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Effect of Long-Term Proton Pump Inhibitor Therapy on Nutritional Status in Elderly Hospitalized Patients

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Summary The purpose was to investigate the association between proton pump inhibitor (PPI) therapy and nutritional status in elderly hospitalized patients. Participants were 190 elderly patients admitted to the long-term care wards, convalescence rehabilitation wards, and community integrated care wards in January 2015. Nutritional status was assessed using the mini nutritional assessment short-form (MNA-SF). The PPI use group was compared with the PPI non-use group regarding nutrition status. Logistic regression analysis was used to examine whether the period of PPI therapy was associated independently with malnutrition following adjustment for covariates including gender, age, and serum albumin level. Forty-one patients were male (22%) and 149 patients were female (78%), with a mean age of 85.4±8.4. Fifty-three patients (28%) took PPIs (with a median prescription period of 91 d, ranging from 51 to 227). With a MNA-SF score of 7 points or lower designated as malnutrition, there was no significant difference in nutritional status between the PPI and non-PPI groups (p=0.172). The median MNA-SF scores in the PPI and non-PPI groups were 9 vs 7 points, respectively. Logistic regression analysis showed that long-term PPI therapy (odds ratio, 0.994; 95% confidence interval 0.990–0.999) was significantly associated with improved nutritional status. The presence or absence of PPI therapy is not associated with malnutrition in elderly hospitalized patients. Longer-term PPI therapy may improve nutritional status.

Key Words hospital, malnutrition, proton pump inhibitors (PPIs), polypharmacy

Proton pump inhibitors (PPIs) are among the most commonly utilized agents for the elderly (*1*). There were administration limits on this treatment in 1999 when H_2 blockers predominated in Japan. From the 2000s, the increasing numbers of PPI prescriptions led to the removal of the administration limit restrictions due to *Helicobacter pylori* eradication, including the use in maintenance therapy for the treatment of gastroesophageal reflux disease (GERD). PPI therapy has continued to increase and is inclusive of other drug combinations (*2*). Therefore, PPIs are widely used for diseases in elderly Japanese people.

Inappropriate recommendation of PPI is a matter of concern (*3*). Inappropriate PPI therapy does not comply with correct drug use in the clinical setting. Furthermore, failure to discontinue before hospital discharge is considered inappropriate PPI therapy. Several studies indicated the presence of adverse effects with long-term PPI therapy (*4*). Risk of *Clostridium difficile*-associated diarrhea (*5*), community-acquired pneumonia (*6*), hip fracture (*7*), vitamin B_{12} deficiency and malabsorption were increased by PPI utilization (*8*). Empirical unnecessary PPI treatment is increasing (*9*). Over 70% of patients in hospitals receive PPI inappropriately. Moreover, 40% continued PPI therapy following discharge (*10*). This has become a problem of polypharmacy (*11*, *12*) as they are discharged from acute care hospitals while continuing PPI therapy.

Malnutrition is an important factor in medication during hospitalization. Many of the hospitalized elderly exhibit malnutrition (*13*). Malnutrition causes infection and is associated with poor rehabilitation outcomes (*14*). Aging causes an altered drug metabolism as a consequence of the deterioration of organ function and bioavailability, thereby leading to malnutrition (*15*).

There are few reports examining the association between PPI and nutritional status. PPI therapy was significantly associated with the parameters of nutritional risk screening in patients scheduled for cardiovascular rehabilitation after treatment for ischemic and valvular heart disease (*16*). Male PPI users had an increase in body weight over the previous year compared with non-users, while female PPI users had no significant increase in body weight (*17*). However, the association between PPI and malnutrition in elderly hospitalized patients is unknown. PPI is used widely, regardless of gender or comorbidity in elderly hospitalized patients. Longer PPI therapy may lead to malnutrition by malabsorption of vitamins and nutrients in elderly hospitalized patients. The aim of this study was therefore to examine the effect of long-term PPI therapy on malnutrition in elderly hospitalized people.

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Table 1. Characteristics of the study patients.

	Total	PPI use	No PPI use	*p*-value
Age (y), mean±SD	85.4±8.4	85.5±7.4	85.5±8.7	0.984[1]
Gender, number (%)				0.073[2]
Male	41 (22%)	16 (30%)	25 (18%)	
Female	149 (78%)	37 (70%)	112 (82%)	
Height (m)	1.49±0.11	1.49±0.10	1.49±0.11	0.583[1]
Body weight (kg)	43.2±9.9	45.1±10.2	42.5±9.7	0.113[1]
BMI (kg/m^2)	19.5±4.2	20.4±4.1	19.2±4.1	0.077[1]
Serum albumin (g/dL)	3.1±0.5	3.1±0.5	3.1±0.6	0.570[1]
Hemoglobin (g/dL)	11.6±1.8	11.2±1.8	11.8±1.8	0.059[1]
Hospitalization (d)	99 (60–240)	91 (62–227)	104 (58–240)	0.692[3]
Nutrition administration route				
Oral	153 (81%)	48 (91%)	105 (77%)	
Gastric Fistula	35 (18%)	5 (9%)	30 (22%)	
Nasogastric feeding	2 (1%)	0	2 (1%)	
FOIS, median (25%, 75%)	6 (4–7)	7 (5–7)	5 (4–7)	0.017[3]
FIM, median (25%, 75%)	49 (24–86)	73 (36–93)	45 (22–83)	0.007[3]
Number of drugs	6 (4–9)	9 (6–11)	5 (3–7)	$p<0.001$[3]
MNA-SF	8 (6–10)	9 (6–10)	7 (6–9)	0.235[3]
Malnutrition, number (%)	94 (50%)	22 (42%)	72 (53%)	0.172[2]
No malnutrition, number (%)	96 (50%)	31 (58%)	65 (47%)	
At risk of malnutrition, number (%)	82 (43%)	28 (53%)	54 (39%)	
Normal nutritional status, number (%)	14 (7%)	3 (5%)	11 (8%)	

BMI: body mass index, MNA-SF: mini nutritional assessment short form, FOIS: functional oral intake scale, FIM: functional independence measure.
[1] *t*-test, [2] chi-square test, [3] Mann-Whitney *U* test.

MATERIALS AND METHODS

Participants. The inclusion criteria were an age of 65-y and older, the ability to evaluate nutritional status, and hospitalization in a long-term care ward, convalescence rehabilitation ward, or community integrated care ward in January 2015. The exclusion criteria were an age below 65 y old, acutely illness, adaptation disease during PPI therapy, parenteral nutrition only, or missing data. The adaptation-diseases were gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellisom syndrome and *Helicobacter pylori* gastritis. Uneroded gastroesophageal reflux disease, recurrent suppression of gastric or duodenal ulcer at the time of low-dose aspirin, and NSAID administration were not excluded.

The Independent Ethics Committee of the Haradoi Hospital approved this study (2015-01). Written informed consent was waived, because the data were collected from the electronic record health system and the study was not beyond the scope of routine medical care. Additionally, the patient burden was very low.

Measurements. The PPI use group was defined from admission to the evaluation point, with the start and finish of therapy in the hospital. PPI therapy start was defined as after the conclusion of the adaptation period. The PPI non-use group was defined as those with no PPI therapy. Nutrition status was evaluated using the mini nutritional assessment short-form (MNA-SF) (*18–20*) at the time of evaluation point. The MNA-SF includes six questions regarding decreased food intake, weight loss, mobility, psychological stress or acute disease, neuropsychological issues and body mass index (BMI). Patients with MNA-SF scores of 7 points or less were considered malnourished, scores of 8–11 were at risk of malnutrition, and scores of more than 12 points were considered as having a normal nutritional status.

Age, gender, body height, body weight, BMI, laboratory data (serum albumin, hemoglobin), hospitalization, administration route, dysphagia, and activities of daily living (ADLs), as well as number of drugs and current medical history were evaluated at the time of evaluation point.

Dietary intake routes were classified as oral, gastric fistula, oral and gastric fistula, nasal tube administration, or intravenous nutrition. Dysphagia was evaluated using the functional oral intake scale (FOIS) (*21*). FOIS was used to characterize the level of the patient's oral intake. ADLs were assessed by the functional independent measurement (FIM) (*22*), which measures patient mobility, cognitive capabilities, and daily living independence.

Statistical methods. Parametric data were reported as the mean±SD, whereas nonparametric data were

Table 2. Results of logistic regression analysis for the presence or absence of malnutrition.

	Regression coefficient	Odds ratio	95% Confidence interval		*p*-value
Age (1 y)	0.024	1.024	0.983	1.068	0.251
Gender (female)	−0.621	0.537	0.235	1.227	0.140
Serum albumin (1 g/dL)	−1.548	0.213	0.107	0.424	<0.001
Duration of PPI therapy	−0.006	0.994	0.990	0.999	0.011

Dependent variable=0 for no malnutrition, =1 for malnutrition.
Gender=0 for males, =1 for females.
Lower serum albumin level and shorter PPI therapy was independently associated with malnutrition.

expressed as the median and interquartile range. The chi-square test, *t*-test, and Mann-Whitney *U* test were used to analyze the differences between the two groups stratified by PPI use and non-use. The chi-square test was used to analyze the differences between PPI use and non-use regarding malnutrition. An MNA-SF score of 7 points or lower was defined as malnutrition. Logistic regression analysis was used to examine whether the period of PPI therapy was associated independently with malnutrition following adjustment for covariates including gender, age, and serum albumin level. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) version 11 software (IBM Corporation; Armonk, NY). A p-value <0.05 was considered significant.

RESULTS

During the research period, 326 patients were hospitalized in the long-term care, convalescence rehabilitation, and community integrated care wards. Fourteen patients under 65-y-old, 31 patients with acute-illness, 9 patients with adaptation disease, 21 patients with intravenous nutrition only, 26 patients with missing data, and 35 patients in whom it was impossible to measure ADLs at the rehabilitation start time and evaluation were excluded. The remaining 190 patients were included in the study.

Table 1 summarizes the characteristics of the PPI use group and PPI non-use group. Forty-one patients were male (22%) and 149 patients were female (78%), with a mean age of 85.4±8.4. Current medical histories included orthopedic diseases (25%), pneumonia (15%), cerebrovascular diseases (14%), dementia (7%) and malignancy (3%). In the history of present pneumonia, 5 and 8 cases were aspiration pneumonia in the PPI use and non-use groups, respectively. The median prescription period was 91 d, ranging from 51 to 227 d. About half of the PPI use group was taking Lansoprazole.

The MNA-SF scores were not significantly different between the PPI use group and PPI non-use group according to the chi-square test ($p=0.172$, Table 1). The median MNA-SF scores in the PPI and non-PPI groups were 9 vs 7 points, respectively. The PPI non-use group was lower than the PPI use group, as measured by the FOIS.

Table 2 shows the results of logistic regression analysis. Using an MNA-SF score of 7 points or lower as the independent variable, logistic regression analysis of each variable, adjusted for the period of PPI therapy, gender, and serum albumin level showed that long-term PPI therapy (odds ratio [OR], 0.994; 95% confidence interval [CI], 0.990–0.999) and serum albumin levels (OR, 0.213; 95% CI, 0.107–0.424) were significantly associated with nutritional status. Patients with longer-term PPI therapy had an improved nutritional status.

DISCUSSION

In this study we carried out a clinical observation of PPI therapy and malnutrition in elderly hospitalized patients. First, the presence or absence of PPI therapy was not associated with malnutrition. Second, longer-term PPI therapy was independently associated with improved nutritional status.

The presence or absence of PPI therapy was not associated with malnutrition. Most PPI therapy was not high dose or maintenance dose. There was almost no active gastroenterological indication. PPI therapy was administered to 28% of the patients, who were aged 65-y and older, with a potentially less favorable side-effect profile (*23*) and low BMI. The number of female patients was higher than male patients, as with PPI therapy. Our results differed from a previous study in which patients had higher BMIs and there was a higher number of men than women (*16*). Although, there was no difference in daily intake, FOIS and FIM were significantly different between the presence and absence of PPI therapy. Furthermore, the FOIS and FIM scores were lower for patients in the absence of PPI therapy than with PPI therapy. The reason that the MNA-SF did not show a significant difference between the absence and presence of PPI therapy may be related to low ADL, difficulty swallowing and malnutrition (*24*).

In this study, the most common medical history was orthopedic disorders. In patients before hip fracture, 17% were malnourished and 38% were at risk of malnutrition (*25*). Malnutrition has an increased chance of developing from hip fracture (*26*), dementia (*27*) and malignancy (*28*). Patients with orthopedic disorders and hip fractures tended to have a high prevalence of oropharyngeal dysphagia (*29*). Oropharyngeal dysphagia may be related to the presence of neurological disorders, respiratory co-morbidities, postoperative delirium,

residential aged care facility, and increasing age. Furthermore, dysphagia with dementia is associated with functional independence and malnutrition (*30*). The above findings demonstrate that the presence or absence of PPI therapy may be not associated with malnutrition.

Longer-term PPI therapy was independently associated with improved nutritional status. Thus, long-term PPI therapy does not lead to malnutrition. In a previous study, body weight remained unchanged for 1 y (*17*). The median duration of PPI therapy was about 3 mo in our study. We did not exclude patients with uneroded gastroesophageal reflux disease or recurrent suppression of gastric or duodenal ulcer from low-dose aspirin usage in the study. This may have affected the association between about 3 mo of PPI therapy and nutritional status. There were patients with orthopedic diseases (25%), pneumonia (15%) and cerebrovascular diseases (14%) in our study. PPI therapy was prescribed predominantly due to use of NSAIDs and low-dose aspirin. GERD increases the risk of aspiration pneumonia, and acid hypersecretion risk increases with age. Risk of GERD and gastric ulcer by NSAIDs was likely reduced by administration of PPI. Therefore, GERD and gastric ulcer prevention rather than nutrient malabsorption, such as vitamin B_{12}, may affect nutrition status improvement.

As serum albumin levels were independently associated with improved nutritional status, they may a nutritional marker in patients without infection. On the other hand, in patients with marked infection, serum albumin levels are not a suitable nutritional marker, because serum albumin decreases with infection (*31*, *32*).

This study had a few limitations. Firstly, the study was cross-sectional so the causal relationship between PPI therapy and malnutrition was not clear. Secondly, the sampling method was not random. Thirdly, The MNA-SF showed high sensitivity and low specificity in older people at a geriatric care hospital (*33*). However, the MNA-SF was a useful nutritional assessment tool in the elderly (*34*), and was used to establish two categories of the MNA-SF score (0–7 and 8–14: malnourished or not) (*35*). Fourth, differences in diseases and comorbidities with medication were not considered. Further studies should compare nutritional status with the stopping or continuation of inappropriate PPI therapy at admission.

In conclusion, the presence or absence of PPI therapy is not associated with malnutrition. Longer-term PPI therapy is independently associated with improved nutritional status. Longer-term PPI therapy may also affect nutritional status.

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