Evaluation of IL-17A and IL-17F genes polymorphism in Iranian dyspeptic patients

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Abstract: Helicobacter pylori (*H.pylori*) colonize the gastric mucosa of approximately 50 % of the world's population that involved in chronic gastritis. The relationship between Hp colonization and gastric inflammation is widely accepted. Polymorphisms in inflammation related genes such as cytokines were thought to partly determine the outcome of Hp infection and progression of gastritis. Interleukin IL -17A and IL-17F are inflammatory cytokines expressed by a novel subset of CD4+ Th cells, play important function in inflammation. **Aimed**: we evaluate association of IL-17A G197A and IL-17F A7488G polymorphisms with gastritis, Polymorphonuclear (PMN) and Monoculear (MN) infiltration in related to Hp. **Methods**: According to rapid urease test, PCR 16srRNA, urea and histological examination of biopsies, patients were classified Hp-infected and Hp-uninfected. The histological severity of gastritis was graded from normal to severe based on the degree of MN cell and PMN leukocyte infiltration, chronic gastritis and chronic active gastritis. Polymorphism in IL-17A G197A and IL-17F A7488G were evaluated by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). **Results**: AG, GG, AG/AA carriers of IL-17A G197A and AA, GA, GG, GA/GG carriers of IL-17F A7488G polymorphisms were not associated with MN infiltration, PMN infiltration, chronic gastritis and Chronic active gastritis in Hp-infected and Hp-uninfected groups ($p > 0.05$). AA genotype of IL-17A G197A was related to chronic gastritis and PMN infiltration in Hp-uninfected group. **Conclusion**: IL-17A G197A substitution may be a risk factor for development gastritis in Hp-uninfected patients, also affect the pathway MN cell production pathways.
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Introduction

Hp is a spiral-shaped gram negative flagellate bacterium that colonizes the gastric mucosa of approximately 50 % of the world's population (1). Hp infection induces inflammation in gastric mucosa that involved in chronic gastritis (2-4). Hp-associated inflammatory reaction is defined by an immense mucosal infiltration of macrophages, PMN leukocytes, T cells, and plasma (5-7). Gastritis may progress to other steps such as gastric atrophy, intestinal metaplasia, and finally gastric cancer. It may also lead to precancerous lesions looking like monoclonal lymphocytic proliferation, lymphoid follicle (LF) development and later primary gastric lymphoma (PGL) which develop only in a portion of individual with gastritis because of multifactorial effects of host virulence and bacterial factors that vary among different racial and social groups (8, 9). Studies on the evolution of gastric cancer report that genetic susceptibility and chronic Hp infection are important parts of a complex interaction to launch gastric carcinogenesis. Genetic variations in inflammation-associated genes, especially cytokines, are seems to play a role in the outcome of Hp infection and development of gastric lesions (10-13). Among host factors several inflammatory proteins including chemokines, cytokines and growth factors have been known to control adaptive immune response in contrast to Hp infection (14, 15). Firstly, El-Omar was reported an association between gastric cancer risk and interleukin 1 gene cluster polymorphisms (16). Studies from the western world show roles of anti - and pro -inflammatory cytokine genes such as interleukin (*IL*)-*1β,* its receptor

antagonist (*IL-1RN), IL-10,* and tumor necrosis factor (*TNF*-α) gene polymorphisms affect risk for gastritis (17) and GC (18), including its precursors (16, 19, 20). However Asian studies did not find any such association (21-23). Recently, an inflammation pathway of IL-23/IL-17 axis reported to play fundamental role in inflammatory and autoimmune diseases (24), such as psoriasis (25), lupus nephritis (26), and intestinal inflammation (27). lately, a lineage of CD4+ T helper cells that named Th17 cells has been specified as a unique subset of effector T helper cells, which undermine the Th1 and Th2 lineages (28, 29). Th17 cells, in particular according to the production of IL-17A and IL-17F, are generally accepted as a proinflammatory now. These cells have been related with pathogenesis of a raising list of inflammatory and autoimmune diseases, such as inflammatory bowel diseases, psoriasis and rheumatoid arthritis (30, 31). The six members IL-17 family of cytokines contains, IL-17A (also called IL-17), IL-17B, IL-17C, IL-17D, IL-17E and IL- 17F as IL-17A is the founding member. Despite the fact that little is known about the others but IL-17F was indicated is involved intense homology to IL-17A. IL-17F was reported to induce the expression of various cytokines, chemokines and adhesion molecules also these features shown to IL-17A, but reported IL-17F had significantly weaker activity than IL-17A (32). Furthermore, growing evidences suggested the role of IL-17A in Hp-related gastric diseases (32). Recently, Polymorphisms of IL-17A G197A (rs2275913) and IL-17F A7488G (p.His161Arg rs763780) have been recognized to be related with the susceptibility to rheumatoid arthritis and ulcerative colitis, respectively (33, 34). Anyway, they have not been evaluated with respect to precancerous risk. In the present study, we evaluated the IL-17A G197A and IL-17F A7488G polymorphisms of each single nucleotide polymorphism (SNP) with types of gastritis, chronic active gastritis and chronic gastritis, according to its clinicopathological features, interactions with cellular infiltration and role of Hp in a population from central Iran.

Subjects and Methods

A total of 435 patients with nonulcer dyspepsia (NUD) who were undergoing upper gastrointestinal endoscopy were tested for Hp infection using in-house RUT. Hp-infected and uninfected patients were determined by the rapid urease test, PCR 16srRNA, urea and histological examination of biopsies taken from the corpus. Patients were classified as Hp-infected only if the three tests were positive and Hp-uninfected if the three tests were negative, respectively. Demographic and clinical data were obtained through interview using a standard clinical pro forma. Exclusion criteria included history of gastric neoplasm or surgery, liver disease, and previous treatment with nonsteroidal anti-inflammatory drugs, proton pump inhibitors, antibiotics, or bismuth salts. Informed consents for participation were signed by all the study subjects. The study protocol was approved by the Clinical Research Ethics Committee of the Shahrekord University of Medical Sciences.

Histological examination

Sections of biopsy specimens were embedded 10 % buffered formalin and stained with hematoxylin and eosin to examine gastritis and with giemsa to detect Hp. The histological severity of gastritis was blindly graded from normal to severe based on the grade of PMN leukocyte and MN cell infiltration, chronic gastritis and chronic active gastritis according to the updated sydney system (Manxhuka-Kerliu et al., 2009) on a four-point scale: 0, no; 1, mild; 2, moderate; and 3, severe changes.

DNA isolation

Genomic DNA was extracted from biopsies taken from the corpus using Biospin Tissue Genomic DNA Extraction Kit (Bio Flux, Japan). All extracted DNA was resuspended in UltraPure RNAse/DNAse-Free Distilled water.

Genotyping for IL-17A G197A and IL-17F A7488G polymorphisms

Genotyping analysis IL-17A and IL-17F genotyping were performed by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) as reported by Wu et al (32). Primer sequences for IL-17A G197A and IL-17F A7488G variations are shown in Table I. The PCR amplification was performed in a total volume of 25 µL mixture containing: 100-ng genomic DNA, 1.0 µM of each primer, 200 µM of each dNTP, 2.0 mM of MgCl2 and 1.0 U Taq DNA polymerase and 10X Taq buffer (Fermentas) using the Biometra Tgradient 96 (Biometra, Germany). PCR conditions were as follows: denaturation at 96 °C for 5 min, followed by 33 cycles of 95 °C for 60 s, 65 °C for 60 s, and 72 °C for 50 s. A final extension was carried out at 72 °C for 7 min for IL-17A; denaturation at 95 °C for 6 min, followed by 33 cycles of 95 °C for 60 s, 65 °C for 55 s, and 72 °C for 60 s. A final extension was carried out at 72 °C for 6 min for IL-17F and products cooling down to 4 °C. The PCR products were digested by restriction endonuclease XagI (Fermentas) for IL-17A G197A and NlaIII (Fermentas) for IL-17F A7488G, according to the manufacturer's instructions, at 37°C overnight and then separated by 10% polyacrylamide gel electrophoresis. Gel analysis was performed after staining with ethidium bromide. PCR products were shown to be digested into three types of fragments (Fig. 1). To confirm the genotyping results,

selected PCR samples in both groups including samples of each genotype were re-genotyped by other laboratory personnel. There was no difference after genotyping the randomly selected samples.

Table I .PCR primers for amplification of IL-17A G197A and IL-17F A7488G genes

Primer	Primer sequence	Size of PCR product (bp)	References
IL-17A	Sense 5′-AACAAGTAAGAATGAAAAGAGGACATGGT-3′ anti-sense 5′-CCCCCAATGAGGTCATAGAAGAATC-3′	102 bp	(32)
IL-17F	sense 5′-ACCAAGGCTGCTCTGTTTCT-3′ anti-sense 5′-GGTAAGGAGTGGCATTTCTA-3′	143 bp	(32)

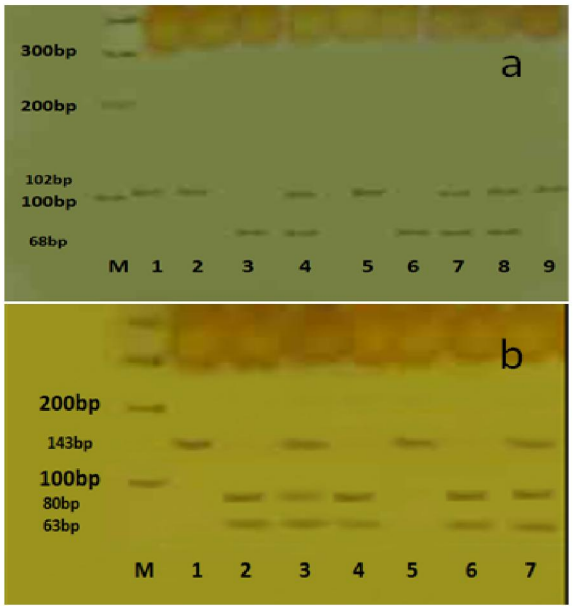

Fig 1: PCR-RFLP polyacrylamide gel electrophoresis of the IL-17A G197A and IL-17F A7488G polymorphisms indicating (a) IL-17A G197A, No.1, 2, 5, 9 (AA = 102 bp) 4,7,8 (AG = 102, 68, 34 bp*) 3,6 (GG= 68, 34 bp) genotypes and (b) IL-17F A7488G, No. 2, 4, 6 (AA = 80, 63 bp) 3,7 (GA = 143, 80, 63 bp) 1,5(GG= 143 bp) genotypes; * 34 bp is too short to detect and is not present in the gel.

Statistical analysis

Data were analyzed using SPSS 16.0(SPSS Inc., Chicago, IL). Hardy–Weinberg equilibrium in all subjects was analyzed with the x2 goodness-of-fit test before the ensuing analyses. The confounding effects of age and gender were adjusted using conditional logistic regression. Logistic regression analyses were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for gastritis in association with genotypes. Also statistical analysis was performed by non paired t test depending on the data set. Values of $p < 0.05$ were considered as significant.

Results

Demographic and clinical characteristics

Genomic DNA was obtained among the 193 (44.4%) Hp-infected and 242(55.6%) Hp-uninfected gastritis then the DNA all subjects were genotyped. The demographic data of all subjects were demonstrated in Table II. There was no significant difference between the two groups with respect to the age and gender distribution ($p > 0.05$).

Table II. Demographic data of study subjects

Variable	Hp-infected (%)	Hp-Uninfected (%)	*P* value
Overall	193(44.4%)	242(55.6%)	
Gender **Male** **Female**	 78(41.9%) 115(46.2%)	 108(58.1%) 134(53.8%)	 0.377
Age Mean±SD (year)	47.24 ±17.28	48.29 ±19.49	0.556

IL-17F 7488 and IL-17A 197 genotypes and Hp infection susceptibility

The frequencies of the polymorphism in cases and controls are shown in Table III. Frequencies of IL-17A 197 (AA, 7.9%; AG, 44.7% and GG, 47.4%; AG/AA, 51.9%) and IL-17F 7488 (AA, 81.2%; GA, 17.0% and GG, 1.7%; GA/GG, 18.8%) genotypes in Hp-infected were compared those (AA, 7.3%; AG, 46.3% and GG, 46.1%; AG/AA, 53.5%) and (AA, 81.2%; AG, 16.9% and GG, 1.9%; GA/GG, 18.8%) in Hp-uninfected respectively.

Table III. Adjusted Odds Ratios (ORs) and 95% confidence intervals (CIs) for Hp-infected in relation to IL-17F 7488 and IL-17A 197 genotypes

Genotype	Hp-infected (%)	Hp-Uninfected (%)	*P* value	*OR*[#] *(95% CI)*
IL-17A G197A				
AA	15(7.9%)	16(7.3%)	0.489	0.924(0.444-1.923)
AG	85(44.7%)	101(46.3%)	0.412	1.066(0.721-1.576)
GG	90(47.4%)	101(46.1%)	0.439	0.951(0.644-1.404)
AG/AA*	98(51.9%)	116(53.5%)	0.412	1.066(0.722-1.576)
IL-17F A7488G				
AA	143(81.2%)	173(81.2%)	0.550	0.998(0.599-1.664)
GA	30(17.0%)	36(16.9%)	0.538	0.990(0.582-1.685)
GG	3(1.7%)	4(1.9%)	1.000	1.105(0.244-5.003)
GA/GG**	33(18.8%)	40(18.8%)	0.550	1.002(0.601-1.671)

[#] Adjusted for age and gender.
*A allele, common between homozygote (AA) and heterozygote (AG) situation of IL-17A G197A genotype.
**G allele, common between homozygote (GG) and heterozygote (GA) situation of IL-17F A7488G genotype.

Table IV. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for gastritis in relation to IL-17A G197A and IL-17F A7488G genotypes in Hp-infected subjects

Genotype	Hp-infected (%)	Chronic active Gastritis(%)	Chronic Gastritis(%)	*P* value	*OR*[#] *(95% CI)*
IL-17A G197A					
AA	11(8.3%)	5(7.0%)	6(9.7%)	0.406	0.707(0.205-2.441)
AG	61(45.9%)	33(46.5%)	28(45.2%)	0.509	1.055(0.532-2.090)
GG	61(45.9%)	33(46.5%)	28(45.2%)	0.509	1.055(0.532-2.090)
AG/AA*	72(54.5%)	38(53.5%)	34(55.7%)	0.468	0.914(0.460-1.819)
IL-17F A7488G					
AA	99(81.8%)	55(85.9%)	44(77.2%)	0.157	1.806(0.707-4.612)
GA	19(15.7%)	7(10.9%)	12(21.1%)	0.101	0.461(0.168-1.265)
GG	3(2.5%)	2(3.1%)	1(1.7%)	1.000	1.839(0.162-20.828)
GA/GG**	22(18.2%)	9(14.1%)	13(22.8%)	0.157	0.554(0.217-1.415)

[#] Adjusted for age and gender.
*A allele, common between homozygote (AA) and heterozygote (AG) situation of IL-17A G197A genotype.
**G allele, common between homozygote (GG) and heterozygote (GA) situation of IL-17F A7488G genotype.

IL-17A G197A and IL-17F A7488G polymorphisms and gastritis

In our study population, IL-17A G197A (AA, AG, GG, AG/AA) and IL-17F A7488G (AA, GA, GG, GA/GG) variants and alleles evaluated in Hp-infected and Hp-uninfected population. All genotypes and G (GA/GG) allele of IL-17F A7488G also some genotypes (GA, GG) and A (AG/AA) allele of IL-17A G197A were not associated with chronic active gastritis and chronic gastritis in both groups ($p > 0.05$). AA genotype of IL-17A G197A was associated with decreased risk for chronic gastritis ($p = 0.017$) in Hp-uninfected subjects (Table IV and V).

IL-17A G197A and IL-17F A7488G polymorphisms and cellular infiltration

IL-17A G197A and IL-17F A7488G genotypes evaluated with grade of MN and PMN infiltration on Hp-infected and Hp-uninfected groups. The results are compared in Table VI and Table VII. All genotypes of IL-17F A7488G also some genotypes of IL-17A G197A (GA, GG) were not associated with MN and PMN infiltration in both groups ($p > 0.05$). AA genotype of IL-17A G197A was related with increased PMN infiltration ($p = 0.007$) in Hp-uninfected subjects.

Table V Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for gastritis in relation to IL-17A G197A and IL-17F A7488G genotypes in Hp-Uninfected subjects

Genotype	Hp-uninfected (%)	Chronic active Gastritis(%)	Chronic Gastritis(%)	*P* value	OR[#] (95% CI)
IL-17A G197A					
AA	9(12.2%)	6(27.3%)	3(5.8%)	0.017	6.125(1.372-27.352)
AG	33(44.6%)	8(36.4%)	25(48.1%)	0.252	0.617(0.221-1.720)
GG	32(43.2%)	8(36.4%)	24(46.2%)	0.303	0.667(0.239-1.859)
AG/AA**	42(56.8%)	14(63.6%)	28(53.8%)	0.303	1.500(0.538-4.183)
IL-17F A7488G					
AA	61(82.4%)	20(90.9%)	41(78.8%)	0.321	1.500(0.538-4.183)
GA	12(16.2%)	2(9.1%)	10(19.2%)	0.491	0.420(0.084-2.099)
GG	1(1.3%)	0(0.0%)	1(1.9%)	1.000	0.689(0.591-0.803)
GA/GG**	13(17.6%)	2(9.1%)	11(21.2%)	0.321	0.373(0.075-1.844)

[#] Adjusted for age and gender.
*A allele, common between homozygote (AA) and heterozygote (AG) situation of IL-17A G197A genotype.
**G allele, common between homozygote (GG) and heterozygote (GA) situation of IL-17F A7488G genotype.

Table VI Association of IL-17A G197A and IL-17F A7488G genotypes with cellular infiltration in Hp-infected subjects

Genotype	No.	Monoculear infiltration*	Polymorphonuclear infiltration*
IL-17A			
AA	11	1.09 ±0.701 (0-3)	0.45 ±0.522 (0-3)
AG	60	1.42 ±0.641 (0-3)	0.57 ±0.563 (0-3)
GG	72	1.32 ±0.728 (0-3)	0.49 ±0.531 (0-3)
***P* value**		0.434	0.691
IL-17F			
AA	108	1.36 ±0.703 (0-3)	0.52 ±0.520 (0-3)
GA	22	1.23 ±0.757 (0-3)	0.38 ±0.590 (0-3)
GG	3	1.33 ±0.577 (0-3)	0.67 ±0.577 (0-3)
***P* value**		0.652	0.367

*The histopathological parameters were scored as: 0, none; 1, mild; 2, moderate; 3, severe

Table VII Association of IL-17A G197A and IL-17F A7488G genotypes with cellular infiltration in Hp- Uninfected subjects

Genotype	No.	Monoculear inflitration*	Polymorphonuclear infiltration*
IL-17A			
AA	9	1.67 ±0.707 (0-3)	0.67 ±0.500 (0-3)
AG	44	1.11 ±0.784 (0-3)	0.18 ±0.390 (0-3)
GG	42	1.02 ±0.780 (0-3)	0.24 ±0.532 (0-3)
***P* value**		0.081	0.007
IL-17F			
AA	76	1.21 ±0.805 (0-3)	0.29 ±0.512 (0-3)
GA	17	0.76 ±0.562 (0-3)	0.12 ±0.332 (0-3)
GG	2	0.50 ±0.707 (0-3)	0.00 ±0.00 (0-3)
***P* value**		0.053	0.317

*The histopathological parameters were scored as: 0, none; 1, mild; 2, moderate; 3, severe

Discussion

In this study, we evaluated relationships between polymorphisms of IL-17A and IL-17F genes and gastritis in Iranian population. In the present study we found that frequencies of IL-17A and IL-17F genotypes and alleles were not comparable in infected-Hp patients and uninfected Hp subjects. In other hand we found that genotype of IL-17F 7488AA was related to gastritis in non-infected HP subjects but not in Hp-infected patients that suggest this genotype

of IL-17F may be independent on Hp intraction is associated with gastritis. Though, we found that variants of IL-17A gene, GG, AG, AA, and IL-17F, GA, GG, were not associated with gastritis in non-infected patients and patients infected with Hp. These findings suggest that IL-17A and IL-17F polymorphisms may independent of the presence or absence of Hp has no effect on gastritis (chronic active gastritis and chronic gastritis). Previously Arisawa et al showed that IL-17F 7488 polymorphism and Hp infection increase the activity and inflammation scores significantly in Japanese populations (35). The disparity between the results of this study and studies reporting significant risks associated with some of these alleles may be due to different patient groups, different populations, sample size power, differing clinical characteristics, controls drawn from high risk areas for chronic gastritis, multiple comparisons involving several genotypes and several histological endpoints, or confounding factors from other environmental co-factors. Whereas, one study suggest that the IL-17F 7488GA and GG genotype significantly increased gastric cancer risk tended to vary with tumor sites and histological types (32). We suggest this incoherence may indicate that the effect of some IL-17F genotypes on inflammatory processes varied with both inflammatory response steps and site of gastritis. This is consistent with the different mechanisms of inflammation so that in precancerous and gastritis stages some of cytokines are dominant and have specific role in start of inflammation process but as stage progress, another cytokines participate therefore we observe many cytokines affection in the latter stages. Also IL-17F polymorphism may influence the some steps of gastric carcinogenesis bot not all of them. As there is no enough biological report that revealed the function of IL-17F polymorphism, especially in precancerous, it is difficult to fully elucidate this phenomenon about our study. A study don't found association between the IL 17A 197 polymorphism and gastric cancer susceptibility (32) that has more accordance with our study. Also another study reported no significant difference in mucosal IL-17A(IL-17) mRNA expression between Hp-infected and non-infected patients (36) that may accordance with our study too. In other hand several studies shown that Hp-infection is also associated with a marked production of Th17 cytokines (37-39). Also demonstrated that IL-17 as a proinflammatory cytokine is upregulated in Hp-infected stomach biopsy in comparison to Hp-uninfected specimens (38). Another study report that Hp-motivated DCs subsequently activate autologous CD4+ T cells and induce IL-17 production (40). Regarding Hp, Mizuno et al. showed that infection with Hp is related with IL-17 production at the site of infection (39). According to disease outcome, IL-17 production seems to be related with ulcerogenesis (39). It has been reported that IL-1 and IL-23 seem to have major role in the induction of the observed IL-17 production. Also recent report indicating that IL-23 contributes to maintaining IL-17 production in Hp-infected gastric mucosa (41). According our data we suggest that IL 17A 197 polymorphism may not affect the IL-17A increasing. However, as other reports shown, further study such as evaluation of IL-1 polymorphism, IL-23, IL-17 and IL-1 cytokines will be necessary to clarify the function and interaction of these polymorphism regarding the histologic response and role of Hp infection.

IL-17F genotypes was not found to be associated with neutrophil and lymphocyte infiltration in HP-infected and HP-uninfected which suggest IL-17F genotypes don't affect the production of neutrophil and lymphocyte pathway. Also we don't observed relationship between IL-17A genotypes and MN inflitration that indicate these genotypes may not affect production of lymphocyte pathway. But we found significant association between IL-17A polymorphism (AA) and PMN infiltration that suggest AA genotype may affect production of neutrophil pathway. Since this relationship observed in HP-uninfected but not in HP-infected subjects, we suggest that presence or absence HP may affect production of neutrophils. About IL-17F, our results may contradict to those study that suggest IL-17F 7488 polymorphism interact with Hp-infection to increase the activity and inflammation scores. Albeit, These study related to cancer and not pre-cancerous stage (32). Also another in vitro and no in vivo study report a new role for DCs in the recognition of Hp by indicating their capability to conduct a Th17 response against Hp and show the presence of IL-17-secreting lymphocytes in the gastric mucosa during Hp infection (40). In this study in particular, we have demonstrated that all genotypes of IL-17F and genotypes of GG and AG from IL-17A doesn't play a role in control of Hp-induced gastritis but AA genotype of IL-17A may, depend on presence or absence of HP, have a role in gastritis. As a report shown immune response during Hp infection, especially during the chronic stage of infection, may induced both Th1 and Th17 (42). We suggest that may be an induced inflammatory response by Hp that more caused by Th1 cells. Whether these cytokines are independent mediator in the pathogenesis of gastritis or not cannot be excluded with safety from the presented findings. Further investigation is necessary to elucidate fully the exact role of IL-17A and IL-17F in the pathogenesis of gastritis.

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