

# Reflux Esophagitis and Fatigue: Are They Related?

**Sung-Goo Kang**

Catholic University of Korea

**Hyun jee Hwang**

Catholic University of Korea

**Youngwoo Kim**

Catholic University of Korea

**Junseak Lee**

Catholic University of Korea

**Jung Hwan Oh**

Catholic University of Korea

**Jinsu Kim**

Catholic University of Korea

**Chul-Hyun Lim**

Catholic University of Korea

**Seung Bae Youn**

Catholic University of Korea

**Sung Hoon Jung** (✉ [shjung74@catholic.ac.kr](mailto:shjung74@catholic.ac.kr))

Catholic University of Korea <https://orcid.org/0000-0001-9075-2027>

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## Research article

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# Abstract

**Background:** Gastroesophageal reflux disease (GERD) is a chronic, recurrent disease. Reflux esophagitis can interfere with sleep via acid reflux, which could cause daytime sleepiness or fatigue. However, little is known about the association between reflux esophagitis and fatigue

**Objectives:** We evaluated the association between fatigue and reflux esophagitis in subjects seen at health check-ups.

**Methods:** Consecutive patients who were scheduled for screening endoscopy were enrolled prospectively at the Comprehensive Medical Examination Center of St. Vincent Hospital and Eunpyeong St. Mary's Hospital, Korea. Three validated questionnaires were used to assess fatigue, daytime hypersomnolence, anxiety, and depression: the Multidimensional Fatigue Inventory-Korean version (MFI-K), Epworth Sleepiness Scale (ESS), and Hospital Anxiety and Depression Scale (HADS).

**Results:** We investigated 497 consecutive eligible subjects. The reflux esophagitis and symptomatic GERD groups comprised 103 (20.7%) and 92 (18.5%) subjects, respectively. The MFI-K total, ESS, HADS-anxiety, and HADS-depression scores did not differ between the esophagitis and non-esophagitis groups ( $50.0 \pm 11.5$  vs.  $49.7 \pm 10.9$ ,  $P=0.769$ ;  $6.2 \pm 2.8$  vs.  $6.1 \pm 3.1$ ,  $P=0.819$ ;  $5.8 \pm 3.1$  vs.  $5.2 \pm 3.2$ ,  $P=0.069$ ;  $6.2 \pm 3.6$  vs.  $6.0 \pm 3.3$ ,  $P=0.527$ ). However, the MFI-K total, ESS, HADS-anxiety, and HADS-depression scores were higher in the symptomatic group than in the non-symptomatic group ( $54.7 \pm 12.7$  vs.  $48.6 \pm 10.3$ ,  $P<0.001$ ;  $7.1 \pm 3.5$  vs.  $5.9 \pm 2.9$ ,  $P=0.002$ ;  $6.4 \pm 3.3$  vs.  $5.1 \pm 3.1$ ,  $P<0.001$ ;  $7.5 \pm 4.0$  vs.  $5.7 \pm 3.1$ ,  $P<0.001$ ). In addition, HADS-depression was correlated with the MFI-K score ( $P<0.001$ ).

**Conclusion:** There was no evidence of reflux esophagitis causing daytime sleepiness, fatigue, anxiety, or depression, but GERD symptoms were associated with these. Depression was also associated with fatigue. Further studies should clarify the association between fatigue and reflux esophagitis.

## Introduction

Gastroesophageal reflux disease (GERD) is a chronic, recurrent disease with a prevalence of 20% in western countries, and disease-related symptoms are common in these populations.[1, 2] Recently, the prevalence of GERD has increased significantly in Korea and symptomatic GERD is also increasing.[3] Although a few studies have identified asymptomatic reflux esophagitis in some patients, most patients report regurgitation and heartburn,[4–6] and atypical symptoms can include various other esophageal and extra-esophageal symptoms.[7] Reflux symptoms can also cause sleep disturbances or emotional dysfunction, while anxiety and depressive symptoms can conversely be associated with reflux symptoms.[8, 9]

Fatigue is a very subjective symptom and can be caused by a variety of organic disorders, including malignant diseases, and by psychological disorders, such as depression.[10–12] Sleep disturbances can also cause fatigue, and reflux esophagitis is likely to cause sleep disturbances because of acid

regurgitation.[13, 14] To our knowledge, however, no study has directly examined the relationship between fatigue and reflux esophagitis. Recently, the author verified the reliability and validity of the Multidimensional Fatigue Inventory Korean version (MFI-K) as a multidimensional instrument for assessing fatigue in the Korean population.[15]

Therefore, this study evaluated the association between fatigue and endoscopy-proven reflux esophagitis. We also compared the various correlations between psychological disorders and daytime sleepiness, which could cause fatigue in reflux esophagitis.

## **Materials And Methods**

### **Patients and Study Design**

This prospective survey study was conducted at the Comprehensive Medical Examination Center of St. Vincent Hospital and Eunpyeong St. Mary's Hospital, Korea.. The study was approved by the Institutional Review Board of The Catholic University of Korea (PC19QESI0025) on 16 April 2019. Written informed consent was obtained from all subjects. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

Consecutive patients who were scheduled for screening endoscopy at the Comprehensive Medical Examination Center of both hospitals were enrolled prospectively. The exclusion criteria were advanced stomach cancer, peptic ulcer disease (active gastric or duodenal ulcer), anemia (male < 14 g/dL, female < 12 g/dL), positive stool occult blood, and other severe co-morbidities.

All patients underwent gastro-duodenoscopy by well-trained endoscopists and the findings were reviewed by expert endoscopists. The presence and extent of reflux esophagitis was classified using the Los Angeles (LA) classification. Minimal change in reflux esophagitis was excluded. The presence of GERD symptoms was distinguished by the presence of regurgitation and heartburn.

### **Questionnaires**

Three validated questionnaires were administered to assess fatigue, daytime hypersomnolence, anxiety, and depression.

### **Multidimensional Fatigue Inventory-Korean version (MFI-K)**

Useful tools for assessing fatigue are either one- or multidimensional instruments. The most commonly used one-dimensional instruments for fatigue are the Visual Analogue Scale (VAS) and Fatigue Severity Scale (FSS).[16, 17] One of the most useful multidimensional scaling tools for fatigue research is the MFI, which has five subscales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.[18] The MFI-K has proven validity and reliability.[15] We used the MFI-K to assess fatigue in this study.

## Epworth Sleepiness Scale (ESS)

The ESS was used to assess daytime sleepiness. This tool is a self-assessment tool consisting of eight questions, each of which is scored on a Likert scale from 0 to 3 points. The higher the ESS score, the worse the daytime sleepiness; a score above 10 indicates excessive daytime sleepiness.[19]

## Hospital Anxiety and Depression Scale (HADS)

The HADS was developed to measure the anxiety and depression of patients who visit a hospital for a short time; the Korean version of HADS has proven validity and reliability.[20] The HADS consists of 14 questions, with seven odd-numbered ones assessing anxiety and seven even-numbered ones for depression. Each is scored on a 4-point scale (0–3 points). The higher the score, the greater the anxiety and depression. We used the HADS to assess anxiety and depression in this study.

## Statistical analyses

The categorical variables in each group are presented as numbers with percentages and were compared using the chi-square test. The continuous variables in each of the two groups are presented as means  $\pm$  standard deviations and were compared using the *t*-test. The correlations of MFI-K with ESS and HADS were tested using Pearson's correlation. *P*-values less than 0.05 were defined as statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) ver. 18.0 (SPSS, Chicago, USA).

## Results

### Baseline Characteristics

The study initially enrolled 500 subjects. Three were excluded and the remaining 497 eligible cases were analyzed; their mean age was  $50.52 \pm 10.13$  years and 308 (62%) were males. The reflux esophagitis and symptomatic GERD groups comprised 103 (20.7%) and 92 (18.5%) subjects, respectively. Table 1 lists the baseline characteristics of each group. Eighty-eight patients (17.7%) had hypertension, 44 (8.9%) had type 2 diabetes, and 62 (12.5%) had dyslipidemia. The mean fasting blood sugar was  $101.2 \pm 20.2$  and the mean low-density lipoprotein cholesterol was  $118.2 \pm 33.8$ .

Table 1  
Baseline characteristics of the study population.

	Reflux esophagitis No	Reflux esophagitis Yes	P- Value	GERD Symptoms No	GERD Symptoms Yes	P- Value
Age (years)	50.5 ± 10.0	50.7 ± 10.6	0.809	50.5 ± 10.2	50.4 ± 9.8	0.936
Sex			0.111			0.721
Men	237 (60.2)	71(68.9)		249(61.5)	59(64.1)	
Women	157 (39.8)	32(31.1)		156(38.5)	33(35.9)	
BMI (kg/m <sup>2</sup> )	23.3 ± 6.1	22.0 ± 8.6	0.160	23.2 ± 6.7	22.3 ± 6.9	0.242
WC (cm)	85.1 ± 9.2	85.8 ± 10.2	0.567	85.5 ± 9.3	84.4 ± 9.8	0.374
Smoking			0.859			0.002
Non-smoker	188(47.7)	46(44.7)		193(47.7)	41(44.6)	
Ex-smoker	108(27.4)	28(27.2)		112(27.7)	24(26.1)	
Current smoker	59 (15.0)	16(15.5)		51(12.6)	24(26.1)	
No answer	39(9.9)	13(12.6)		49(12.1)	3(3.3)	
Medical History						
Hypertension	66(16.8)	22(21.4)	0.310	71(17.6)	17(18.5)	0.880
Type 2 diabetes	31(7.9)	13(12.6)	0.171	39(9.7)	5(5.5)	0.306
Dyslipidemia	50(12.7)	12(11.7)	0.868	48(11.9)	14(15.2)	0.384
Alcohol			0.392			0.902
< 1 time / week	133(37.5)	29(32.2)		129(36.2)	33(37.1)	
≥1 time / week	222(62.5)	61(67.8)		227(63.8)	56(62.9)	
SBP (mmHg)	125.9 ± 15.2	125.2 ± 15.8	0.707	126.0 ± 15.1	124.4 ± 16.2	0.379

Data are mean ± SD or N(%). P values were obtained by independent T-tests or chi-square tests.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TC, total cholesterol; LDL, low density lipoprotein; WBC, white blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase;

	Reflux esophagitis  No	Reflux esophagitis  Yes	P- Value	GERD Symptoms  No	GERD Symptoms  Yes	P- Value
DBP (mmHg)	76.5 ± 11.3	77.6 ± 11.5	0.393	76.9 ± 11.2	76.1 ± 11.9	0.567
FBS (mg/dl)	100.3 ± 20.2	105.1 ± 19.9	0.029	101.9 ± 20.9	98.3 ± 16.6	0.116
TC (mg/dl)	202.1 ± 45.1	202.4 ± 45.4	0.957	203.0 ± 42.8	198.6 ± 54.3	0.404
LDL (mg/dl)	117.9 ± 33.1	119.0 ± 36.3	0.783	119.2 ± 34.6	113.4 ± 29.5	0.144
WBC	5.5 ± 1.9	5.5 ± 2.3	0.888	5.4 ± 2.0	5.8 ± 2.0	0.157
AST	29.4 ± 14.5	29.1 ± 12.8	0.885	29.5 ± 14.8	28.5 ± 11.0	0.535
ALT	29.4 ± 27.9	31.2 ± 20.5	0.523	30.2 ± 27.6	27.9 ± 21.0	0.470
γGTP	36.5 ± 38.2	42.6 ± 29.8	0.134	38.1 ± 35.6	36.4 ± 41.5	0.685
Creatinine	0.8 ± 0.3	0.8 ± 0.1	0.601	0.8 ± 0.3	0.8 ± 0.2	0.483
Data are mean ± SD or N(%). P values were obtained by independent T-tests or chi-square tests.						
Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TC, total cholesterol; LDL, low density lipoprotein; WBC, white blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase;						

## Questionnaires: MFI-K, ESS and HADS

The mean MFI-K total score did not differ between the esophagitis and non-esophagitis groups ( $50.0 \pm 11.5$  vs.  $49.7 \pm 10.9$ ,  $P = 0.769$ ), although it was higher in the symptomatic group than in the non-symptomatic group ( $54.7 \pm 12.7$  vs.  $48.6 \pm 10.3$ ,  $P < 0.001$ ). There were no differences in scores with or without esophagitis for each MFI-K subscale. However, all subscales scored higher in the symptom group (Table 2). The mean ESS score did not differ between the esophagitis and non-esophagitis groups ( $6.2 \pm 2.8$  vs.  $6.1 \pm 3.1$ ,  $P = 0.819$ ), while the mean ESS score was higher in the symptomatic group than in the non-symptomatic group ( $7.1 \pm 3.5$  vs.  $5.9 \pm 2.9$ ,  $P = 0.002$ ). In HADS, there were no differences in scores with or without esophagitis, but the anxiety and depression scales scored higher in the symptomatic group ( $P < 0.001$ ).

Table 2  
MFI-K (Multidimensional Fatigue Inventory-Korean version) and reflux esophagitis

	Reflux esophagitis  No	Reflux esophagitis  Yes	P- Value	GERD Symptoms  No	GERD Symptoms  Yes	P- Value
MFI-K						
General and Physical Fatigue	17.1 ± 4.6	17.3 ± 5.0	0.691	16.7 ± 4.5	19.1 ± 5.2	< 0.001
Mental Fatigue	13.7 ± 3.7	13.7 ± 3.9	0.923	13.4 ± 3.5	15.2 ± 4.1	< 0.001
Reduced Activity	8.7 ± 2.6	8.7 ± 3.0	0.814	8.5 ± 2.7	9.4 ± 2.9	0.003
Motivation	10.2 ± 3.1	10.3 ± 2.7	0.863	10.0 ± 2.9	11.0 ± 3.4	0.008
MFI-K total score	49.7 ± 10.9	50.0 ± 11.5	0.769	48.6 ± 10.3	54.7 ± 12.7	< 0.001
ESS	6.1 ± 3.1	6.2 ± 2.8	0.819	5.9 ± 2.9	7.1 ± 3.5	0.002
HADS						
Anxiety	5.2 ± 3.2	5.8 ± 3.1	0.069	5.1 ± 3.1	6.4 ± 3.3	< 0.001
Depression	6.0 ± 3.3	6.2 ± 3.6	0.527	5.7 ± 3.1	7.5 ± 4.0	< 0.001
Data are means ± SD.						
Abbreviations: MFI-K, Multidimensional Fatigue Inventory-Korean version; ESS, Epworth sleepiness scale; HADS, The Hospital Anxiety-Depression scale.						

Table 3 shows that the non-erosive reflux esophagitis (NERD) group had higher MFI-K, ESS, and HADS scores, especially the MFI-K total score and HADS depression subscale ( $P=0.002$ ,  $P=0.008$ ) compared with the asymptomatic erosive esophagitis group. Regardless of the presence of erosive esophagitis, MFI-K, ESS, and HADS were correlated ( $P<0.001$ ) (Table 4).

Table 3  
Comparison of Asymptomatic erosive esophagitis group and Non-erosive reflux esophagitis (NERD) group

	<b>Asymptomatic erosive esophagitis eRE + GERD Sx – (n = 87)</b>	<b>NERD eRE – GERD Sx+ (n = 76)</b>	<b>P-Value</b>
MFI-K			
General and Physical Fatigue	16.5 ± 4.4	18.4 ± 4.9	0.008
Mental Fatigue	13.3 ± 3.4	15.0 ± 3.8	0.003
Reduced Activity	8.5 ± 2.9	9.3 ± 2.8	0.073
Motivation	10.0 ± 2.4	10.8 ± 3.4	0.081
MFI-K total score	48.2 ± 9.8	53.6 ± 11.9	0.002
ESS	6.0 ± 2.8	7.0 ± 3.6	0.062
HADS			
Anxiety	5.4 ± 2.8	6.1 ± 3.1	0.152
Depression	5.7 ± 3.1	7.2 ± 3.8	0.008
Data are means ± SD.			
Abbreviations: eRE, erosive reflux esophagitis; GERD, gastroesophageal reflux disease; NERD, non-erosive reflux disease; MFI-K, Multidimensional Fatigue Inventory-Korean version; ESS, Epworth sleepiness scale; HADS, The Hospital Anxiety-Depression scale.			



Table 4  
Correlation between MFI-K and ESS and HADS score

	<i>r</i>	P-Value
MFI-K		
General and Physical Fatigue	0.802	< 0.001
Mental Fatigue	0.795	< 0.001
Reduced Activity	0.716	< 0.001
Motivation	0.759	< 0.001
		< 0.001
ESS	0.260	< 0.001
HADS		
Anxiety	0.529	< 0.001
Depression	0.630	< 0.001
P values were obtained by Pearson's correlation analysis.		

## Discussion

Fatigue is a vague subjective symptom that is one of the most common symptoms encountered in primary care. Fatigue can accompany many different diseases, which range from organic to psychological and can affect the quality of life.[11, 12, 21] As in Western countries, GERD is increasing in Asia and Korea.[22, 23] Theoretically, GERD can cause fatigue and daytime sleepiness via sleep disturbance due to acid regurgitation. We examined whether there is a connection between GERD and fatigue.

The study results showed that fatigue and erosive esophagitis were not correlated with the MFI-K total score or the general or physical fatigue, mental fatigue, reduced activity, or motivation subscales. Daytime sleepiness was not associated with erosive esophagitis. These findings are inconsistent with epidemiology studies that reported that people who experience nighttime heartburn have sleep disorders that alter daytime performance.[14, 24–27] One systematic review found GERD was associated with sleep disturbance, and this association appeared to be bidirectional.[13] Although not all sleep disturbances due to acid regurgitation cause daytime sleepiness, night sleep disturbance could cause daytime sleepiness. However, the ESS score was not higher in endoscopy-proved erosive esophagitis in this study. This suggests that acid contact and regurgitation alone cannot cause daytime sleepiness and that a variety of other factors, including psychological causes, cause daytime sleepiness. Similarly, fatigue may also represent a psychophysiological symptom complex. A few studies have found relations between reflux esophagitis and fatigue, while just one study found no correlation of fatigue with active

reflux esophagitis or peptic ulcer.[28] Those authors emphasized that psychosocial stress affects reflux esophagitis and is correlated with the severity of reflux esophagitis. That earlier study used the FSS, a one-dimensional instrument of fatigue. We used the MFI-K, a more complex multidimensional measure of fatigue, to find a more detailed link between fatigue and erosive esophagitis, but found no correlation.

Anxiety and depression were also not linked to erosive esophagitis in this study. This is similar to the earlier study that reported that stress tasks did not influence objective parameters of acid reflux. However, most of the GERD studies involving anxiety and depression focused on patient symptoms and, in almost all studies, anxiety and depression seemed to affect GERD symptoms bidirectionally.[8, 29–31] In our subgroup analysis of GERD symptoms, depression and anxiety were strongly associated with symptoms, similar to other studies. In contrast to the comparison of the groups with or without endoscopy-proven erosive esophagitis, GERD symptoms such as heartburn and regurgitation were correlated with fatigue in the MFI-K total and subscale scores. The ESS score was also much higher in the GERD symptom group. These findings indicate that the presence of symptoms is related more to fatigue and daytime sleepiness than to the endoscopic findings.

GERD can be classified into erosive (ERD), non-erosive (NERD), and asymptomatic erosive esophagitis. Asymptomatic erosive esophagitis has a reported prevalence of 20 ~ 45%.[4–6, 32] The overall prevalence of NERD and asymptomatic erosive esophagitis was 15.3% and 17.5%, respectively. Interestingly, 84.5% of those with ERD had no symptoms, probably because only typical symptoms such as heartburn or degeneration are considered GERD symptoms and most patients had relatively mild erosive esophagitis, such as LA grades A and B. In the present study, fatigue and depression were common in the NERD group. Daytime sleepiness also tended to increase in the NERD group, but the difference was not significant. These findings suggest that organic causes, visceral sensitivity, esophageal motility, and psychological factors can affect NERD, as proposed in other studies.[33, 34] Furthermore, fatigue was correlated with depression, anxiety, and daytime sleepiness regardless of the presence of erosive esophagitis. In mild erosive esophagitis, psychological factors can cause fatigue and daytime sleepiness, rather than organic factors, such as acid regurgitation.

This study had several limitations. First, only a relatively small number of the study participants with erosive esophagitis had LA class C (n = 12) or D (n = 1) reflux esophagitis. Therefore, it is necessary to investigate relationships between fatigue, anxiety, and depression in patients with LA-C or LA-D reflux esophagitis. Second, few variables related to socioeconomic status, such as household income and marital status, which may affect patient fatigue, depression, and anxiety, were included. Nevertheless, this study has strengths. First, it is the first study to use the MFI-K, a multidimensional scaling tool for fatigue validated by the author, to examine the relationship between GERD and fatigue. Second, all subjects underwent endoscopy by well-trained endoscopists and the findings were reviewed by expert endoscopists.

In conclusion, there was no evidence that reflux esophagitis causes daytime sleepiness, fatigue, anxiety, or depression, although GERD symptoms were associated with all of these. Depression was also

associated with fatigue. Therefore, psychological factors are likely to cause fatigue and daytime sleepiness, rather than organic factors related to acid regurgitation. Further studies should clarify the association between fatigue and reflux esophagitis.

## List Of Abbreviations

GERD: Gastroesophageal reflux disease, NERD: non-erosive reflux esophagitis, MFI-K: Multidimensional Fatigue Inventory-Korean version, ESS: Epworth Sleepiness Scale, HADA: Hospital Anxiety and Depression Scale

## Declarations

## Ethics approval

This study was approved by the Institutional Review Board of the Catholic University of Korea (PC19QESI0025).

## Consent for publication

Not applicable

## Availability of data and materials

The datasets generated or analysed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interest.

## Funding

Not applicable

## Author's contributions

SHJ and SGK planned and designed the review. HJH, YWK and JSL carried out data collection. Data analysis was performed by JSK, CHL and SBY under the supervision of JHO. SHJ and SGK supervised the writing of the manuscript. All authors reviewed and approved the final draft of the manuscript.

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