, hyperplasia of the epithelial basal cell layer, dilatation of papillary vessels, and epithelial erosion.<sup>18,19</sup> Erosions are readily identified on endoscopy as localized erythema, and mucosal breaks indicate reflux esophagitis. High-resolution endoscopy by a skilled endoscopist reveals inflammatory cell infiltration of the epithelium and dilatation of papillary vessels as whitish turbidity and erythema, respectively. In fact, Takubo et al.<sup>20</sup> reported that histologically red changes show dilation of multiple intrapapillary vessels, while white ones show acanthosis with or without keratinization of the epithelium. The classification of NERD into grades M and N on the basis of such minimal changes in the lower esophageal mucosa has thus been proposed.<sup>10–12</sup> However, NERD has been classified into these grades without sufficient clarification of their clinical significance, and some researchers have questioned the validity of this system. In the present study, endoscopy was performed at 11 medical institutions with considerable experience in GERD diagnosis and treatment, mostly university hospitals. Physicians specializing in esophageal endoscopy classified NERD patients into grades M and N, and then compared clinical features, symptoms, QOL score, and extent of esophageal acid exposure and SI (from ambulatory 24-h esophageal pH monitoring) between groups.

No significant differences were identified in symptoms, clinical features, or QOL score between grades M and N. Differentiation of grade M NERD from grade N NERD is thus not clinically significant. However, grade M patients tended to display a higher frequency of esophageal hiatal hernia and a lower frequency of *H. pylori* infection than grade N patients (esophageal hia-

tal hernia,  $P = 0.167$ ; *H. pylori* infection,  $P = 0.185$ ). Several studies comparing clinical characteristics between reflux esophagitis and NERD have similarly reported that reflux esophagitis is associated with higher frequency of esophageal hiatal hernia and lower frequency of *H. pylori* infection.<sup>3,21</sup> Grade M NERD may therefore be associated with clinical features similar to those of reflux esophagitis.

Ambulatory 24-h esophageal pH monitoring showed that grade M patients experienced more frequent esophageal acid reflux than grade N patients. In addition, the median percentage time with pH < 4.0 was 6.4% in grade M and 1.5% in grade N patients. The frequency of pathological acid reflux in the esophagus was thus higher in grade M than in grade N patients, suggesting that the presence of pathological reflux can be ascertained to some degree on the basis of minimal endoscopic changes. However, no marked differences in SI were identified between grades M (75.0%) and N (70.9%). Grade M patients were more likely than grade N patients to experience pathological acid reflux, and symptoms were more likely to be attributable to acid reflux. On the basis of pH monitoring, grade M NERD more closely resembles reflux esophagitis than grade N NERD does.

These findings suggest that grade M NERD, which is associated with heartburn and minimal changes such as erythema without sharp demarcation and whitish turbidity of the lower esophageal mucosa, resembles reflux esophagitis. Prospective, multicenter, double-blinded studies of PPI administration to larger populations of grade M and N NERD patients are therefore warranted to ascertain differences in therapeutic efficacy.

In conclusion, endoscopic examination was used to classify NERD into grades M and N on the basis of minimal changes in the lower esophagus. Grade M patients appear more likely than grade N patients to experience pathological acid reflux in the esophagus.

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