Table 2 Bivariate relationships between BMI and HRQOL by age, gender and chronic disease

		BMI categories				*Differences between BMI categories*[a]			*Overall P*
		UW −18.4	*NW 18.5−*	*OW 25−*	*OB 30−*	*UW − NW*	*OW − NW*	*OB − NW*	
Age									
18–44	PCS	49.9	50.1	50.0	48.4	−0.2	−0.1	−1.7	0.62
	MCS	46.0	47.1	47.6	47.7	−1.1	0.5	0.6	0.18
45–64	PCS	47.9	49.6	47.9	51.1	−1.7	−1.7	1.5	0.04
	MCS	47.3	48.6	49.5	40.6	−1.3	0.9	−8.0[b]	<0.001
65−	PCS	41.5	45.6	43.4	38.1	−4.1	−2.2	−7.5	0.003
	MCS	47.2	50.2	48.9	50.7	−3.0	−1.3	0.5	0.07
Gender									
Male	PCS	48.5	49.5	49.2	49.7	−1.0	−0.3	0.2	0.75
	MCS	47.0	48.5	48.4	44.5	−1.5	−0.1	−4.0	0.08
Female	PCS	48.5	48.9	45.1	46.3	−0.3	−3.7[b]	−2.6	<0.001
	MCS	46.2	47.8	48.8	47.4	−1.6[b]	1.0	−0.4	0.01
Chronic disease[c]									
Healthy	PCS	50.7	51.5	50.9	51.3	−0.8	−0.6	−0.2	0.53
	MCS	47.7	48.8	48.9	46.4	−1.1	0.1	−2.4	0.32
Ill	PCS	47.5	47.8	46.6	46.2	−0.3	−1.2	−1.6	0.07
	MCS	45.8	47.7	48.4	46.3	−1.9[b]	0.7	−1.4	0.003

UN, underweight (BMI < 18.5); NW, normal weight (18.5 ≤ BMI < 25) (reference); OW, overweight (25 ≤ BMI < 30); OB, obese (BMI ≥ 30); PCS, physical component summary; MCS, mental component summary.

[a]Cell numbers represent the difference between the group in that column and the normal weight (reference) group.

[b]Indicates significance at $P < 0.05$.

[c]Healthy represents individuals with no chronic disease; ill represents individuals with ≥1 chronic disease.

between physical and mental HRQOL and BMI by modeling the impact of sex, age, income, chronic diseases and education (Table 3). Thus, it seems that the optimal BMI is discrepant between physical and mental HRQOL domains.

Although many studies have reported the effect sizes of SF-6D, SF-12 and SF-36, less is known about effect sizes of SF-8.[15,34] It is known that the SF-36, SF-12 and SF-8 were constructed in the same framework, but the SF-8 is shorter than the SF-36.[29,35] Our previous study showed that SF-8 more effectively recognizes people with relatively poor HRQOL compared with those with relatively better HRQOL.[30] As the present study examined the general population, which is relatively healthy, the possibility exists that the SF-8 possesses less power in examining the relationship between BMI and HRQOL across the Japanese populace.

This is the first study to examine the relationship between self-reported BMI and HRQOL in a relatively large Japanese general population. The obligatory medical examination in Japan, which was implemented for all Japanese citizens aged 40–74 years in 2008, increased public concern over metabolic syndrome and excess weight.[18] It is important to generate the epidemiologic data of BMI and HRQOL from the viewpoint of public health, as it is necessary to examine how interventional examinations affect HRQOL. If being overweight correlates with impaired physical HRQOL as we showed, this examination could improve physical HRQOL. Moreover, our principal finding of a disjunction between physical and mental HRQOL in overweight people may have important public health implications. The fact that moderately overweight individuals do not have impaired mental HRQOL may prevent them from striving towards weight loss. A stable mental HRQOL in the face of rising weight challenges public health officials during interventions such as diet control and weight reduction programs, and should be incorporated into future strategies.

In conclusion, our results suggest that being either underweight or overweight correlates with an impaired physical HRQOL in Japan. However, while being underweight or obese seems to lead to impaired mental HRQOL, being overweight does not. As these differences were relatively

Table 3 Multivariable relationships between BMI as categorical variables and HRQOL ($n = 2399$)

	Coefficient (95% CI)			
	Underweight	*Normal weight (ref)*	*Overweight*	*Obesity*
PCS				
Model 1	−0.6 (−1.6, 0.4)	0	−1.3 (−2.1, −0.5)	−1.6 (−3.8, 0.6)
Model 2	−1.2 (−2.2, −0.2)	0	−1.1 (−1.9, −0.3)	−1.5 (−3.6, 0.6)
Model 3	−1.0 (−2.0, −0.04)	0	−1.0 (−1.7, −0.2)	−1.3 (−3.3, 0.8)
MCS				
Model 1	−1.7 (−2.7, −0.8)	0	0.4 (−0.3, 1.2)	−1.8 (−3.9, 0.4)
Model 2	−1.2 (−2.1, −0.2)	0	0.07 (−0.7, 0.9)	−1.7 (−3.8, 0.4)
Model 3	−1.0 (−2.0, −0.03)	0	0.2 (−0.6, 0.9)	−1.5 (−3.6, 0.6)

Underweight (BMI < 18.5); Normal weight (18.5 ≤ BMI < 25) (reference); Overweight (25 ≤ BMI < 30); Obese (BMI ≥ 30); PCS, physical component summary; MCS, mental component summary.
Model 1: unadjusted; Model 2: adjusted by sex, age, sex × age; Model 3: adjusted by sex, age, sex × age, chronic diseases.

Table 4 Multivariable relationships between BMI as continuous variables and HRQOL among participants who were normal weight, overweight or obese ($n = 2197$)

	Coefficient (95% CI)
PCS	
Model 1	−0.1 (−0.2, −0.02)
Model 2	−0.06 (−0.1, 0.01)
Model 3	−0.05 (−0.1, 0.02)
MCS	
Model 1	0.04 (−0.03, 0.1)
Model 2	0.002 (−0.07, 0.07)
Model 3	0.007 (−0.06, 0.07)

See Table 3.

small, the disjunction between physical and mental HRQOL in moderately overweight people should be confirmed by future studies.

Limitations of this study

We recognize several limitations of this study. First, participants were based on a nationally representative random sample and their demographic characteristics were similar to those obtained in the national census in Japan,[23] but the initial response rate from households agreeing to participate was low (34.5%). As participants might be more likely to represent those who are health conscious and having the time to fill out the diary, selection bias may have affected our results.

Second, weight and height were self-reported in this study, allowing for possible misclassification. Compared to the National Health and Nutrition Survey, the proportion of overweight and obese females in this study (10.7%) was much lower than that reported by the National Health and Nutrition Survey (20.6%). This is consistent with previous studies which show that overweight and obese people are more likely to under-report their weights and over-report their height.[17,36,37] However, self-reports for height and weight are generally known to be accurate, and self-reported BMI was shown to be highly correlated with direct measurements of BMI.[3,17] Hence, self-reported height and weight data are valid for identifying relationships in epidemiologic studies.[38] As overweight participants were likely to underestimate their weight, misclassification likely underestimated the association of BMI with HRQOL in the present study.[13] In order to address misclassification, we developed regression models that used BMI as a continuous exposure variable. The results obtained from these were consistent with those from regression models that use BMI as a categorical variable.

Third, as a general limitation of observational studies, the cross-sectional design limits conclusions regarding causal relationships between excess weight and HRQOL.

Finally, the present study used the SF-8 to evaluate HRQOL. As HRQOL differences in the present study were small, this may not be clinically important. However, being underweight, overweight or obese are very common issues, and thus small differences may be important at the population level.[13] Although the short length of the SF-8 provides a useful alternative to facilitate responder cooperation, little is known about effect sizes and the threshold for clinical importance for the SF-8. The present work may serve as a reference for future studies of clinically important differences in HRQOL.

Author contributions

Y.T. performed the data analysis and drafted the manuscript. M.S. and T.N. provided valuable advice regarding data analysis and manuscript preparation. Y.T., O.T., S.O. and S.F. designed the protocol and participated in data collection. T.F. conceived the study, designed the protocol and supervised the cohort study. T.S. also supervised the preparation of the manuscript.

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Original article

Histological features of nodular gastritis and its endoscopic classification

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OBJECTIVES: To clarify the histological features and endoscopic classifications of nodular gastritis (NG).

METHODS: Overall 40 996 patients who had undergone an upper gastrointestinal endoscopy were enrolled. NG is defined as a uniform and diffuse protrusion from the antrum to angulus, which has two types at endoscopy: nodular (N) and granular (G). Three biopsy specimens were taken from the antrum, angulus and corpus. The histological features were evaluated using the updated Sydney System (USS). The topography of gastritis (antrum-predominant, pangastritis or corpus-predominant) and the prevalence of lymphoid follicles were also investigated.

RESULTS: Overall 89 patients (0.22%) were diagnosed with NG, which tended to decrease in prevalence over age and predominantly affected women. All the patients were *Helicobacter pylori*-positive. Among these, 65 patients underwent biopsy. Activity and inflammation were mostly moderate or severe, while intestinal metaplasia and atrophy were mostly absent at all three sites. Pangastritis was the most frequent (72%) type of gastritis. Lymphoid follicles were found in 69% at the antrum, 65% at the angulus and 51% at the corpus. There were no significant differences between N and G types in clinical features, USS scores, topography of gastritis, and prevalence of lymphoid follicles.

CONCLUSIONS: Atrophy and intestinal metaplasia are rare but activity and chronic inflammation are severe at the antrum, angulus and corpus in NG. Pangastritis is the commonest type of gastritis. Lymphoid follicles affect everything up to the upper corpus, contrary to endoscopic protrusion found only at angulus. There was no correlation with pathological features between N and G types.

KEY WORDS: *Helicobacter pylori*, histological feature, lymphoid follicle, nodular gastritis, updated Sydney System.

INTRODUCTION

Endoscopically nodular gastritis (NG) is characterized by a unique protruding pattern from gastric antrum to gastric angle.[1–4] Previous studies have reported that NG affects predominantly young women[5,6] and is accompanied by duodenal ulcers,[5–7] as well as being strongly associated with *Helicobacter pylori* (*H. pylori*)

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infection.[1,5,8] A potential correlation between NG and diffuse-type gastric cancer in young adults has recently been identified.[9–11]

The pathological findings associated with protrusions in NG are characterized by lymphoid follicles with germinal centers and infiltration of mononuclear cells.[5,12] Previous reports have indicated that patients with NG show inflammation extending beyond the antrum into the corpus.[5,13] The topography of histological gastritis in NG patients is thus likely to be pangastritis, which has rarely been demonstrated.[14] As pangastritis is considered to be a risk factor for undifferentiated gastric cancer,[15,16] identifying the topography of histological gastritis in NG patients might reveal a correlation between NG and undifferentiated gastric cancer. Although histological findings of intestinal metaplasia and atrophy are considered to be risk factors for differentiated gastric cancer, the reasons for the low frequency of these findings and poor histological scores in NG patients remain undetermined.

An endoscopic examination of NG shows the extension of protrusions up to the gastric angle. Identifying the extent of inflammation around the gastric angle and presence of atrophy or intestinal metaplasia, or both, is therefore essential for elucidating the pathogenesis of NG. However, no studies focused on NG patients have yet examined the biopsy specimens obtained from tissue around the gastric angle. Moreover, only a limited number of cases of NG have been examined in previous pathological studies. In this study, patients who had received a biopsy at three sites, including the gastric angle, were subjected to gastritis assessment on the basis of the updated Sydney System (USS) and the type of histological gastritis and frequency of lymphoid follicles was identified. In addition, as NG can be endoscopically categorized into two types,[5] the differences in the histopathological findings between these two types were also examined.

MATERIALS AND METHODS

Patients

We studied 40 996 patients who underwent upper gastrointestinal (GI) endoscopy at the National Center for Global Health and Medicine from August 2003 to December 2009. Patients taking an H_2-receptor blocker or proton pump inhibitor (PPI) during the 4 weeks prior to the endoscopic examination were excluded, together with those with a history of gastric surgery or *H. pylori* eradication therapy. This study was conducted in accordance with the Declaration of Helsinki and the requirements of the Ethics Committee of the National Center for Global Health and Medicine (Tokyo, Japan).

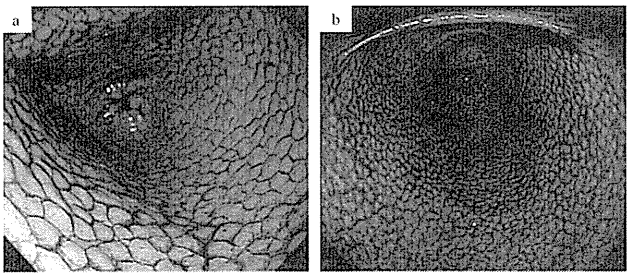

Figure 1. Endoscopic features of (a) nodular type: uniform protrusions ≥5 mm in diameter and (b) granular type of nodular gastritis: uniform protrusions <5 mm in diameter.

Endoscopic assessment

All the endoscopies had been performed by well-trained endoscopists using a Q240 or Q260H videoendoscope (Olympus, Tokyo, Japan). We defined NG as uniform and diffuse protrusion at sites from the gastric antrum to the angulus. Moreover, NG was divided into nodular (N) or granular (G) types on the basis of endoscopic appearance and assessed according to the size of elevated nodular lesions at the antrum (Fig. 1a, b), as previously reported.[5]

Histological assessment

The biopsied specimens were taken from each of the three sites in the stomach: the greater curvature of the antrum, the angulus on the lesser curvature and the greater curvature of the gastric body (Fig. 2). The specimens were fixed in formalin and stained with hematoxylin–eosin and toluidine blue. A score of 0–3 (0, absent; 1, mild; 2, moderate; 3, severe), according to USS scores, was assigned for the following parameters: activity (granulocytic infiltration), inflammation (lymphocytic and plasma cell infiltration), intestinal metaplasia and glandular atrophy.[17] The presence of lymphoid follicles was also evaluated (Fig. 3). The topography of gastritis was classified into three categories as antrum-predominant gastritis, pangastritis and corpus-predominant gastritis according to the activity score, as previously reported.[16] The histological grading was evaluated by one pathologist who was blinded to clinical information and endoscopic findings.

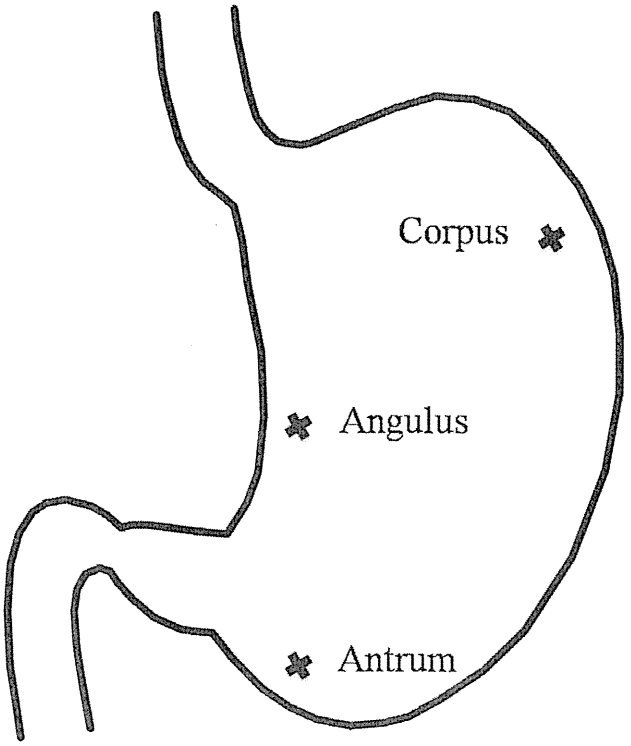

Figure 2. Biopsy sites. One specimen each was taken from the greater curvature of the antrum (antrum), the angulus on the lesser curvature (angulus) and the greater curvature of the gastric body (corpus). Histological grading (activity, inflammation, intestinal metaplasia, glandular atrophy) was evaluated according to the updated Sydney System.

Assessment of *H. pylori* infection

H. pylori infection was evaluated based on the presence of immunoglobulin G antibodies against *H. pylori*, the ^{13}C urea breath test, the rapid urease test or the histological examination. If the result of any of these four methods was positive, *H. pylori* infection was considered to exist.

Statistical analysis

All statistical analyses were performed using Stata version 10 (StataCorp, Lakeway Drive College Station, TX, USA). Relevant data on the prevalence of NG were summarized for every decade of the patients' age. Changes in prevalence between each age group were analyzed using χ^2 test for trends. The χ^2 test was also used to compare the prevalence between genders. NG patients were divided into two groups (N and G types) on the basis of endoscopic appearance, and patients' characteristics were then examined to identify differences between these groups. Fisher's exact probability test was used to compare gender ratio and the prevalence of dyspeptic symptoms. Student's *t*-test was used to compare the patients' age between groups. To evaluate the histological features of NG, we investigated the percentage of activity, inflammation, intestinal metaplasia and atrophy according to USS scores. Moreover, to analyze the differences between groups, the nonparametric Mann–Whitney *U*-test was used for USS scores and Fisher's exact probability test was used for the prevalence of lymphoid follicles and topography of gastritis. A *P* value less than 0.05 were considered statistically significant.

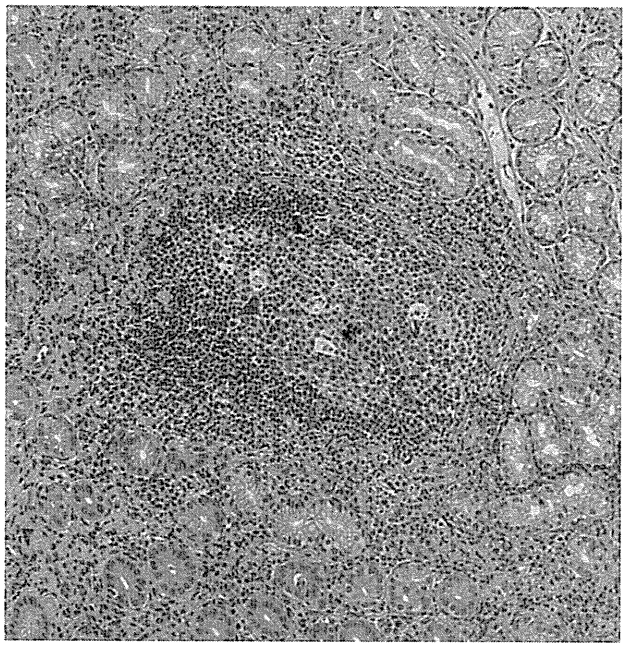

Figure 3. Histological finding of lymphoid follicule. Lymphoid follicle hyperplasia is seen in the lamina propria at the gastric body of greater curvature (HE staining, ×200).

RESULTS

Patients' characteristics

A total of 89 patients were diagnosed as having NG. The prevalence of NG in adults who had undergone an endoscopy was 0.22% (Fig. 4). The prevalence of NG tended to decrease with the increase of patients' age: <20 years, 5.9%; 20–29 years, 3.0%; 30–39 years, 1.3%; 40–49 years, 0.32%; 50–59 years, 0.16%; 60–69 years, 0.043%; ≥70 years, 0.019% ($P < 0.001$). In comparison, NG was more frequently found in women (women, 71/16 662; men, 18/24 334; $P < 0.001$). Overall 54 patients were diagnosed with N-type NG and 35 were diagnosed with G-type NG.

The patients' characteristics are shown in Table 1. All the patients examined showed positive results for the presence of *H. pylori* infection. Dyspeptic symptoms such as abdominal pain and abdominal discomfort were seen in 49 of the 89 patients (55%) with NG. Associated lesions in the upper digestive tract included duodenal ulcer in 15 patients, gastric ulcer in 3 patients and gastric cancer in one patient. Gastroesophageal reflux disease was seen in one of the 89 patients. Patients' characteristics did not differ significantly between N and G types.

Histological features

Of the 89 patients with NG, 65 (N type, $n = 40$; G type, $n = 25$) had a biopsy. The histological results are shown in Table 2. Scores for activity and inflammation were mostly moderate or severe at all three sites. Scores for intestinal metaplasia and atrophy, however, were mostly absent or mild at all three sites. The histological scores for activity, inflammation, intestinal metaplasia and atrophy did not differ significantly between N and G types at any of the three sites (Table 3).

The prevalence of lymphoid follicles was 69% at the antrum, 65% at the angulus and 51% at the corpus. No significant difference in the prevalence of lymphoid follicles was seen between these types (Table 4). With respect to the topography of gastritis 14% were antrum-predominant, 72% were of pangastritis and 14% were corpus-predominant. No significant differences in the topography of gastritis were identified between the N and G types (Fig. 5).

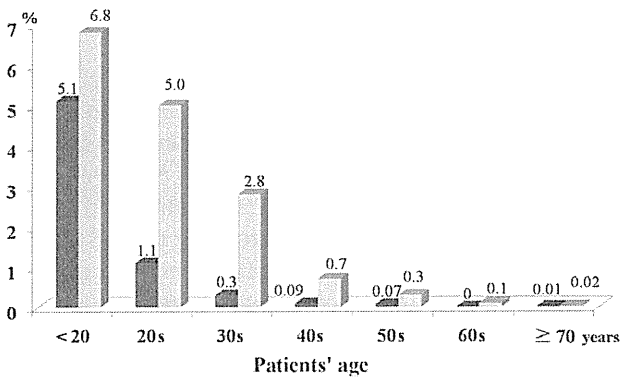

Figure 4. Prevalence of (■) male and (▒) female patients with nodular gastritis by age.

DISCUSSION

The clinical findings related to NG in this study included duodenal ulcers and *H. pylori* infection

Table 2. The updated Sydney System score of nodular gastritis ($N = 65$)

	0	1	2	3
Antrum score (%)				
Activity	3	9	**84**	4
Inflammation	0	2	14	**84**
Intestinal metaplasia	**97**	3	0	0
Atrophy	**45**	28	3	0
Angulus score (%)				
Activity	6	8	**86**	0
Inflammation	0	3	22	**75**
Intestinal metaplasia	**93**	2	3	2
Atrophy	**38**	38	10	2
Corpus score (%)				
Activity	8	6	**77**	7
Inflammation	2	11	32	**55**
Intestinal metaplasia	**100**	0	0	0
Atrophy	**68**	23	4	0

Text in bold shows the highest score in each measurement.

Table 1. Patients' characteristics

	Nodular gastritis ($N = 89$)	Nodular type ($N = 54$)	Granular type ($N = 35$)	*P*
Age (years, mean ± SD)	37.2 ± 14.5	35.6 ± 14.1	39.6 ± 14.9	0.21*
Gender (n, M/F)	18/71	8/46	10/25	0.18**
Dyspeptic symptoms (n)	49	31	18	0.66**
Helicobacter pylori infection (n)	89	54	35	
Complications (n)				
Duodenal ulcer	15	9	6	
Gastric ulcer	3	1	2	
Gastric cancer	1	0	1	
Gastroesophageal reflux disease	1	1	0	

*Student's *t*-test, **χ^2 test. SD, standard deviation; M/F, male/female.

Table 3. Comparison of updated Sydney System scores in the two types of nodular gastritis

	Nodular type, $n = 40$				Granular type, $n = 25$				P*
	0	1	2	3	0	1	2	3	
				Antrum score (%)					
Activity	5	5	**87**	3	0	16	**80**	4	0.69
Inflammation	0	3	15	**82**	0	0	12	**88**	0.71
Intestinal metaplasia	**97**	3	0	0	**96**	4	0	0	0.75
Atrophy	**45**	20	3	0	**44**	40	4	0	0.22
				Angulus score (%)					
Activity	8	5	**87**	0	4	13	**83**	0	0.66
Inflammation	0	3	25	**72**	0	4	18	**78**	0.81
Intestinal metaplasia	**94**	0	3	3	**96**	4	0	0	0.29
Atrophy	**43**	35	13	3	30	**52**	4	0	0.84
				Corpus score (%)					
Activity	10	8	**80**	2	4	4	**76**	16	0.10
Inflammation	3	8	37	**52**	0	4	24	**72**	0.13
Intestinal metaplasia	**100**	0	0	0	**100**	0	0	0	
Atrophy	**63**	23	6	0	**76**	24	0	0	0.55

*Mann–Whitney *U* test.
Text in bold shows the highest score in each measurement.

Table 4. Prevalence of lymphoid follicles at the three sites in the stomach

	All cases ($n = 65$) (%)	Nodular type ($n = 40$) (%)	Granular type ($n = 25$) (%)	P (χ^2 test)
Antrum	69	75	56	0.10
Angulus	65	65	64	1.00
Corpus	51	48	56	0.80

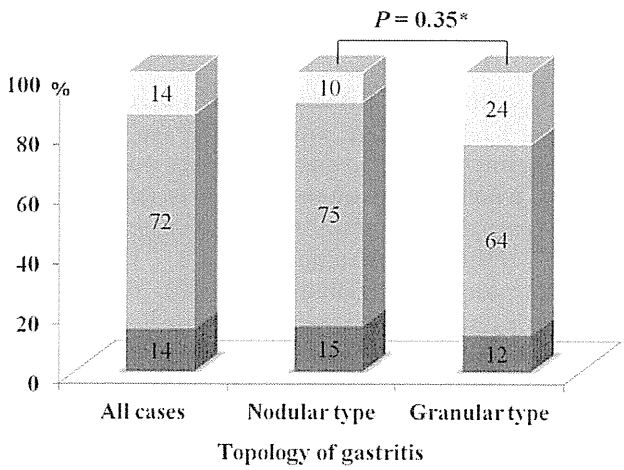

Figure 5. Prevalence of ( ) corpus-predominant gastritis, (▒) pangastritis and (■) antrum-predominant gastritis histological topography.* χ^2 test.

(especially in young women). These findings are consistent, while less common, with results from previous studies.[5,6] Dyspeptic symptoms were observed in more than half of the patients in this study.

Several reports have described the histological features of NG.[5,13,14,18–21] In the present study, a histological assessment was conducted in the gastric mucosa, including not only the corpus and the antrum but also the angulus, as intestinal metaplasia is thought to originate from the gastric angulus.[22] We found that NG patients rarely showed atrophy or intestinal metaplasia, which were related to the development of differentiated gastric cancer. Although identifiable protrusions were found only in the area ranging from the gastric antrum to the angulus under the endoscopy, scores for neutrophilic and lymphocytic infiltration were high at all three sites of the gastric mucosa. The commonest topography of gastritis was pangastritis, which has been considered as the risk factor for undifferentiated gastric cancer.[16] In the present study, one NG patient was suffering from undifferentiated gastric cancer in the histology.

We examined the prevalence of lymphoid follicles in the area extending from the gastric antrum to the corpus. The prevalence of lymphoid follicles was more than 50% at all three sites. In the present study, biopsies at protrusions were not intentionally targeted but a novel finding was revealed in this regard: the

lymphoid follicles were not present at the sites of endoscopically identifiable protrusions. Patients with endoscopically diagnosed NG showed protrusions in areas ranging from the gastric antrum to the gastric angulus, but histological features of NG were observed in areas extending from the antrum to the corpus.

In previous study, NG was divided into N and G types on the basis of protrusions appearance.[5] However, the clinical and histological features of these types have not yet been established. Our study found no significant differences between N and G types in clinical characteristics and histological scores. The most prevalent topographic gastritis was pangastritis in both types, with no significant difference between them. A recent study classified NG into diffuse and non-diffuse types, according to the mode of distribution of the protrusions[13] and revealed that non-diffuse-type NG exhibited a significantly higher score for histological atrophy than that in the diffuse type. We defined NG as having uniform, diffuse protrusions on endoscopy. We thus believe that none of our patients had non-diffuse-type NG, as reported elsewhere.

Some limitations of this study should be noted. First, this was a retrospective, single-center study. Second, the assessment of endoscopic findings was based on images, which might cause some bias. Nonetheless, as endoscopically identifiable protrusions of the gastric antrum including erosions, hyperplastic polyps, mucosa-associated lymphoid tissue lymphoma, intestinal metaplasia and other lesions,[23–25] it was considered possible that the patients included in this study could have any of these lesions. Endoscopic NG were therefore assessed and judged by well-trained endoscopists.

In conclusion, the histological examination of NG reveals that activity and chronic inflammation affect not only the gastric antrum but also the gastric angle and upper corpus. Conversely, atrophy and intestinal metaplasia, the risk factors for differentiated gastric cancer, were rarely observed. Classifying endoscopic NG on the basis of the size of protrusions might not be clinically relevant.

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BRIEF ARTICLE

Diagnostic value of antigenemia assay for cytomegalovirus gastrointestinal disease in immunocompromised patients

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Abstract

AIM: To investigate the utility of the cytomegalovirus (CMV) antigenemia assay for the diagnosis of CMV gastrointestinal disease (GID).

METHODS: One hundred and thirty immunocompromised patients were enrolled in this study. Patients with a history of anti-CMV treatment and who had not undergone examination using the antigenemia assay were excluded. CMV-GID was defined as the detection of large cells with intranuclear inclusions alone or associated with granular cytoplasmic inclusions by biopsy. Biopsy sections were stained with hematoxylin and eosin and immunohistochemically stained with anti-CMV. We evaluated the association between CMV-GID and patient characteristics (symptoms, underlying disease, medication, leukocyte counts, and antigenemia assay). All patients were checked with an human immunodeficiency virus (HIV) antibody test before endoscopic examination. White blood cell (WBC) counts were obtained from medical records within 1 wk of endoscopy. Leukopenia was defined as a total WBC count < 5000 cells/mm^3. For HIV patients, we also checked CD4+ counts from medical records.

RESULTS: A total of 99 patients were retrospectively selected for analysis. Of the immunocompromised patients, 19 had malignant disease, 18 had autoimmune disease, 19 had disorders of biochemical homeostasis, three had undergone transplantation, and 45 had HIV infection. A total of 50 patients had received immunosuppressive therapy. No patients had inflammatory bowel disease. Fifty-five patients were diagnosed as having CMV-GID. Univariate analysis indicated an association between HIV infection, leukopenia, and positive antigenemia and CMV-GID ($P < 0.05$). Multivariate analysis using logistic regression revealed that HIV infection and positive antigenemia were the only independent factors related to CMV-GID ($P < 0.01$). The sensitivity, specificity, positive predictive value, and negative predictive value of antigenemia for CMV-GID were 65.4%, 93.6%, 91.9%, and 71.0%, respectively. In a subgroup analy-

sis, patients with leukopenia displayed low sensitivity and high specificity. Minimal differences in accuracy were seen among patients with or without leukopenia. HIV-infected patients displayed low sensitivity and high specificity. Accuracy barely differed between HIV-positive and -negative patients. In HIV-infected patients, CD4 count < 50 cells/μL resulted in low sensitivity and high specificity. Differences in accuracy among patients were minor, regardless of CD4 count. In patients who had undergone both quantitative real-time polymerase chain reaction (PCR) and antigenemia assay, real-time PCR was slightly more accurate in terms of sensitivity than the antigenemia assay; however, this difference was not statistically significant (P = 0.312).

CONCLUSION: If the antigenemia test is positive, endoscopic lesions are acceptable for the diagnosis of CMV-GID without biopsy. The accuracy is not affected by HIV infection and leukopenia. Either PCR or the antigenemia assay are valid.

Key words: Cytomegalovirus; Gastrointestinal disease; Antigenemia assay; Real-time polymerase chain reaction; Human immunodeficiency virus infection

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INTRODUCTION

As the number of patients with immune deficiency has been increasing dramatically in recent years, the number of patients with cytomegalovirus (CMV) disease has also been increasing. CMV gastrointestinal disease (CMV-GID) frequently occurs in immunocompromised patients, particularly among those with human immunodeficiency virus (HIV) infection, transplantation, autoimmune diseases, or secondary immunodeficiency[1-8]. CMV-GID has also been described following the use of steroids, immunosuppressants, or cancer chemotherapy[1,2]. In immunocompromised patients, CMV-GID in the absence of therapy is a major cause of morbidity and mortality due to events such as massive bleeding or perforation. Therefore, diagnosis at an early stage is essential[1,2,9-12]. However, diagnosis of this infection is difficult because of wide variations in symptoms and endoscopic features depending on the infected organs[1,2].

Although the utility of various diagnostic tests for CMV-GID has been reported, the best approach is to conform the presence of CMV by histological analysis, including immunological staining by endoscopy[1-3,5,13,14]. Endoscopic examination is generally tolerated, but tissue biopsy can possibly lead to hemorrhage or perforation after endoscopic examination[10,11,15]. Endoscopists therefore hesitate to perform biopsy when deep, large, and bleeding ulcerous lesions are encountered. Patients receiving antithrombotic drugs or with thrombocytopenia also require careful consideration before biopsy.

On many occasions in recent years, noninvasive methods such as the CMV blood antigenemia assay have been applied instead of biopsy to avoid adverse effects[3,16-22]. However, few reports have examined the diagnostic value of the CMV antigenemia assay for CMV-GID, and the clinical utility of this method in immunodeficiency remains unclear[3,20-22]. Moreover, the CMV antigenemia assay requires sufficient granulocytes, and leukopenia and low CD4+ counts in patients with HIV infection could thus be expected to influence assay accuracy[3]. However, no reports have yet clarified this issue.

The aims of this study were to clarify the utility of the CMV antigenemia assay for diagnosing suspected CMV-GID, and to evaluate the accuracy of this assay under different clinical settings.

MATERIALS AND METHODS

Patient selection

One hundred and thirty immunocompromised patients with endoscopic findings who had undergone biopsy were enrolled in this study at the National Center for Global Health and Medicine (NCGM) from January 2002 to September 2009. Patients with a history of treatment with anti-CMV therapy were excluded, as were cases not examined using the CMV antigenemia assay test within 1 wk of endoscopy. Written informed consent was obtained from all patients prior to endoscopy and biopsy. All study protocols were approved by the ethics committee of NCGM.

Immunocompromised patients

Immunocompromised patients are associated with secondary immune deficiency, particularly HIV infection, hematopoietic stem cell transplantation, autoimmune diseases, malignancy, disorders of biochemical homeostasis, and use of steroids, immunosuppressants, or cancer chemotherapy.

Underlying autoimmune diseases included Rheumatoid arthritis, Systemic lupus erythematosis, Still's disease, Behcet's disease, Polymyositis, and Dermatomyositis. Diabetes mellitus, renal insufficiency/dialysis, and hepatic cirrhosis were included among the disorders of biochemical homeostasis. All patients were checked with an HIV antibody test before endoscopic examination.

Clinical manifestations

Gastrointestinal symptoms were collected from medical records written by the doctor who interviewed each per-

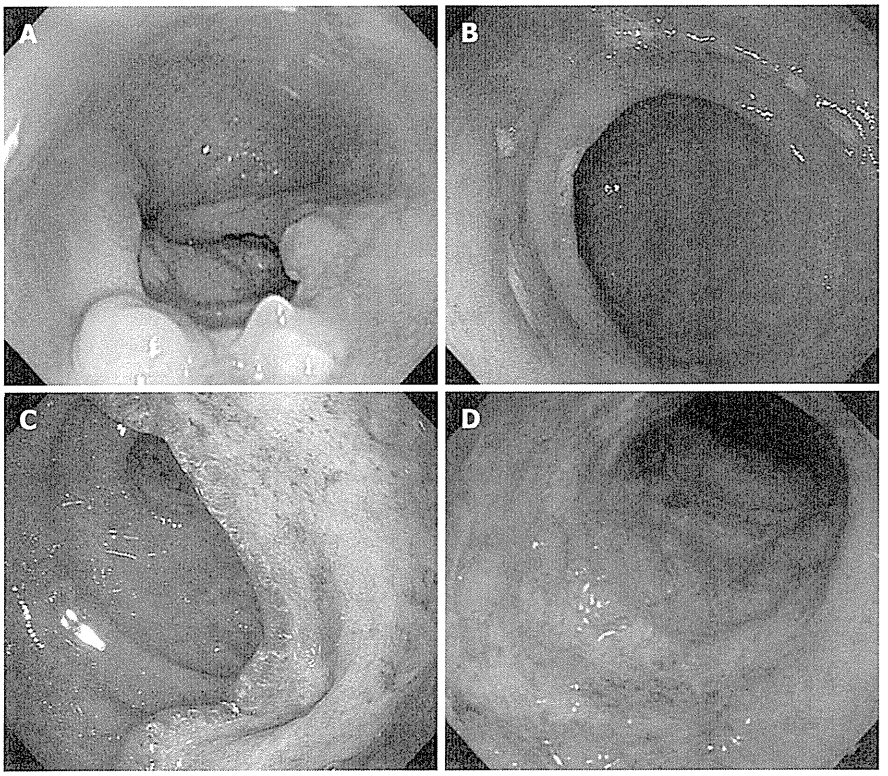

Figure 1 Endoscopic features in cytomegalovirus gastrointestinal disease. A: Deep, punched-out ulcer in the esophagus; B: Multiple, shallow ulcers in the gastric antrum; C: Large, deep ulcer in the duodenum; D: Multiple erosions and edematous mucosa with ulcer in the sigmoid colon.

son face-to-face before endoscopy. Those without records were treated as symptom free. Gastrointestinal symptoms included compromised odynophagia, epigastralgia, nausea, lower abdominal pain, diarrhea, and hematochezia. White blood cell (WBC) counts were obtained from medical records within 1 wk of endoscopy. Leukopenia was defined as a total WBC count < 5000 cells/mm^3. For HIV patients, we also checked CD4+ counts from medical records.

Antigenemia assay and quantitative real-time polymerase chain reaction

Antigenemia assay using C10/C11 monoclonal antibodies (Mitsubishi Chemical Medience, Tokyo, Japan) was performed as previously reported[16,19,20]. A positive result for the CMV antigenemia assay was defined as ⩾ 1 CMV-positive cell per 150 000 granulocytes applied.

A total of 47 patients underwent additional examination with real-time polymerase chain reaction (PCR), performed basically as previously reported[3,23,24]. The minimum detection level was 200 copies/mL of plasma. A positive result for real-time CMV PCR was defined as > 200 copies/mL.

Diagnosis of CMV-GID

CMV-GID was suspected based on endoscopic findings, such as patchy erythema, edematous mucosa, multiple erosions, and ulcers (Figure 1)[25,26]. Biopsy was therefore performed when such endoscopic findings were encountered. CMV-GID was defined as the detection of large cells with intranuclear inclusions alone or associated with granular cytoplasmic inclusions by histological testing of biopsy specimens[1]. Biopsy sections were stained with hematoxylin and eosin, and immunohistochemically stained with anti-CMV (Figure 2). The results were considered positive when the above-mentioned cells showed marked brown coloration in both nuclei and cytoplasm.

Statistical analysis

We divided patients into two groups based on the presence or absence of CMV-GID. Patient characteristics and clinical findings were then compared between groups. Fisher's exact test was used to compare frequencies for patient characteristics and clinical findings, and Mann-Whitney *U* test was used for comparing age and CD4 counts. To identify clinical factors independently associated with a diagnosis of CMV-GID, stepwise logistic regression modeling was used. Sensitivity, specificity, and positive and negative predictive values of CMV antigenemia for diagnosing CMV-GID were calculated. The difference in accuracy between CMV real-time PCR and CMV antigenemia assay was compared according to the area under the curve (AUC). Values of $P < 0.05$ were considered significant. All statistical analyses were performed using Stata software (version 10, Stata Co., USA).

RESULTS

Clinical features

We excluded 10 patients who had received anti-CMV

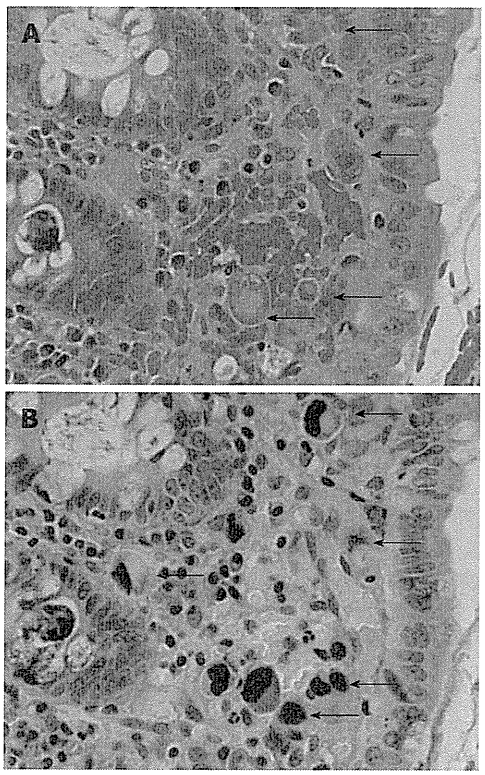

Figure 2 Pathological features in cytomegalovirus gastrointestinal disease. A: Large cells with intranuclear inclusions or associated with granular cytoplasmic inclusions (hematoxylin and eosin stain); B: Cytomegalovirus (CMV)-infected cells (arrows) show brown coloration in both nuclei and cytoplasm (immunohistochemical staining with anti-CMV).

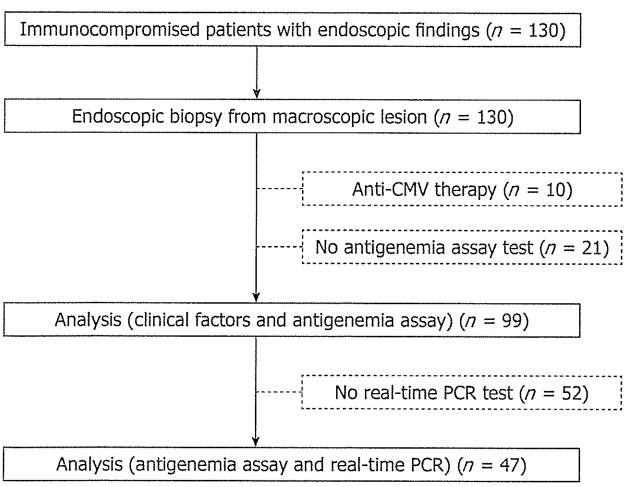

Figure 3 Study design. CMV: Cytomegalovirus; PCR: Polymerase chain reaction.

treatment, along with 21 patients who had not been examined using the CMV antigenemia assay. Thus, a total of 99 patients were retrospectively selected for analysis (Figure 3). Of the immunocompromised patients, 19 (19.1%) had malignant disease, 18 (18.1%) had autoimmune disease, 19 (19.1%) had disorders of biochemical homeostasis, three (3%) had undergone transplantation, and 45 (45.5%) had HIV infection. A total of 50 patients (50.1%) had received immunosuppressive therapy. No

Table 1 Clinical factors for cytomegalovirus gastrointestinal disease (univariate analysis)

	CMV-GID (n = 52)	Non-CMV-GID (n = 47)	P-value
Age (yr, mean ± SD)	46.8 ± 16.2	56.6 ± 17.8	0.050
Male sex	30	41	0.098
Immunodeficiency disease			
HIV infection	33	12	< 0.001
Malignancy	9	10	0.617
Solid cancer	1	3	
Hematological cancer	8	7	
Autoimmune disease	7	11	0.200
Disorders of biochemical homeostasis	8	11	0.312
Chronic renal failure	1	2	
Liver cirrhosis	0	2	
Diabetes mellitus	7	7	
Transplantation	1	2	
Immunosuppressive therapy	25	25	0.611
Steroids	22	19	
Immunosuppressants	8	4	
Chemotherapy	4	4	
Positive CMV antigenemia	34	3	< 0.001
Leukopenia	35	21	0.023
With gastrointestinal symptoms	34	34	0.456

HIV: Human immunodeficiency virus; CMV: Cytomegalovirus; GID: Gastrointestinal disease.

patients had inflammatory bowel disease (IBD). Fifty-five patients were histologically diagnosed with CMV-GID. Univariate analysis (Table 1) identified HIV infection (P < 0.001), leukopenia (P = 0.023), and positive CMV antigenemia assay (P < 0.001) as being associated with CMV-GID. Multivariate analysis revealed HIV infection [odds ratio (OR), 6.57; 95% CI: 2.1-20.2, P = 0.001] and positive CMV antigenemia assay (OR, 33.3; 95% CI: 8.1-136.2, P < 0.001) as the only factors independently correlated with CMV-GID.

HIV-infected patients included 44 men (97.8%) and their mean age was 42.1 years (range, 25-74 years). Median CD4 count was 57 (interquartile range, 17-111). Patients with CMV-GID showed significantly lower CD4 counts than those without CMV-GID (median CD4 count; CMV-GID *vs* non-CMV-GID: 24 *vs* 150, P < 0.001).

Accuracy of CMV antigenemia assay for diagnosing CMV-GID

A positive CMV antigenemia assay showed low sensitivity and high specificity (Table 2). In a subgroup analysis, patients with leukopenia displayed low sensitivity and high specificity. Minimal differences in accuracy were seen among patients with or without leukopenia. HIV-infected patients displayed low sensitivity and high specificity. Accuracy barely differed between HIV-positive and -negative patients. In HIV-infected patients, CD4 count < 50 cells/μL resulted in low sensitivity and high specificity. Differences in accuracy among patients were minor, regardless of CD4 count.

In patients who had undergone both quantitative real-

Table 2 Diagnostic accuracy of cytomegalovirus antigenemia for detecting cytomegalovirus gastrointestinal disease

Subgroups	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All patients (n = 99)	65.40% (55.4-74.9)	93.60% (87.3-97.7)	91.90% (84.7-96.4)	71.00% (60.7-79.4)
Patients with leukopenia (n = 56)	68.60% (54.0-79.7)	100% (93.6-100)	100% (93.6-100)	65.60% (52.2-78.2)
Patients without leukopenia (n = 43)	58.80% (42.1-73.0)	88.50% (74.9-96.1)	76.90% (61.4-88.2)	76.70% (61.4-88.2)
HIV-infected patients (n = 45)	63.60% (48.8-78.1)	100% (92.2-100)	100% (92.2-100)	50.00% (35.8-66.3)
Non-HIV-infected patients (n = 54)	68.40% (54.5-80.5)	91.40% (79.7-96.9)	81.30% (68.6-90.7)	84.20% (70.7-92.1)
HIV-infected patients with CD4 count < 50 (n = 22)	61.90% (40.7-82.8)	100% (84.6-100)	100% (84.6-100)	11.10% (1.12-29.2)
HIV-infected patients with CD4 count ≥ 50 (n = 23)	66.70% (42.7-83.6)	100% (85.2-100)	100% (85.2-100)	73.30% (51.6-89.8)

HIV: Human immunodeficiency virus; PPV: Positive predictive value; NPV: Negative predictive value.

Table 3 Comparison of diagnostic accuracy for detecting cytomegalovirus gastrointestinal disease between antigenemia assay and quantitative real-time polymerase chain reaction (n = 47)

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
CMV real-time PCR	73.00% (57.4-84.4)	100% (92.5-100)	100% (92.5-100)	50.00% (36.1-65.9)
CMV antigenemia assay	64.90% (50.7-79.1)	100% (92.5-100)	100% (92.5-100)	43.50% (28.3-57.8)

CMV: Cytomegalovirus; PPV: Positive predictive value; NPV: Negative predictive value; PCR: Polymerase chain reaction.

time PCR and antigenemia assay (Table 3), real-time PCR was slightly more accurate in terms of sensitivity than the antigenemia assay; however, this difference was not statistically significant (P = 0.312).

DISCUSSION

CMV-GID is a major cause of morbidity and mortality in immunocompromised patients; therefore, diagnosis at an early stage is essential[1,2,5,8,9]. However, clinical diagnosis of this disease can be difficult, as physicians need to consider various underlying diseases and clinical presentations. Patients at high risk of CMV-GID have been reported as those with HIV infection or undergoing steroid therapy or cancer therapy[1]. The present study identified HIV infection as one of the independent factors in secondary immunodeficiency diseases. This is because the number of eligible subjects was small and included immunocompromised patients while excluding immunocompetent patients.

Among the various clinical manifestations, a positive CMV antigenemia assay was found to be a useful factor for diagnosing CMV-GID. The CMV antigenemia assay is one of the most widely used methods for detecting reactivation of CMV infection, but few studies have examined the diagnostic value for CMV-GID[3,21,22]. Our findings demonstrated 65% sensitivity and 94% specificity of the CMV antigenemia assay for diagnosing CMV-GID. Mori *et al*[3] reported that only four of 19 patients (21%) developed a positive CMV antigenemia assay before developing CMV-GID; however, all 19 patients subsequently tested positive for CMV antigenemia after diagnosis of CMV-GID. There is a possibility that patients with CMV-GID will develop a positive CMV antigenemia assay at follow-up, but our study did not assess this process after diagnosis of CMV-GID. Fica *et al*[21] also reported that the CMV antigenemia assay result was positive for 18 of 31 patients (58%) with CMV end-organ disease, with CMV-GID (71%) as the most frequent cause. However, these studies were limited in that the number of subjects was small and the specificity of the CMV antigenemia assay was unknown. Jang *et al*[22] recently reported that the sensitivity and specificity of the CMV antigenemia assay for diagnosing CMV-GID were 54% and 88%, respectively, in patients with secondary immunodeficiency disease. The reports mentioned above showed that the CMV antigenemia assay has low sensitivity for the diagnosis of CMV-GID, which is consistent with our results.

It has been reported that sufficient granulocytes are essential in evaluating CMV using the antigenemia assay. Previous studies using the antigenemia assay to diagnose CMV-GID have reported that most of the patients were transplant recipients and were mostly HIV-negative[3,21,22]. No studies have compared the assay among groups of HIV-positive/-negative patients and among groups with or without leukopenia. In patients with HIV infection, most cases of CMV-GID have known to occur with CD4 counts < 50 cells/μL[2,4]. However, whether the accuracy of the antigenemia assay is affected by the immunosuppressed state has not been elucidated. We suspected that such different groups would show differences in the accuracy of CMV antigenemia assay, but found little difference. This suggests that our results are applicable to these different groups in clinical practice.

Besides the CMV antigenemia assay, quantitative real-time PCR is also used for detecting reactivation of CMV infection, and is considered more useful for predicting CMV disease than the CMV antigenemia assay[23,24]. In our study, quantitative real-time PCR and CMV antigenemia assay were performed simultaneously on 47 patients. The PCR method showed a tendency toward slightly higher sensitivity, but no significant differences were evident. In Japan, the CMV PCR method has not been widely used in

clinical practice because of the higher costs compared to the antigenemia assay. We thus do not recommend use of PCR methods in the sub-diagnosis of CMV-GID, as the antigenemia assay is just as valid.

One limitation of this study was the single-center, retrospective nature of the investigation. A significant difference might not have been confirmed among independent factors due to the small number of patients. Further studies of more patients are needed. Another limitation is the verification bias, which is dependent on the physician's decision to perform the antigenemia assay.

The diagnosis of CMV-GID is considered as the gold standard for identifying CMV cells in tissue samples from endoscopic biopsy[1,2,13]. Various endoscopic findings are present in CMV-GID, such as ulcer and mucosal inflammation[25,26]; however, physicians may not perform a biopsy in cases only showing mucosal inflammation without ulcer. Even in cases of severe ulceration that is deep or bleeding, physicians may hesitate to perform a biopsy. In such cases, a diagnosis of CMV-GID may not be reached. Our results suggest that the CMV antigenemia assay is useful for the sub-diagnosis of CMV-GID in immunocompromised patients with endoscopic findings. Considering the high specificity of the test, the use of this method before endoscopy could potentially avoid complications due to biopsy. Positive antigenemia is also useful for evaluating improvements in CMV-GID after anti-CMV treatment. However, the low sensitivity means that if the antigenemia assay yields negative results, biopsy and immunohistochemical staining of specimens with anti-CMV will be required for diagnosis. Negative antigenemia assay results may require a repeat examination at a different time[3]. Moreover, the use of different non-invasive methods such as quantitative PCR should be considered.

In conclusion, the CMV antigenemia assay is highly useful for diagnosing CMV-GID. If the antigenemia assay provides positive results, the presence of endoscopic lesions should allow diagnosis of CMV-GID without biopsy. The accuracy of the test is unaffected by the presence of HIV infection or leukopenia.

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COMMENTS

Background

Cytomegalovirus (CMV) gastrointestinal disease (GID) is a major cause of morbidity and mortality in immunocompromised patients; therefore, diagnosis at an early stage is essential. However, clinical diagnosis of this disease can be difficult, as physicians need to consider various underlying diseases and clinical presentations.

Research frontiers

The diagnosis of CMV-GID requires an endoscopic biopsy, which is invasive and may lead to complications. While the CMV antigenemia assay is one of the most widely used methods for detecting reactivation of CMV infection, few studies have examined its diagnostic value for CMV-GID. In this study, the authors demonstrate that the CMV antigenemia assay was highly useful for diagnosing CMV-GID.

Innovations and breakthroughs

There were no studies of diagnosis on CMV-GID related factors using multivariate analysis. In this study, among the various clinical manifestations, human immunodeficiency virus (HIV) infection and positive CMV antigenemia assay were found to be a useful factors for diagnosing CMV-GID by multivariate analysis. As for accuracy of CMV antigenemia for diagnosing CMV-GID, recent reports have highlighted that the sensitivity and specificity were 54% and 88%, respectively, in patients with secondary immunodeficiency disease. However, no studies have compared the assay among groups of HIV-positive/-negative patients and among groups with or without leukopenia. In this study, the sensitivity, specificity, positive predictive value, and negative predictive value of antigenemia for CMV-GID were 65.4%, 93.6%, 91.9%, and 71.0%, respectively. In addition, its accuracy was not affected by the presence of HIV infection and leukopenia. These results are very useful for diagnosing CMV-GID by clinical physicians.

Applications

Considering the high specificity of the test, use of this method before endoscopy could potentially avoid complications due to biopsy. However, the low sensitivity means that if the antigenemia assay yields negative results, biopsy and immunohistochemical staining of specimens with anti-CMV will be required for diagnosis. Negative antigenemia assay results may require repeat examination at a different time. Moreover, the use of different non-invasive methods such as quantitative polymerase chain reaction should be considered.

Peer review

This paper is interesting and it could be valuable for other researchers.

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ORIGINAL ARTICLE

Association between weight gain, obesity, and sleep duration: a large-scale 3-year cohort study

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Abstract
Objective Previous research suggests that sleep duration is associated with obesity and weight gain. However, the majority of these studies are of cross-sectional design, with only a few cohort studies. In order to validate previous findings in a more real-world context, we evaluated the association between sleep duration, obesity, and weight gain in a large, 3-year cohort study.
Methods A retrospective cohort study was conducted involving 21,469 apparently healthy individuals aged 20 years or older who underwent annual health check-ups at the Center for Preventive Medicine, St. Luke's International Hospital, between 2005 and 2008. The participants were divided into four groups according to their self-reported average nightly sleep duration (≤5, 6, 7, and ≥8 h). We identified individuals with obesity (body mass index ≥25 kg/m^2) and weight gain. Multivariate linear regression analysis and logistic regression analysis were used to explore the association between these variables and sleep duration, adjusting for age, gender, alcohol consumption, current smoking, past medical history, and level of physical activity.
Results Compared with those who slept 7 h, the individuals who slept ≤5 h night were more likely to experience weight gain (β coefficient=0.03; 95% CI=0.03–1.1) and to become obese (OR=1.5; 95% CI=1.1–2.0). No significant difference was seen between subjects who slept more than 8 h and those sleeping 7 h (OR=1.3; 95% CI=0.9–1.8).
Conclusion Short sleep (≤5 h) is significantly associated with weight gain and obesity in both male and female adults.

Keywords Sleep duration · Obesity · Japan · Weight gain · Cohort

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Introduction

The prevalence of obesity is increasing worldwide, especially in developed countries [1]. Prior to 1980, the prevalence was generally below 10% and has doubled or tripled in most of these countries. For example, in almost half of Organisation for Economic Co-operation and Development countries, 50% or more of the population is overweight [1]. Although Japan was an exception in that the prevalence of obesity was only 3.4% in 2008, markedly lower than that of other developed countries, Japan was not immune to the gradual rise [2].

Obesity is associated with significant morbidity and mortality, most strongly in cardiovascular diseases. For example, it is associated with hypertension [3], diabetes [4], dyslipidemia [5] and coronary vascular disease [6, 7], and mortality [8]. Therefore, preventing obesity is important for all developed countries.

Previous studies have shown an association between obesity and short sleep duration [9]. However, most studies on sleep and weight are cross-sectional and thus are unable to determine causality [10]. Only a few cohort studies were conducted in the past in limited populations such as male Japanese workers [11, 12] or young women [13].

Given the paucity of data, the association between obesity and sleep duration among men and women in the general adult population remains unclear. Our goal was to explore this association using a large sample of Japanese individuals who underwent annual health check-up over a 3-year period.

Methods

Study participants

We consecutively enrolled all participants seen in the annual health check-up program between 2005 and 2008 at the Center for Preventive Medicine at St. Luke's International Hospital in Tokyo, Japan. Attracting a large number of apparently healthy individuals, the purpose of this program is to promote public health through early detection of chronic diseases and their risk factors. In our center, around 80% of the participants is an employee of the various companies and local governmental organizations in Tokyo, as well as their dependents. Twenty percent of participants independently registered for the program. St. Luke's International Hospital Ethics Committee institutional review board approved all aspects of this study.

Data collection

Pre- and post-examination data were collected from adults (>20 years old) undergoing annual health check-up at our center. For linear analysis, we excluded obese individuals (BMI ≥25 kg/m^2) at baseline. Two investigators independently extracted and recorded information using a structured format. A consensus was reached by discussion for any points of disagreement. To preserve patient confidentiality, direct patient identifiers were not collected in the process of creating the dataset.

Measurements

Annual check-up consisted of self-reported demographic and lifestyle information (pre-exam questionnaire), medical history, initial evaluation (vital signs and laboratory data), and information about comorbidity (diabetes mellitus, hypertension, dyslipidemia) and past medical history (myocardial infarction, cerebral infarction), current medications, and any treatments received. Regular alcohol consumption was defined as drinking any amount of alcohol one or more times per week. Height and body weight were measured as part of annual check-up. Weight gain was defined as body mass index (BMI) increase from 2005 to 2008. In the questionnaire, participants reported their average duration of sleeping time per night at 2005, which was classified into four categories (≤5, 6, 7, and ≥8 h), as well as weekly frequency of physical activity. Based on the Japan Society for the Study of Obesity criteria, obesity was defined as BMI ≥25 kg/m^2 [14], and the prevalence of obesity between 2005 and 2008 was compared for new diagnoses of obesity.

Statistical methods

All analyses were conducted using SPSS 15.0J statistical software (SPSS Japan, Tokyo, Japan). Responses were analyzed using descriptive statistics, including mean, variance, standard deviation (SD), and percents. Chi-square or Fisher's exact tests were used for cross-tabulated data and *t* tests were used to compare means of continuous data. Ninety-five percent confidence intervals (95% CI) were calculated using normal approximation methods.

Excluding obesity (BMI ≥25 kg/m^2) participants in 2005, we constructed multivariate linear regression model for BMI change, calculating adjusted odds ratios (ORs) and 95% CIs. Logistic regression models were constructed to evaluate the adjusted associations between new diagnoses of obesity and duration of sleeping time.

Results

Between 2005 and 2008, 21,469 individuals underwent annual check-ups and were included in this study. Patients' baseline characteristics are summarized in Table 1. The participants were divided into four groups according to average sleep duration (≤5, 6, 7, and ≥8 h) by their initial questionnaires. The mean age of each group, respectively, was 43.3, 46.8, 50.2, and 56.3 years old (SD 11.0, 11.7, 12.8, and 14.4), and males comprised 44.3%, 43.0%, 44.6%, and 45.9% of the participants. Baseline BMI was 21.2 (SD 2.1–2.2) in all groups. The mean BMI (SD) is 21.2 (2.2), 21.2 (2.2), 21.4 (2.2), and 22.4 (2.2), respectively. Per self-reported data, 6.5% of the participants had hypertension, 2.2% had diabetes, and 4.4% had dyslipidemia; 59.1% drank alcohol regularly and 17.3% of the participants was current smokers. Only 5 participants