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ORIGINAL ARTICLE

ASSOCIATION BETWEEN *HELICOBACTER PYLORI* INFECTION AND ATROPHIC GASTRITIS, AND SERUM SELENIUM CONCENTRATION

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Abstract *Helicobacter pylori* infected gastric mucosa causes chronic inflammation which induces atrophic gastritis (AG), and causes gastric cancer. It is suggested that selenium (Se) has preventive effects on gastric cancer incidence. However, the association between *H. pylori* infection/AG and the serum Se level has not yet been clarified. In this research, we investigated this association in a general population.

The subjects were 728 people (252 men and 476 women) who participated in the health check-up during the Iwaki Health Promotion Project. The levels of IgG antibody for *H. pylori* in serum, *H. pylori* antigen in stools, serum pepsinogen I, serum pepsinogen II and serum Se concentration were measured.

Serum Se level was decreased by both *H. pylori* infection and AG, and it negatively correlated with serum pepsinogen I level. Thus, this study suggests that AG with gastric cancer decreases serum pepsinogen I secretion, and leads to decreased absorption of Se.

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Key words: *Helicobacter pylori*; atrophic gastritis; selenium.

原　著

Helicobacter pylori 感染及び萎縮性胃炎が血清 Se 濃度に及ぼす影響

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抄録 *Helicobacter pylori* が感染した胃粘膜では，慢性炎症が引き起こされ，萎縮性胃炎(AG)となり，最終的に胃がんに至る．一方，胃がんの発症に対して，Selenium(Se)は抑制効果がある可能性が指摘されている．そこで，一般住民を対象に，*H. pylori* 感染および AG と血清 Se 濃度の関連について調査・検討した．

2005年岩木健康増進プロジェクト・プロジェクト健診を受診した728名(男性252名，女性476名)を対象とした．測定項目は *H. pylori* 便中抗原価と血清抗体価，AG 判定として血清ペプシノゲン(PG) I と PGⅡ，血清 Se 濃度とした．

血清 Se 濃度は，*H. pylori* 感染の影響は受けず，AG により低下する可能性が示唆された．また，PG I 濃度が低下すると，血清Se濃度も低下する傾向がみられた．これらの結果から，PG I 低下によるSeの消化吸収能の障害が胃がん発症過程におけるSe低下の機序であることが示唆された．

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Introduction

The incidence rate of gastric cancer has decreased worldwide, although it is still one of the main causes of death in Japan[1-4]. In terms of cancer deaths, gastric cancer was the second leading site for both males and females in 2009[5]. The incidence number was the largest in males and the second largest in females in 2005[6]. Therefore, certain preventive measure needs to be taken to decrease gastric cancer incidence in Japan.

Helicobacter pylori is one of the main causes of gastric cancer. *H. pylori* infected gastric mucosa causes chronic inflammation[7, 8], which induces atrophic gastritis. Also, atrophic gastritis is known to develop into to gastric cancer at a high rate[9]. As part of its prevention, selenium (Se) has been found to have inhibitory effects on the inflammation process[10]. A prospective study showed that people with low level of serum Se have a higher risk of developing gastric cancer[11]. It was also reported that the serum Se level of patients with gastric cancer is lower than normal population[12], and gastric cancer with low serum Se level results in a higher risk of death[13-15]. Therefore, the role of Se in lowering gastric cancer incidence or its development has been gaining attention, although its detailed mechanisms are yet unclear.

To date, the association between *H. pylori* infection and Se level of gastric mucous has been clarified, though the association between *H. pylori* infection and serum Se level has not been clarified. That is, the *H. pylori* infected gastric mucous was reported to have higher Se levels than non-infected gastric mucous, and mucosal Se level decreases after completion of *H. pylori* eradication therapy[16]. This finding shows that Se moves towards the inflamed area to suppress its reaction[17, 18]. If the gastritis caused by *H. pylori* infection proceeds chronically, it progresses gastric mucosa atrophy, then inflammation of gastric mucosa diminishes[19, 20], and eventually results in gastric cancer[21, 22]. However, there have been no studies to examine the association between atrophic gastritis on the basis of the pepsinogen method and serum Se level, though some studies to investigate the association between atrophic gastritis and serum Se level on the basis of morphological diagnosis have been conducted in the past[23, 24].

Atrophic gastritis causes decreased secretion of pepsinogen[25, 26]. It is a proenzyme of pepsin which is required for digesting protein. Consequently, decreased pepsin secretion in the body lead to reduce absorption of substances such as iron and vitamin B_{12}, as they are bound to protein in the body[27-29]. Se is an essential micronutrient in human body, which cannot be synthesized within the body. Therefore, serum Se level is purely affected by the dietary intake[30]. Furthermore, it is known that absorption of Se depends on digestion of protein, as Se is bound to protein exist as selenoprotein in the body[31-33]. Therefore, if the pepsinogen secretion decreases due to atrophic gastritis, it inhibits Se absorption, and leads to decline the level of serum Se concentration.

According the previous studies, following associations between *H. pylori* infection and atrophic gastritis and serum Se concentration have been suggested;

1) Serum Se level decreases when it moves towards the area of inflammation which caused by *H. pylori* infection in the stomach.

2) By the time of atrophic gastritis, serum Se level decreases not only by the inflammation but also from the decreased Se absorption led by a decreased pepsinogen secretion.

Therefore, it is necessary to review the association among serum Se level, atrophic gastritis, and *H. pylori* infection comprehensively. However, there has been no such previous research in the past.

Also, it was reported that low intake of serum Se leads to a higher risk of gastric cancer incidence, and it is more common for men than for women[12]. Therefore, gender difference also has to be considered.

In this study, we investigated the association between *H. pylori* infection/atrophic gastritis and serum selenium concentration among the Japanese general population, and made a comparison between the genders.

Subjects and Methods

1. Subjects

The subjects were 728 volunteers (252 males and 476 females, over 20 years old) who participated in the Iwaki Health Promotion Project 2005, and completed the self-completed questionnaires. All of them were residents in Iwaki area in Aomori Prefecture, located in northern Japan. Any subjects with following conditions were excluded from the study; hemorrhagic disorder, anemia[27], previous history of peptic ulcers[34] gastric cancer surgery, and users of $NSAID_S$ or proton-pump inhibitors.

2. Measurement items and methods

We measured the IgG antibody against *H. pylori* in serum and *H. pylori* antigen in stools to determine *H. pylori* infection, serum pepsinogen for atrophic gastritis, and serum Se concentration. Height and weight of subjects were also measured, and each questionnaire was checked by well-trained interviewers.

1) Biochemical blood test

Blood samples were taken from the median cubital vein under fasting condition in the early morning. The serum was separated from 10 ml of blood sample by centrifugation for 10 minutes at 3,000 rpm (radius was 12 cm), and kept frozen at -30°C until analysis. The serum samples were tested for the presence of IgG antibody against *H. pylori* by performing Enzyme immune-assay (EIA) using an E-plate (Eiken, Tokyo, Japan). The pepsinogen I (PGI) and pepsinogen II (PGII) were measured by radioimmunoassay. Serum concentration of Se was measured by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

2) Stool test

The subjects were asked to collect early-morning stool samples on the day of mass survey by using a collection device containing sample diluents. Stool samples were stored at –80 °C and tested for the presence of *H. pylori* antigen by EIA using commercial kits[35] (Wakamoto Pharmaceutical, Kanagawa, Japan and Kyowa Medex, Tokyo, Japan).

3) Height, weight and BMI

Body weight of subjects was measured by the Tanita Model TBF 310 GS Weight Scale (Tanita Corp, Tokyo, Japan). Subjects were asked to wear lightweight clothing without shoes. Their height was measured using a wall-mounted stadiometer after taking off their shoes. Subjects' BMI was computed from the height and weight measurements (kg/m^2).

4) Medical interviews

For the medical interview, we used a self-administered questionnaire including the questions regarding the following items: age, past and present medical history, current medication, age of menopause, the number of cigarettes smoked per day and the years of smoking. The subject's "Number of pack years" was computed by the following formula: the number of packs of cigarettes smoked per day × years of smoking.

3. Definition and diagnosis of *H. pylori* infection

H. pylori infection was defined using stool antigen and serum antibody. We regarded stool

antigen ≧ 0.14 U/mL[35, 36] as positive antigen and serum antibody ≧ 10 U/mL[37] as positive antibody. A case with positive stool antigen and positive serum antibody was diagnosed as positive *H. pylori* infection and a case without them was done as negative *H. pylori* infection. The others were excluded from this study. We defined *H. pylori* infection using stool antigen and serum antibody because false positive cases were often recognized when *H. pylori* infection was defined using stool antigen only or serum antibody only.

4. Definition and diagnosis of atrophic gastritis

Atrophic gastritis was defined as PGI ≦ 70 μg/L and PGI/II ≦ 3.0[38]. A previous study reported that subjects with PGI ≦ 40 μg/L would be classified to have moderate atrophic gastritis by morphological diagnosis[39], and those with PGI ≦ 30 μg/L were classified to have gastric cancer[21]. Based on theses previous studies, we defined and diagnosed atrophic gastritis into two groups of 1) 40 < PGI ≦ 70 μg/L (mild atrophic gastritis), and 2) PGI ≦ 40 μg/L (moderate to atrophic gastritis).

5. Statistical analysis

Subjects were classified by their gender and the status of *H. pylori* infection (Hp) and atrophic gastritis (AG) as follows; Hp (−)/AG (−), Hp (+)/AG (−), Hp (+)/AG (+). Hp (+)/AG (+) group was further classified into two groups: 40 < PGI ≦ 70 μg/L and PGI ≦ 40 μg/L.

The data was adjusted for age, numbers of pack years and menopause[40-43]. These items were adjusted based on the previous studies where they found *H. pylori* infection and atrophic gastritis progressed with age[40], and smoking cigarettes correlated with degree of atrophic gastritis[41, 42]. Also female hormones produced during anti-inflammatory activity were suggested to suppress gastric cancer[43].

Differences of collected data (age, BMI, number of pack years, *H. pylori* antigen level, *H. pylori* IgG antibody level, PGI and PGII) among four groups were tested using one-way analysis of variance (ANOVA) and Tukey's method.

Serum Se levels among four groups were tested using an analysis of covariance (ANCOVA) and Bonferroni method after adjusting age, number of pack years and menopause as covariates.

Data analysis was performed with SPSS version 17.0J for Windows. The statistical differences were considered to be significant at $p < 0.05$, and to be marginally significant at $p < 0.1$.

6. Ethical consideration

Prior to the investigation, following points were explained to all participants and written consents were obtained; 1) the use of the documents obtained during the research will only be used for study purposes, 2) participants have a right to decline or withdraw from the project at any time, 3) confidentiality and anonymity of subjects will be protected, and 4) the storage of data will be properly and securely managed. The Iwaki Health Promotion Project is approved by the Ethics Committee of Hirosaki University Graduate School of Medicine.

Results

1. Overall characteristics of *H. pylori* infection and atrophic gastritis (Tables 1, 2, 3)

Characteristics of subjects are listed in Table 1. Values were presented as a mean ± standard deviation (SD) for each gender. Among all subjects (252 men and 476 women), 156 men (61.9%) and 273 women (57.4%) were *H. pylori* infection positive. Also, total of 94 men (37.3%) and 190 women (39.9%) were found to be atrophic gastritis positive.

Among both men and women, the means of age, *H. pylori* antigen level, and *H. pylori* IgG

Table 1 General characteristics of the subjects

	Men	Women
N	252	476
Age (year)	54.5 ± 14.4	56.7 ± 14.0
BMI (kg/m^2)	23.5 ± 2.9	23.1 ± 3.3
Number of pack years	22.5 ± 26.0	2.0 ± 7.2
Menopause	—	348
Helicobacter pylori infection positive	156	273
Hp Antigen Levels in Stool (U/mL)	1.0 ± 1.1	1.1 ± 1.2
Hp IgG Antibody Levels in Serum (U/mL)	48.3 ± 66.6	53.8 ± 71.3
Atrophic gastritis positive	94	190
Pepsinogen I (μg/L)	51.8 ± 22.7	48.8 ± 20.6
Pepsinogen I/II	3.4 ± 1.7	3.2 ± 1.5

Data are expressed as mean ± standard deviation (SD) or numbers.
Helicobacter pylori infection was defined as Hp Antigen Level in Stool ≧ 0.14 U/ml and Hp IgG Antibody Level in Serum ≧ 10 U/ml.
Atrophic Gastritis was defined as PGI ≦ 70 μg/L and PGI/II ≦ 3.0.

Table 2 Characteristics of *Helicobacter pylori* infection and atrophic gastritis in males

	Hp(−)/AG(−)	Hp(+)/AG(−)	Hp(+)/AG(+)		*P*-value
			40 < PG I ≦ 70	PG I ≦ 40	
N	96	62	47	47	
Age (year)	47.6 ± 14.5	55.2 ± 13.4 *	57.7 ± 12.3 **	64.3 ± 9.7 **†	0.00
BMI (kg/m^2)	23.5 ± 3.0	23.9 ± 3.1	23.1 ± 2.5	23.3 ± 2.7	0.55
Number of pack years	23.0 ± 23.6	22.9 ± 27.9	18.0 ± 22.0	25.5 ± 31.3	0.56
Hp Antigen Levels in Stool (U/mL)	0.0 ± 0.0	1.6 ± 1.1 **	1.6 ± 1.1 **	1.8 ± 1.0 **	0.00
Hp IgG Antibody Levels in Serum (U/mL)	2.9 ± 1.7	73.2 ± 57.8 **	69.9 ± 62.9 **	86.3 ± 93.3 **	0.00
Pepsinogen I (μg/L)	49.6 ± 15.2	75.4 ± 18.8 **	55.6 ± 7.6 ††	21.3 ± 9.4 **††‡‡	0.00
Pepsinogen I/II	5.1 ± 1.0	3.1 ± 1.0 **	2.2 ± 0.4 **††	1.4 ± 0.6 **††‡‡	0.00

Data are expressed as mean ± standard deviation (SD) or numbers. One-way ANOVA with Tukey correction was used to compare the values.
Hp: *Helicobacter pylori* infection was defined as Hp Antigen Level in Stool ≧ 0.14 U/mL and Hp IgG Antibody Level in Serum ≧ 10 U/mL.
AG: Atrophic Gastritis was defined as PGI ≦ 70 μg/L and PGI/II ≦ 3.0.
*: Significantly different compared to the Hp (−)/AG (−) group, * $p<0.05$, ** $p<0.01$
†: Significantly different compared to the Hp (+)/AG (−) group, † $p<0.05$, †† $p<0.01$
‡: Significantly different compared to the Hp (+)/AG (+) 40 < PGI ≦ 70 group, ‡‡ $p<0.01$

antibody level was significantly higher in the Hp (+)/AG (+) group than the other groups. The mean level of PGI was also significantly higher in the Hp (+)/AG (−) group, and significantly lower in the Hp (+)/AG (+) & ≦ 40 μg/L group compared to the other groups. The mean level of PGI/II ratio was significantly higher in the Hp (−)/AG (−) group than the other groups. There were no significant differences in BMI and number of pack years among four groups (Tables 2, 3).

2. Serum Se level and *H. pylori* infection (Tables 4, 5)

There was no significant difference in serum Se level between the *H. pylori* infection negative and positive groups in male subjects. For women, serum Se level was significantly lower in *H. pylori* infection positive group than the negative group (p=0.03) (Table 4). However, no significant differences were observed between the two groups in either gender when atrophic

Table 3 Characteristics of *Helicobacter pylori* infection and atrophic gastritis in females

	Hp(−)/AG(−)	Hp(+)/AG(−)	Hp(+)/AG(+)		*P*-value
			40 < PG I ≦ 70	PG I ≦ 40	
N	203	83	105	85	
Age (year)	50.9 ± 15.2	59.2 ± 11.9 **	59.5 ± 11.5 **	64.7 ± 9.3 **†‡	0.00
BMI (kg/m^2)	22.7 ± 3.2	23.2 ± 3.2	23.4 ± 3.3	23.7 ± 3.7	0.06
Number of pack years	2.4 ± 6.6	2.8 ± 9.6	1.7 ± 7.0	0.6 ± 5.6	0.16
Menopause	117	67	85	79	0.00
Hp Antigen Levels in Stool (U/mL)	0.0 ± 0.0	1.8 ± 1.1 **	2.1 ± 1.0 **	1.8 ± 1.0 **	0.00
Hp IgG Antibody Levels in Serum (U/mL)	2.7 ± 1.6	96.5 ± 83.3 **	92.0 ± 71.8 **	86.6 ± 67.6 **	0.00
Pepsinogen I (μg/L)	41.9 ± 12.1	78.4 ± 20.3 **	55.7 ± 8.8 **††	28.0 ± 8.7 **†††‡‡	0.00
Pepsinogen I/II	4.7 ± 0.8	2.6 ± 0.8 **	2.1 ± 0.5 **††	1.5 ± 0.6 **†††‡‡	0.00

Data are expressed as mean ± standard deviation (SD) or numbers. One-way ANOVA with Tukey correction was used to compare the values. χ^2 test was used to compare menopause.
Hp: *Helicobacter pylori* infection was defined as Hp Antigen Level in Stool ≧ 0.14 U/mL and Hp IgG Antibody Level in Serum ≧ 10 U/mL.
AG: Atrophic Gastritis was defined as PGI ≦ 70 μg/L and PGI/II ≦ 3.0.
*****: Significantly different compared to the Hp (−)/AG (−) group, ****** $p<0.01$
†: Significantly different compared to the Hp (+)/AG (−) group, † $p<0.05$, †† $p<0.01$
‡: Significantly different compared to the Hp (+)/AG (+) 40 < PGI ≦ 70 group, ‡ $p<0.05$, ‡‡ $p<0.01$

Table 4 Serum selenium level and *Helicobacter pylori* infection including atrophic gastritis

	Hp (−)	Hp (+)	*P*-value
Men			
N	96	156	
Serum selenium level (μg/L)	251.0 ± 4.7	245.7 ± 3.6	0.39
Women			
N	203	273	
Serum selenium level (μg/L)	239.3 ± 2.5	231.8 ± 2.2	0.03

Data are expressed as adjusted mean ± standard error. ANCOVA with Boneferroni correction was used to compare the values.
Values are adjusted for Age, Number of pack years and Menopause.
Hp: *Helicobacter pylori* infection was defined as Hp Antigen Level in Stool ≧ 0.14 U/mL and Hp IgG Antibody Level in Serum ≧ 10 U/mL.

Table 5 Serum selenium level and *Helicobacter pylori* infection excluding atrophic gastritis

	Hp (−)	Hp (+)	*P*-value
Men			
N	96	62	
Serum selenium level (μg/L)	252.7 ± 4.3	249.4 ± 5.4	0.64
Women			
N	203	83	
Serum selenium level (μg/L)	239.0 ± 2.4	236.3 ± 3.8	0.56

Data are expressed as adjusted mean ± standard error. ANCOVA with Boneferroni correction was used to compare the values.
Values are adjusted for Age, Number of pack years and Menopause.
Hp: *Helicobacter pylori* infection was defined as Hp Antigen Level in Stool ≧ 0.14 U/mL and Hp IgG Antibody Level in Serum ≧ 10 U/mL.

gastritis was removed from the analysis (Table 5).

3. Serum Se level and atrophic gastritis (Table 6)

For men, serum Se level tended to be lower in the atrophic gastritis positive group than those in the negative group (p=0.09). For

Table 6 Serum selenium level and Atrophic gastritis

	AG (−)	AG (+)	*P*-value
Men			
N	158	94	
Serum selenium level (μg/L)	251.7 ± 3.6	241.1 ± 4.7	0.09
Women			
N	286	190	
Serum selenium level (μg/L)	238.6 ± 2.1	229.6 ± 2.6	0.01

Data are expressed as adjusted mean ± standard error. ANCOVA with Boneferroni correction was used to compare the values.
Values are adjusted for Age, Number of pack years and Menopause.
AG: Atrophic Gastritis was defined as PGI ≦ 70 μg/L and PGI/II ≦ 3.0.

Table 7 Serum selenium level, *Helicobacter pylori* infection and Atrophic gastritis

	Hp(−)/AG(−)	Hp(+)/AG(−)	Hp(+)/AG(+)		*P*-value
			40 < PG I ≦ 70	PG I ≦ 40	
Men					
N	96	62	47	47	
Serum selenium level (μg/L)	251.9 ± 4.7	252.0 ± 5.5	252.0 ± 6.4	229.2 ± 6.7 *†‡	0.03
Women					
N	203	83	105	85	
Serum selenium level (μg/L)	239.4 ± 2.5	236.9 ± 3.8	229.6 ± 3.4	229.4 ± 3.9	0.06

Data are expressed as adjusted mean ± standard error. ANCOVA with Boneferroni correction was used to compare the values.
Values are adjusted for Age, Number of pack years and Menopause.
Hp: *Helicobacter pylori* infection was defined as Hp Antigen Level in Stool ≧ 0.14 U/mL and Hp IgG Antibody Level in Serum ≧ 10 U/mL.
AG: Atrophic Gastritis was defined as PGI ≦ 70 μg/L and PGI/II ≦ 3.0.
*: Marginally significant compared to the Hp (−)/AG (−) group, $p<0.1$
†: Marginally significant compared to the Hp (+)/AG (−) group, $p<0.1$
‡: Marginally significant compared to the Hp (+)/AG (+) 40 < PGI ≦ 70 group, $p<0.1$

women, serum Se level was significantly lower in the atrophic gastritis positive group than those in the negative group (p=0.01).

4. Serum Se level according to *H. pylori* infection and atrophic gastritis (Table 7)

For men, serum Se levels tended to be lower in the Hp(+)/AG(+) and PGI ≦ 40 μg/L group compared to other groups (p<0.1), and the differences among the four groups were significant (p=0.03). For women, it tended to be lower in both Hp (+)/AG (+) groups than other two groups (HP(−)/AG(−) group or HP (+)/AG(−) group) (p=0.06).

Discussion

It has been suggested that Se plays an important role in the incidence and exacerbation of gastric cancer[10-15]. However, the relationship between serum Se level and atrophic gastritis caused by *H. pylori* infection, and its effect on gastric cancer incidence has yet been thoroughly investigated.

In this study, the prevalence of *H. pylori* infection and atrophic gastritis were significantly higher with aging in men and women, which was compatible with the previous studies[40]. Serum PGI level was significantly increased by *H. pylori* infection and was decreased by

atrophic gastritis[22]. Moreover, PGI/II was decreased with deterioration of mucosal inflammation[22, 39]. Diagnostic criteria of atrophic gastritis was serum PGI level ≦ 70 μg/L and PGI/II ≦ 3.0, of which sensitivity and specificity were recognized to be high[38].

It is reported that *H. pylori* infection causes inflammation and Se level of gastric mucosa would be higher on the infected area as an anti-inflammatory activity[16]. Therefore, serum Se level was assumed to be lower in *H. pylori* infected subjects. In this study, there was no significant difference in serum Se level between the *H. pylori* infection negative and positive groups in male subjects. For women, serum Se level was significantly lower in *H. pylori* infection positive group than the negative group. However, no significant differences were observed between the *H. pylori* infection negative and positive groups in either gender when atrophic gastritis was removed from the analysis. Thus, the atrophic gastritis (atrophy of gastric mucosa) was suggested to be a factor influencing serum Se concentration, rather than the presence of *H. pylori* infection.

The studies by Chen et al.[23] and Zhang et al.[24] showed that serum Se level had no association with morphologically diagnosed atrophic gastritis. However, in the present results, serum Se level was significantly decreased by atrophic gastritis among women, and there was a marginally significant decrease among men. This result suggested that serum Se level is affected by the atrophic gastritis (atrophy of gastric mucosa) for both genders. Previous studies showed that inflammation diminished on gastric mucosa with atrophic gastritis[19, 20]. Thus, it is assumed that decrease of serum Se level is influenced by functional deterioration of gastric mucosa.

Se-binding proteins intake as foods are digested by proteases secreted as gastric and pancreatic juices, and then they are absorbed in small intestine. The previous studies have reported that decreased secretion of pepsinogen, zymogen of pepsin, drives impaired digestion and absorption of iron and vitamin B_{12}, which are bound by proteins[27-29]. In the same way, because Se, which is one of the essential trace elements in human[31-33], is bound by proteins, absorption of Se is depend on digestion and absorption of proteins. Hence, we regarded decline of serum Se level as the result of impaired digestion and absorption of Se caused by decline of pepsinogen secretion.

Serum Se level is correlated with the intake quantity[30] and metabolic products are excreted to urine within one day[44]. In other word, contents of food intake have influence on serum Se level and it is metabolized and excreted immediately. On the other hand, individuals with atrophic gastritis often have complaints of stomachache and other abdominal discomfort. Therefore, decreased serum Se level among participants with atrophic gastritis could be caused by decreased intake of Se. There is the limitation to describe an association between decreased serum Se level and decreased intake of Se because this study did not investigate the Se dietary intake.

We observed the tendency that decreased serum Se level needed atrophic gastritis and serum PGI level ≦ 40 μg/L in men, but decreased serum Se level was not detected in women when women participants were divided into mild atrophic gastritis group and moderate or severe group. That is, there is a gender difference between the function of gastric mucosa and serum concentration of Se. The previous studies have reported that the incidence rate of gastric cancer in men is higher than that in women[3] and that the incidence rate of gastric cancer among individuals with atrophic gastritis in men is higher than that in women[22]. Acceleration of Se absorption caused by estrogen is also reported[45]. From the above

mentioned, we suggested that decreased serum Se level when the function of gastric mucosa declined in women was milder than that in men because estrogen kept absorption of Se in women.

According to the results obtained from the present research, the atrophic gastritis (atrophy of gastric mucosa) was suggested to affect reduced serum Se concentration in adults. In other words, *H. pylori* infection causes atrophic gastritis leading to gastric atrophy, and then to reduced pepsinogen secretion. When protein absorption is limited due to absence of pepsinogen, selenoprotein absorption also becomes limited, and consequently leads to reduced serum Se concentration.

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