Impact of *Helicobacter pylori* Immunoglobulin G Levels and Atrophic Gastritis Status on Risk of Metabolic Syndrome

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Abstract

Background

*Helicobacter pylori* (HP) infection is implicated in gastric and extra-gastric diseases. While gastritis-related chronic inflammation represents a known trigger of metabolic disturbances, whether metabolic syndrome (MetS) is affected by gastritis status remains unclear. We aimed to clarify the effect of HP-related gastritis on the risk of MetS.

Materials and Methods

We retrospectively enrolled patients undergoing screening for MetS between 2014 and 2015. Investigations included HP-specific immunoglobulin G (IgG) antibody assays to detect HP infection, and serum pepsinogen assays to evaluate atrophic gastritis status. The risk of MetS was evaluated via multiple logistic regression analyses with two covariates: serum HP infection status (IgG levels) and atrophic gastritis status (two criteria were applied; pepsinogen I/II ratio < 3 or both pepsinogen I levels ≤ 70 μg/L and pepsinogen I/II ratio < 3).

Results

Of 1,044 participants, 247 (23.7%) were HP seropositive, and 62 (6.0%) had MetS. HP seronegative and seropositive patients had similar risks of MetS. On the other hand, AG (defined in terms of serum PG I/II <3) was significant risk of MetS (OR of 2.52 [95% CI 1.05–7.52]). After stratification according to HP IgG concentration, patients with low HP infection status had the lowest MetS risk (defined as an odds ratio [OR] adjusted for age, sex, smoking, drinking and physical activity status). Taking this result as a reference, patients with negative, moderate, and high HP infection status had ORs (with 95% confidence intervals [CI]) of 2.15 (1.06–4.16), 3.69 (1.12–16.7), and 4.05 (1.05–26.8).
Conclusions
HP-associated gastritis represents a risk factor for MetS. Research should determine why low and not negative HP infection status is associated with the lowest MetS risk.

Introduction
*Helicobacter pylori* (HP) is a spiral-shaped bacterium that resides in the human gastric mucosal layer or adheres to the epithelial lining of the stomach. HP infection usually occurs in childhood and persists for a long time. HP infection is involved in gastric diseases such as chronic gastritis, gastric ulcer, and gastric adenocarcinoma [1, 2]. Although most HP infections are limited to the stomach, associations with certain extra-gastric manifestations has been noted, including iron-deficiency anemia [3], vitamin deficiency [4, 5], obesity [6], impaired glucose tolerance [7], insulin resistance [8], and cardiovascular diseases [9].

Metabolic syndrome (MetS) is an insulin-resistant state induced by a combination of risk factors that precedes-type 2 diabetes and may lead to increased cardiovascular morbidity. Recent evidence indicates that HP infection is also associated with MetS. Specifically, a cross-sectional study of a large population of Japanese adults evaluated the concentration of HP-specific immunoglobulin G (IgG) and found that HP-infected subjects had a significantly higher risk of MetS [10]. Another study reported a similar relationship [11], while others did not [12, 13]. These discrepancies may be related to the variation in HP-infection and gastritis status in the study populations. The underlying mechanisms of the MetS-HP relationship remain unknown, although chronic inflammation is presumed to play a key role. Specifically, HP infection induces chronic gastritis and local chronic inflammation, stimulating the production of response inflammatory proteins and cytokines such as C-reactive protein, tumor necrosis factor alpha (TNF-α), interleukins (IL-1, IL-6, IL-8, IL-10), and eicosanoids [14]. As overexpression of these proteins contributes to the pathogenesis of MetS [15], therefore the risk of MetS is it is expected to be affected by the inflammatory burden associated with HP infection.

From a different perspective, HP infection may also be associated with malnutrition, as growth retardation is suspected in HP-infected children [16], and weight gain has also been observed after HP eradication [17, 18]. Francois et al. reported HP eradication altered circulating meal-associated leptin and ghrelin levels and body mass index (BMI) [19]. The decrease in gastric secretory function may partially account for this HP-related malnutrition, as the levels of gastric hormones such pepsinogen (PG) I, gastrin, and ghrelin are known to decrease with the progression of atrophic gastritis (AG) [20]. The decrease in ghrelin secretion induces loss of appetite, which influences food intake and body weight. This phenomenon likely affects the relationship between MetS and HP infection, suggesting an inverse effect of HP infection on overnutrition and related MetS pathogenesis.

Furthermore, some reports suggested that AG, but not HP infection status, is associated with BMI [21, 22]. Because most of AG were induced by HP infection, the results mean the effect of HP infection on BMI occur by way of AG. Therefore it is also important to evaluate the effect of AG on MetS. To our knowledge, there are few reports that investigated the association between AG and MetS [23].

In the present study, we investigated the effect of HP-infection status (defined in terms of the concentration of HP-specific IgG) and AG status (defined in terms of serum PG levels) on the risk of MetS.
Methods

Study Population

This study enrolled employees of Nagasaki University with middle to high socioeconomic and educational status who underwent a comprehensive health check-up between 2014 and 2015. The analysis included only data regarding the participants who completed the health check-up investigations including anthropometric measurements and blood tests. Further subjects were excluded based on the following criteria: receiving medical treatment for hyperlipidemia or diabetes mellitus; history of antibiotic treatment against HP; inflammatory disease; severe liver or renal dysfunction; and neoplasm.

The study was conducted at the Center for Health and Community Medicine of Nagasaki University in Nagasaki, Japan. All patient data were anonymized before analysis. The study was approved by the ethical committee of Nagasaki University Graduate School of Biomedical Sciences (approval no. 16062492), and written informed consent was obtained from all participants.

Data Collection

All participants completed questionnaires regarding smoking habits (habitually smoking ≥ 1 cigarette per day), physical activity (walking > 30 minutes per day), and alcohol consumption (habitually drinking ≥ 1 alcoholic drink per week). Anthropometric measurements including height, weight, and waist circumference were taken using standardized techniques and calibrated equipment. BMI was defined as weight divided by height squared (kg/m²). Blood pressure was measured serially with an electrical sphygmomanometer (DM-3000; Japan Precision Instruments Inc., Gunma, Japan), after each participant had rested for at least 5 minutes.

Blood samples were collected after the patients had fasted overnight. The following levels were measured: fasting plasma glucose, glycated hemoglobin (via assays certified by the National Glycohemoglobin Standardization Program), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and uric acid.

Definition of MetS

MetS was diagnosed based on the revised National Cholesterol Education Program’s Adult Treatment Panel III guidelines [24] upon fulfilling ≥ 3 of the following criteria: abdominal obesity (waist circumference ≥ 90cm and ≥ 80cm for Asian men and women, respectively); triglyceride levels ≥ 150mg/dL; HDL cholesterol levels ≤ 40mg/dL and 50mg/dL for men and women, respectively; systolic/diastolic blood pressure ≥ 130/85mmHg or receiving medical treatment; and fasting plasma glucose levels ≥ 100mg/dL.

Measurement of HP-Specific IgG Concentration

HP infection was diagnosed based on the levels of HP-specific IgG measured using a commercially available enzyme-linked immunosorbent assay kit (E-Plate Eiken H. pylori antibody kit; Eiken Chemical Co., Ltd., Tokyo, Japan). For the Japanese population, the sensitivity and specificity of this kit were reported to be 95.2–100% and 76.2–80.0%, respectively [25, 26]. As previously reported [27] the subjects were stratified into HP-infection groups according to the concentration of HP-specific IgG as follows: HP seronegative (< 10 U/mL), low HP-specific IgG levels (10–30 U/mL), moderate HP-specific IgG levels (30–50 U/mL), or high HP-specific IgG levels (> 50 U/mL).
Definition of AG

Serum PG (manifested as PG I and PG II) concentration and the PG I/II ratio were shown to reflect the functional and morphologic status of the gastric mucosa. AG is typically associated with a lower PG I/II ratio because the serum levels of PG I decrease, while those of PG II remain fairly constant. We therefore diagnosed AG based on the serum levels of PG I and II, which were measured using the Lumipulse Presto pepsinogen I and Lumipulse Presto pepsinogen II kits (Fujirebio Inc., Tokyo, Japan). Subjects with PG I levels of < 70 μg/L and a PG I/II ratio of < 3 were diagnosed with AG [28]. This criteria showed a sensitivity of 70.5% and specificity of 97.0% for AG compared with histology have been reported in Japan [29]. The criteria is optimized for gastric cancer screening [28]. Several other reports defined AG as PG I/II ratio of < 3 solely [30, 31] and this criteria showed 83.3% sensitivity and 87.1% specificity to moderate—severe AG diagnosed with endoscopy [32]. We applied these two criteria on analysis.

Statistical Analysis

All statistical analyses were performed using JMP version 10.0 (SAS Institute, Cary, North Carolina, USA). Student’s t-test and the chi-squared test were applied for continuous and categorical variables, respectively. The risk of MetS of HP infection and AG was assessed by logistic regression analysis. Two AG criteria were applied and both calculated separately. The risk of MetS, expressed in terms of sex and age adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs), was calculated relative to the risk in the HP-seronegative group (Model 1, adjusted for sex and age). Sex and age adjusted ORs with 95% CIs of PG status (Model 2) and HP-seropositivity, PG status, smoking, drinking and physical activity status (Model 3) were also calculated. Thereafter, sex, age, smoking, drinking and physical activity status adjusted ORs with 95% CIs was calculated relative to the risk in the low HP-infection group (Model 4). In Model 5 we classified the participants into eight groups according to the combination of their HP infection status (defined in terms of IgG serum concentration) and AG status (defined in terms of serum PG levels), and compared the ORs of MetS within these eight groups. We also examined the interaction between HP IgG concentration and serum PG I/II ratio using linear regression model (Fig 1). The significance threshold was set at p < 0.05.

Results

Of the 3,735 individuals who underwent the health check-up, 1,238 underwent anthropometric measurements and blood tests. After applying the exclusion criteria, a total of 1,044 participants (498 men) were enrolled in the study (Table 1). Of these, 247 (23.7%) were HP seropositive, and 62 (6.0%) were diagnosed with MetS. The HP-seropositive and seronegative groups differed in terms of age (46.6 ± 9.2 years and 42.9 ± 7.7 years, respectively; p < 0.0001) but not sex. Blood pressure was significantly higher in the HP-seropositive group (systolic blood pressure, 120.0 ± 16.0 versus 117.6 ± 14.1 mmHg, p = 0.03; diastolic blood pressure, 74.7 ± 12.1 versus 72.9 ± 11.1 mmHg, p = 0.003). Serum LDL-C concentration was significantly higher in the HP-seropositive group (120.3 ± 29.1 vs. 116.0 ± 30.4 mg/dL; p = 0.05), as were the serum levels of PG (p < 0.0001), although the PG I/II ratio was significantly lower in the HP-seropositive group, as expected (p < 0.0001). There were no differences between the HP-seropositive and seronegative groups in terms of smoking, drinking, and physical activity status.

The effect of HP-infection and AG on the risk of MetS was assessed by multiple logistic regression analyses (Table 2). No significant association was detected between positive HP-infection status and the risk of MetS after adjusting for age and sex (Model 1). On the other hand, AG (defined in terms of serum PG I/II <3) was significant risk of MetS (Model 2).
When MetS risk of HP-infection status and AG status was calculated together, AG was significant risk but HP-infection lower the MetS risk (Model 3). The group with low HP infection (i.e., with lowest serum concentration of HP IgG) showed the lowest OR adjusted for age, sex, smoking, drinking, and physical activity status. Taking this group as a reference, patients with negative, moderate, and high HP infection status had ORs (with 95% confidence intervals [CI]) of 2.16 (1.06–4.16), 3.69 (1.12–16.7), and 4.05 (1.05–26.8). Smoking, drinking, and physical activity status did not have significant influence on the result (Model 3, 4).

The participants were stratified according to the combination of HP infection and AG (Model 5). AG was not noted among HP-seronegative participants. Therefore analysis was performed within seven groups. The subgroup with low HP infection and no AG showed the lowest OR adjusted for age and sex. In examination of the interaction between HP IgG concentration and serum PG I/II ratio using linear regression model (Fig 1), a marginal negative correlation was observed between Helicobacter pylori antibody and serum pepsinogen I/II ratio in the low serum pepsinogen I/II ratio group ($r = 0.19, p = 0.0849$). There was no significant correlation between Helicobacter pylori antibody and serum pepsinogen I/II ratio in other groups.

**Discussion**

In present study we observed differences of MetS risk according to AG and HP IgG concentrations. The findings were; 1) AG as defined PG I/II < 3 is a significant risk of MetS. 2) Low H. pylori Gastritis and Metabolic Syndrome
pylori IgG concentration with non-AG group represented lower risk of MetS compared with H.pylori IgG negative, moderate and high concentration groups.

In most cases, HP infection occurs during childhood, but persists a long time and induces chronic gastritis. In the process of inflammation, HP-specific IgG is produced by activated immunocytes, and the concentration of HP-specific IgG reflects the progression of gastritis. Kishikawa et al. demonstrated that the HP-specific IgG titer was associated with the degree of gastritis progression in a positive and negative manner in individuals diagnosed with non-atrophic and AG, respectively [27].

As gastritis progresses, the time course of HP-specific IgG levels exhibits a unimodal shape. The early stage of HP-associated gastritis is indicated by low HP-specific IgG concentration with non-AG status, which, in our study, was associated with the lowest risk of MetS. Due to the low risk group, the OR of HP seropositive group were lowered (Table 2 model 3, 6). There may be several explanations for our finding that HP-seronegative individuals had higher risk of MetS than did those with low levels of HP-specific IgG. First, HP infection is known to affect micronutrient metabolism [3–5, 33], and several cross-sectional studies have indicated that HP infection causes growth retardation in children [34–36]. Observing 295 children over 3.7 years, after adjusting for other covariates, Mera et al. noted that children who were always HP-negative or who achieved successful HP clearance grew significantly faster than those who remained HP-positive [15]. Moreover, in adults, HP eradication has been shown to be

| Table 1. Characteristics of the study participants. |
|---------------------------------------------------|
| **All** | **HP-seropositive** | **HP-seronegative** | **p-value** |
| Number of patients | 1,044 | 247 | 797 |
| Age (years) | 43.8 ± 8.2 | 46.6 ± 9.2 | 42.9 ± 7.7 | < .0001 |
| Male (%) | 47.7 | 50.2 | 46.9 | 0.38 |
| Height (cm) | 164.6 ± 8.2 | 164.6 ± 8.1 | 164.5 ± 8.3 | 0.94 |
| Weight (kg) | 61.0 ± 12.7 | 61.7 ± 11.9 | 60.8 ± 12.9 | 0.32 |
| Body mass index (kg/m²) | 22.4 ± 3.5 | 22.7 ± 3.6 | 22.3 ± 3.5 | 0.10 |
| Systolic blood pressure (mmHg) | 118.2 ± 14.6 | 120.0 ± 16.0 | 117.6 ± 14.1 | 0.03 |
| Diastolic blood pressure (mmHg) | 73.3 ± 11.4 | 74.7 ± 12.1 | 72.9 ± 11.1 | 0.03 |
| Triglyceride (mg/dL) | 95.2 ± 70.8 | 93.4 ± 55.0 | 95.7 ± 75.1 | 0.66 |
| High-density lipoprotein (mg/dL) | 62.9 ± 14.2 | 61.8 ± 13.5 | 63.3 ± 14.5 | 0.16 |
| Low-density lipoprotein (mg/dL) | 117.0 ± 30.1 | 120.3 ± 29.1 | 116.0 ± 30.4 | 0.05 |
| Fasting plasma glucose (mg/dL) | 90.4 ± 12.4 | 89.9 ± 10.6 | 90.6 ± 12.9 | 0.40 |
| Metabolic syndrome (n) | 62 | 19 | 43 | 0.22 |
| Pepsinogen I (ng/mL) | 38.4 ± 14.6 | 48.6 ± 20.1 | 35.2 ± 10.7 | < .0001 |
| Pepsinogen II (ng/mL) | 9.7 ± 7.0 | 18.5 ± 9.3 | 6.9 ± 2.3 | < .0001 |
| PG I/II | 4.6 ± 1.4 | 2.9 ± 1.1 | 5.2 ± 1.0 | < .0001 |
| HP-specific IgG concentration (U/mL) | 11.8 ± 19.4 | 39.9 ± 23.5 | 3.0 ± 0.4 | < .0001 |
| Low (U/mL) | 103 (20.1 ± 5.6) |
| Moderate (U/mL) | 80 (39.0 ± 6.0) |
| High (U/mL) | 64 (72.9 ± 17.8) |
| Smoking (%) | 11.7 | 12.6 | 11.4 | 0.65 |
| Drinking (%) | 55 | 53.8 | 55.3 | 0.71 |
| Physical activity (%) | 21.3 | 24.3 | 20.3 | 0.18 |

HP: *Helicobacter pylori*; IgG: immunoglobulin G; PG: pepsinogen. Smoking was defined as habitually smoking more than one cigarette per day. Drinking was defined as habitually drinking more than one alcohol drink per week. Physical activity was determined by asking participants whether they walk more than 30 minutes per day.

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followed by weight gain [19, 37]. In contrast, some reports have indicated that HP-related gastric symptoms, not HP infection itself, induce malnutrition [16, 38]. While the effect of this phenomenon on our conclusions cannot be quantified at the moment, our observation that low HP infection, and not negative HP infection status, is associated with the lowest risk of MetS might be explained by the inverse effect of HP infection and associated gastric symptoms on overnutrition. Moreover, several questions remain unanswered. For instance, do these HP-related malnutritional effects occur in early gastritis? Alternatively, if HP infection occurs in childhood, what are the reasons for phenotypical heterogeneity (different levels of HP-specific IgG and gastritis status) in adults? It is possible that certain participants had a specific phenotype for HP infection? Because the levels of HP-specific IgG reflect the inflammatory burden induced by HP infection [39], the participants who showed low HP-specific IgG concentration with non-AG status are considered to have some specific feature that can maintain the effect of HP infection minimally. Low MetS risk in this group indicate that they have common phenotype to prevent progression of both HP infection and MetS. It was previously reported that genetic polymorphisms in host alleles associated with pro-inflammatory and anti-inflammatory cytokines such as IL-1β, TNF-α, IL-6, and IL-10 affect the phenotype of HP-related

Table 2. Odds ratios with 95% confidence intervals for *H. pylori* infection and pepsinogen status for metabolic syndrome.

|                          | OR (95% CI) | p-value |                          | OR (95% CI) | p-value |
|--------------------------|------------|---------|--------------------------|------------|---------|
|                          | (A) Atrophic gastritis defined as PG I > 70 ng/mL and PG I/II < 3.0. |         |                          | (B) Atrophic gastritis defined as PG I/II < 3.0. |         |
| Model 1: Age, Sex, and HP seropositivity | 0.85 (0.48–1.56) | 0.59 |                          | 2.52 (1.05–7.52) | 0.037 |
| HP seropositive/negative | 0.52 (0.28–1.01) | 0.054 |                          | 0.42 (0.22–0.84) | 0.016 |
| Model 2: Age, Sex, Atrophic gastritis | 2.40 (0.94–8.16) | 0.07 |                          | 4.9 (1.75–16.0) | 0.002 |
| Atrophic gastritis/Non-Atrophic gastritis | 3.92 (1.34–14.3) | 0.011 |                          |                 |         |
| HP seropositive/negative | 2.15 (1.06–4.16) | 0.034 |                          |                 |         |
| Low HP infection (reference) | 1         |         |                          | 1         |         |
| Moderate HP infection | 3.69 (1.12–16.7) | 0.03 |                          |                 |         |
| High HP infection | 4.05 (1.05–26.8) | 0.042 |                          |                 |         |
| Model 4: Age, Sex, HP IgG level, Smoking, Drinking and Physical activity |                 |         |                          |                 |         |
| Atrophic gastritis/Non-Atrophic gastritis |                 |         |                          |                 |         |
| HP-seronegative | 3.44 (1.61–6.94) | 0.002 |                          | 3.55 (1.61–7.32) | 0.003 |
| Low HP infection (reference) | 1         |         |                          | 1         |         |
| Moderate HP infection | 5.22 (1.29–35.3) | 0.018 |                          | 3.47 (0.83–23.9) | 0.093 |
| High HP infection | 5.99 (1.04–114.0) | 0.045 |                          | 3.70 (0.62–71.3) | 0.17 |
| Model 5: Combination of HP IgG level and atrophic gastritis status |                 |         |                          |                 |         |
| Atrophic gastritis |                 |         |                          |                 |         |
| Low HP infection | 6.32 (1.54–43.1) | 0.009 |                          | 4.85 (1.34–23.3) | 0.015 |
| Moderate HP infection | 7.30 (1.30–137.7) | 0.021 |                          | 11.3 (2.00–213) | 0.004 |
| High HP infection | 8.54 (1.52–161.0) | 0.011 |                          | 11.5 (2.02–217) | 0.003 |

HP: *Helicobacter pylori*; IgG: immunoglobulin G; PG: pepsinogen; CI: confidence interval; OR: odds ratio. In analysis including atrophic gastritis status (Model 2, 3, 5), atrophic gastritis was defined as: (A) PG I > 70 ng/mL and PG I/II < 3.0, (B) PG I/II < 3.0. Smoking was defined as habitually smoking more than one cigarette per day. Drinking was defined as habitually drinking more than one alcoholic drink per week. Physical activity was determined by asking participants whether they walk more than 30 minutes per day.
Polymorphism in these cytokines associated genes affect gastric inflammation and HP colonization. As these cytokines also play important roles in the pathogenesis of MetS [14], such polymorphisms may affect the prevalence of MetS. There is a possibility that we observed a population who have specific polymorphism which prevent progression of both HP infection and MetS. Furthermore, recent studies suggested the relationship of regulatory T cells (Treg cells) with MetS prevalence and HP infection. Specifically, reduced percentages of CD4(+)Foxp3(+) Treg cells were found in the abdominal fat of mice with genetic or diet-induced obesity [44]. In human studies, the percentages of Treg cells in the peripheral blood were significantly lower in children with MetS than those in healthy children [45], and similar results were noted in obese adults [46]. On the other hand, Treg cells were shown to attenuate HP infection and gastric inflammation [47, 48]. For example, an animal study reported that CD25+/Foxp3+ T cells regulate gastric inflammation including IgG production and HP colonization [47]. Therefore, individuals with high Treg cell function might be protected against MetS pathogenesis and HP-related gastritis. These phenotypical differences might be manifested in our study population and this may be the reason why the participants who showed low HP-specific IgG concentration with non-AG status have lower risk of MetS than HP IgG negative participants.

Our multiple logistic regression analysis revealed that AG was a significant risk factor for MetS. Furthermore, the addition of AG as a covariate weakened the significance of MetS risk in the moderate to high HP IgG concentration groups. This suggested that another background factor is at play between the two factors. The factor is most likely gastric inflammation. HP IgG concentration was reported to reflect serum IL-6 levels [49]. IL-6 is one of the important cytokines that mediate humoral immunity and plays a role in the pathogenesis of gastritis and MetS. In the present study, we observed a trend that MetS risk was increased according to HP IgG concentration. This finding supports the hypothesis that gastric chronic inflammation induces MetS [9–10].

In progressive AG, HP IgG is known to decrease and seronegativity is noted [50]. Therefore, AG with HP-seronegative status represents advanced-stage gastritis. Although we examined the interaction between HP IgG concentration and serum PG I/II ratio to clarify the effects of AG on the HP infection (Fig 1), we could not show the phenomenon that HP IgG concentration decrease along with PG I/II ratio lowering in progressive AG status clearly. In the present study, no participant had AG with HP-seronegative status and there were little subjects who have progressive AG. This characteristics of participants made it difficult to show the correlation between HP IgG and serum PG I/II in progressive AG. According to previous studies [51], in progressive AG, the amount of HP decrease and inflammation stabilizes. Gastric secretory function is disturbed and the secretion of gastric peptides like gastrin and ghrelin decreases [20]. Further research is needed how these changes effect on metabolic status.

This study has some limitations. First, this was a single-center, cross-sectional study. Therefore, we could not detect a causal relationship, and the generalization of our results should be considered with caution. The sample size used in the present study was smaller than that of the studies that showed significant MetS-HP relationships (< 3,000 participants), but larger than that of studies showing non-significant relationships (> 1000 participants) [52]. Discrepancies between the two criteria of AG and wide 95% CI might be caused by this small sample size. As described in method section, the AG criteria defined as PG I/II < 3 is reported to show relatively higher sensitivity than definition of AG as PG I < 70 μg/L and a PG I/II < 3, this different sensitivity may reflect the different results in evaluation of MetS risk for AG. In larger sample, the risk will be significant in both criteria. This study showed a weak trend of MetS risk in the HP seronegative group and moderate to high HP IgG concentration groups, with an OR of 1.84 and 95% CI of 0.77–5.50 (p = 0.18). However, in large populations, such
differences are presumed to be clearly detectable. Second, we did not perform HP virulence tests, measurement of inflammation markers, and measurement of serum ghrelin levels in this study. The investigation of these factors will reveal the precise mechanism involved in the relationship between MetS and HP. Further research is needed to reveal the precise mechanism of this phenomenon, and may yield important piece evidence that sheds light on the relationship between MetS and HP.

In conclusion, HP-associated gastritis appears to represent a risk factor for MetS. However, future research will need to determine why low and not negative HP infection status is associated with the lowest risk of MetS.

Author Contributions

Conceptualization: SS AT JT.
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