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Helicobacter pylori Suppresses Serum Immunoglobulin Levels in Smokers with Peptic Ulcer: Probable Interaction Between Smoking and *H. pylori* Infection in the Induction of Th1 Predominant Immune Response and Peptic Ulceration

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1. Introduction

1.1 T helper cell subset

Helicobacter pylori (*H. pylori*) and smoking are well known risk factors for gastric ulcer, and both are classified as definite carcinogens. Interestingly, the two also reportedly share common immune response features.

With recent advances in immunology, various functions of T lymphocytes (T cells) have been discovered. T cells are divided into suppressor and helper on the basis of immunological functionings, and T helper cells are now known to consist of two distinct groups, as demonstrated using mouse models in the 1980s [Reiner, 2008; Mosman & Coffman, 1989]. Both groups are derived from naïve T cells: interleukin-12 (IL-12) causes naïve T helper cells to differentiate into type 1 (Th1) cells, while augmentation of IL-4 around naïve T cells leads to Th2 differentiation. Th1 cells produce IL-2 and interferon- γ (IFN-γ) to maintain cell mediated immunity against intracellular organisms such as viruses and mycobacteria, and Th2 cells produce IL-4 and IL-13 promoting the differentiation of B cells to plasma cells and the induction of class-switching resulting in IgE production. Differentiated plasma cells produce immunoglobulins which participate in mucosal defense against extracellular organisms including *H. pylori*. Groundbreaking research inspired subsequent studies which finally led to the discovery of Th17 cells [Steinman, 2007] and T regulatory cells (Treg) [Sakaguchi *et al.*, 1995, 2008]. As a consequence of this pioneering research, T helper cells, at present, are sub-grouped into 4 types according to the differences in their cytokine productions (Table 1).

Table 1. T helper subsets

Inductive, Selective T helper subset	Cytokines	Secreted Cytokines
Th1*	IL-12, IFN- γ	IL-2, TNF, IFN- γ
Th2**	L-4, IL-33	IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-25
Th17	TGF-β, IL-6, IL-23	IL-17, IL-6, IL-22, TNF
Treg	TGF- β, IL-10	TGF- β IL-10, CTLA4

Table 1a. Subsets of T helper cells and related cytokines

T helper subset	Protection	Pathology
Th1*	Defense against intracellular organisms	Inflammation
Th2**	Defense against extracellular bacteria at mucosal and epithelial surface	Allergy
Th17	Defense against extracellular bacteria	Autoimmunity Cancer
Treg	Suppression of immune response	Anti-inflammation

Concept of Th1 and Th2 cells originate from the cytokine production pattern of murine T cells. Therefore attention such differences is necessary when considering human immunity.
*Exert cell mediated immunity
**Exert humoral immunity
CTLA4: Cytotoxic T lymphocyte antigen 4
IFN: Interferon
IL: Interleukin
TGF: Tumor growth factor
TNF: Tumor necrosis factor
Table 1: Table by Reiner modified by authors (ref. 1 p412)

Table 1b. Roles of each T helper subset

Th1 cells produce IL-2, IFN- γ, tumor growth factor-β(TGF- β) and so on, thereby exerting cell mediated immunity mainly through IFN- γ.
Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, and so on, thereby up-regulating humoral immunity against extracellular pathogens and inducing allergy mainly through IL-4.
Th17 cells produce IL-17A, IL-17F, IL-22 and so on, thereby eradicating bacterial/fungal infections and might be related to autoimmunity and cancer. Th17 cells produce inflammatory cytokines, and over-expression of such cytokines is associated with autoimmune diseases such as type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis. IL-6 and TGF- β are key cytokines for differentiation into Th17.
Treg produces TGF- β, IL-10, and cytotoxic T lymphocyte antigen 4 (CTLA4), and suppress activated T cells/dendritic cells. Treg can suppress Th1, Th2, and Th17 to terminate immune responses/inflammation and also plays crucial roles in immune tolerance [Sakaguchi *et al.*, 1995, 2008].

As stated above, Th1 cells can down-regulate immunoglobulin production through secretion/production of IFN-γ whereas Th2 cells IL-4-dependently up-regulate immunmoglobulin secretion/production.

1.2 Th1 response in patients with peptic ulcer

As to gastric and duodenal ulcers, *H. pylori* infection has increasingly been reported to exert a Th response on type 1 (Th1 cells) [Hida *et al.,* 1999; Holck *et al.;* 2003; D'Elios *et al.,* 1997, 2003,2005; Itoh *et al.,* 2005; Goll *et al.,* 2007; Ayada *et al.,* 2009; Mohammadi *et al.,* 1996; Fan *et al.,* 1998; Bamford *et al.,* 1998; sommer *et al.,* 1998; Lindholm *et al.,* 1998; Ihan *et al.,* 2000; Smythies *et al.,* 2000; Akhiani *et al.,* 2002; Guiney *et al.,* 2003; Amedei *et al.,* 2006; Taylor *et al,* 2006], and peptic ulcer disease has also been increasingly reported to produce Th1 skew [Hida *et al.,* 1999; D'Elios *et al.,* 2007; Goll *et al.,* 2008; Codolo *et al.,* 2008; Del Prete *et al.,* 2008; Shimada *et al.,* 2008; Watanabe *et al.,* 2010; Hosseini *et al.,* 2010]. In addition, a unique study conducted by Itoh *et al.* suggested Th1 polarization of gastric T cells in the antrum of dyspeptic pateints, irrespective of *H. pylori* infection [Itoh *et al,* 1999].

1.3 Th1 response in patients with *H. pylori* infection

H. pylori has increasingly been reported to show Th1 predominance [Mohammadi *et al.,* 1996; D'Elios *et al.,* 1997, 2003,2005; Bamford *et al.,* 1998; Fan *et al.,* 1998; Lindholm et al., 1998; Sommer *et al.,* 1998; Hida *et al.,* 1999; Ihan et al., 2000; Smythies et al., 2000; Akhiani et al., 2002; Guiney *et al.,* 2003; Holck *et al.;* 2003; Itoh *et al.,* 2005; Amedei *et al.,* 2006; Taylor *et al,* 2006; Goll *et al.,* 2007; Ayada *et al.,* 2009] with only a few studies obtaining opposing results [Bergman *et al.,* 2004; Campbell *et al.,* 2004; Kayhan *et al.,* 2008; Kido *et al.,* 2010]. Therefore, *H. pylori* is presumed to down-regulate immunoglobulin production/secretion.

1.4 Influence of smoking on serum immunoglobulins and Th response

Smoking has been reported to suppress serum immunoglobulin levels [Andersen *et al.,* 1982; Tollerud *et al.,* 1995; Barbour *et al.,* 1997; Gonzalez-Quintela *et al.,* 2007] and some studies have indicated a Th1 skew in smokers [Hallquist *et al.,* 2000; Whetzel *et al.,* 2007; Kikuchi *et al.,* 2008], although controversial data have also been reported [Hagiwara *et al.,* 2001; Zeidel *et al.,* 2002; Cozen *et al.,* 2004].

1.5 Possible mechanisms by which *H. pylori* infection induces Th1 skew

Although a Th1 skew in *H. pylori*-infected patients is suggested by the vast majority of research conducted on this subject, the precise mechanism by which Th1 differentiation is induced has yet to be elucidated. However, some investigators have conducted crucial studies that may explain this phenomenon: Eaton *et al.* reported CD4+ T cells to be essential for the development of *H. pylori*-induced gastritis [Eaton *et al.,* 2001], and Nagai *et al.* showed the coccoid form of *H. pylori* to reach to Peyer's patches and then be phagocytosed by dendritic cells thereby sensitizing CD4+ T cells, and that these sensitized CD4+ T cells homed to the lamina propria of the gastric mucosa [Nagai *et al.,* 2007]. Finally, such dendritic cells produce IL-12 which promotes Th1 differentiation after phagocytosis of *H. pylori* [Codolo *et al.,* 2008].

In addition to mentioned above, a number of investigators have demonstrated a Th1 skew in patients with peptic ulcers, as compared to those with gastritis or gastric cancer [Hida *et al.,* 1999; D'Elios *et al.,* 2007; Goll *et al.,* 2008; Codolo *et al.,* 2008; Del Prete *et al.,* 2008; Shimada *et al.,* 2008; Hosseini *et al.,* 2010; Watanabe *et al.,* 2010].

We therefore conducted the current study to assess the influence of both *H. pylori* and smoking on serum immunoglobulin levels for the purpose of evaluating the presence of Th1 skew in patients with peptic ulcers.

2. Patients and method

2.1 Study design

Study 1. Effects of current smoking on levels of serum immunoglobulins
To evaluate the influences of smoking on serum immunoglobulin levels, serum IgG, IgA, and IgM levels were measured in both peptic ulcer and non-ulcer gastritis patients with and without *H. pylori* infection.
Study 2. Effects of *H. pylori* infection on levels of serum immunoglobulins in peptic ulcer patients
To evaluate the influences of *H. pylori* infection on serum immunoglobulin levels, serum IgG, IgA, and IgM were measured in peptic ulcer patients, both current smokers and non-smokers.
Study 3. As a control for study 2, serum IgG, IgA, and IgM levels were measured in non-ulcer gastritis patients with and without current smoking.

2.2 Patients

Dyspeptic patients and those recommended to undergo fiberscopic examination received gastroduodenoscopic examinations. Those endoscopically diagnosed as having gastric or duodenal ulcers were included in the current study. Following informed consent to check *H. pylori* status and immunohematologic parameters, dyspeptic patients underwent gastrofiberscopic examination. Patients with hematologic, immunologic, rheumatic, malignant, and infectious diseases were excluded. Those taking corticosteroids, antibiotics, and/or immunosuppressive drugs were also excluded. Because non-steroidal anti-inflammatory drugs (NSAIDs) [Franch *et al,* 1994; Mazzeo *et al.,* 1998; Yamaki *et al.,* 2003, 2005; Andreone *et al.,* 2004; Mored *et al.,* 2004] and proton-pump inhibitors (PPIs) [Tsutsumi *et al.,* 2005; Matsukawa *et al.,* 2007] have increasingly been reported to skew the T helper response toward type 2, patients taking these drugs were also excluded. Both smokers and non-smokers with endoscopically diagnosed non-ulcer gastritis were also evaluated as control groups.

2.3 Methods

Following informed consents to measure titers of serum anti-*H. pylori* IgG antibody, serum immunoglobulins and complete blood cell counts, patients with gastric or duodenal ulcer was diagnosed according to the classification of Sakita and Miwa [Matsukawa *et al.,* 1997], and those with non-ulcer gastritis did according to the updated Sydney System [Dixon *et al.,* 1996] under gastrofiberscopic observation. To evaluate *H. pylori* status, biopsy specimens were obtained from the antrum and lower body of the greater curvature in the stomach and from the major lesions. The samples from the antrum and lower body were placed in rapid urease test (RUT) kits, and the results were evaluated 24 hr later. These samples were also prepared for pathologic evaluation. Immediately after completion of the procedure, blood samples were collected to measure IgG, IgA, IgM, and anti-*H. pylori* IgG antibodies. Serum levels of IgG, IgA, and IgM were measured by an automated turbidimetric immunoprecipitation method [Matsukawa *et al., 1997*], and the anti-*H. pylori* antibody was measured by a commercially available ELISA kit. Confirmed *H. pylori* infection required

both RUT and anti-*H. pylori* IgG antibody to be positive. Smoking status was ascertained on the day of the endoscopic examination.

2.3.1 Statistical analysis

Data were expressed as means+/-SD. The statistical significance of differences was anlyzed employing the Student unpaired *t-test* and the χ-square test. We evaluated statistical differences using Macintosh StatView version 4, and p values less than 0.05 were accepted as statistically significant.

3. Results

3.1 Recruited patients and controls

Table 2. Profiles of patients and controlls

Sex	Female	Male
Number	90	146
Age (years)**	60.0+/-11.5	53.4+/-13.6
*H. pylori**	66 (73.3%)	127 (87.0%)
Smokers*	24 (37.5%)	82 (56.2%)

Table 2a. Profiles of patients with peptic ulcer

Sex	Female	Male
Number	408	312
Age (years)	56.6+/-14.3	55.8+/-13.3
*H. pylori**	229 (56.1%)	192 (61.1%)
Smokers*	44 (10.8%)	106 (34.0%)

Smokers: peptic ulcer>non-ulcer gastritis (female.=0001 and male <.0001)
H. pylori prevalence: peptic ulcer>non-ulcer gastritis (<.0001 for females and males)
*P<.0001 **P=.0001

Table 2b. Profiles of patients with non-ulcer gastritis

There were 146 patients with gastric ulcer, 58 with duodenal ulcer, and 32 with both types (Table 3). There were no differences in these lesions between smokers and non-smokers.

Smokers (F:M)			
Body	Angle/Antrum	Duodenum	Multiple
33 (7:26)	30(10:20)	28 (2:26)	15 (5:10)
Non-smokers (F:M)			
Body	Angle/Antrum	Duodenum	Multiple
51 (32:19)	32(15:17)	30 (15:15)	17 (5:12)
Total			
Body	Angle/Antrum	Duodenum	Multiple
84 (39:45)	62(25:37)	58 (17:41)	32 (10:22)

Table 3. Ulcer location (F:M)

Table 2 presents the profiles of both patients with peptic ulcer and those with non-ulcer gastritis serving as controls. In total, 236 patients (F:M=90:146) were diagnosed as having gastric and/or duodenal ulcers and were enrolled in this study. There was an age difference

between female and male patients (F:M=60.0+/-11.5 vs. 53.4+/-13.6 years, p=.0001) (Table 2a). Patients with non-ulcer gastritis consisted of 408 females and 312 males, and there was no difference in age between genders (56.6+/-14.3 vs. 55.8+/-13.3 years) (Table 2b).
Patients with peptic ulcer had higher prevalences of both *H. pylori* infection and smoking, as compared to those with non-ulcer gastritis: p=.0001 for smoking in females and <.0001 for smoking in males, while p<.0001 for *H. pylori* infection in both females and males (Tables 2a and 2b).

3.2 Serum levels of IgG, IgA, and IgM in the current study

3.2.1 The results of study 1

Tables 4 and 5 show the results of study 1, examining the effects of current smoking on serum immunoglobulin levels in patients with petic ulcer and non-ulcer gastritis. There was age difference between smokers and non-smokers with *H. pylori* infection among ulcer patients (p=.0019). Smoking was associated with definite suppressions of serum IgG, IgA, and IgM levels in *H. pylori*-infected patients with peptic ulcer (p<.0001, .0006, and .0009, respectively), whereas ulcer patients without *H. pylori* infection showed no such tendency. Table 5 presents the effects of current smoking on serum immunoglobulin levels in non-ulcer patients with gastritis. There was an age difference between smokers and non-smokers (p<.0001). Among patients with non-ulcer gastritis, smokers had suppressed serum IgG (p<.0001), IgA (p<.05), and IgM levels, although the reduction of IgM in patients with *H. pylori* infection failed to reach statistical significance. Like those with *H. pylori* infection, non-ulcer patients without *H. pylori* infection also showed suppression of both IgG and IgM (p<.05, respectively).
Table 4. Influence of smoking on serum immunoglobulin levels in peptic ulcer patients

	Smokers	Non-smokers	P
N	92	101	
Age	52.2+/-12.2	58.0+/-13.2	.0019
IgG	1178.0+/-250.3	1376.6+/-343.2	<.0001
IgA	218.4+/-98.2	271.4+/-109.1	.0006
IgM	93.8+/-41.9	123.1+/71.1	.0009

Table 4a. Serum immunoglobulin levels in *H. pylori*-infected patients

	Smokers	Non-smokers	P
N	14	29	
Age	56.0+/-13.7	60.7+/-13.7	NS
IgG	1348.6+/-254.7	1463.7+/-286.3	NS
IgA	295.1+/-113.2	253.2+/-99.3	NS
IgM	105.8+/-49.8	123.5+/47.9	NS

IgG: Immunoglobulin G (mg/dl)
IgA: Immunoglobulin A (mg/dl)
IgM: Immunoglobulin M (mg/dl)
N: Number of patients
NS: Not significant
P: Probability

Table 4b. Serum immunoglobulin levels in patients without *H. pylori* infection

Table 5. Effects of smoking on serum immunoglobulin levels in non-ulcer gastritis patients

	Smokers	Non-smokers	P
N	93	325	
Age	53.5+/-11.6	60.0+/-11.4	<.0001
IgG	1224.1+/-264.3	1392.1+/-278.6	<.0001
IgA	236.6+/-97.0	264.0+/-112.7	.0384
IgM	104.7+/-58.6	112.4+/63.5	NS

Table 5a. Serum immunoglobulin levels in *H. pylori*-infected patients

	Smokers	Non-smokers	P
N	57	247	
Age	51.9+/-13.4	57.8+/-13.9	.0071
IgG	1205.5+/-278.6	1295.0+/-237.7	.0228
IgA	254.7+/-118.3	251.0+/-89.7	NS
IgM	83.4+/-42.9	104.8+/69.0	.0408

IgG: Immunoglobulin G (mg/dl)
IgA: Immunoglobulin A (mg/dl)
IgM: Immunoglobulin M (mg/dl)
N: Number of patients
NS: Not significant
P: Probability

Table 5b. Serum immunoglobulin levels in patients without *H.* pylori infection

3.2.2 The results of study 2

Table 6. Effects of *H. pylori* infection on serum immunoglobulin levels in peptic ulcer patients

H. pylori	Positive	Negative	P
N	92	14	
Age	52.6+/-12.2	56.0+/-13.7	NS
IgG	1177.9+/-250.3	1348.6+/-254.7	.0197
IgA	218.4+/-98.2	295.1+/-113.2	.0092
IgM	93.8+/-41.9	105.8+/-49.8	NS

Table 6a. Serum immunoglobulin levels in smokers

H. pylori	Positive	Negative	P
N	101	29	
Age	58.0+/-13.2	60.7+/-13.7	NS
IgG	1376.6+/-343.3	1463.7+/-286.3	NS
IgA	271.4+/-109.1	253.2+/-99.3	NS
IgM	123.1+/-71.1	123.5+/-47.9	NS

IgG: Immunoglobulin G (mg/dl)
IgA: Immunoglobulin A (mg/dl)
IgM: Immunoglobulin M (mg/dl)
N: Number of patients
NS: Not significant
P: Probability

Table 6b. Serum immunoglobulin levels in non-smokers

Table 6 presents the results of study 2, examining the effects of *H. pylori* infection on serum levels of immunoglobulins in peptic ulcer patients. As a whole, patients with peptic ulcer showed decreases in serum IgG, IgA, and IgM levels, although only the decrease in IgG reached statistical significance (data not shown). Among those with peptic ulcer, smokers with *H. pylori* infection showed decreases in both IgG and IgA (p<.0197 and .0092, respectively), whereas the difference in IgM did not reach statistical significance (Table 6a). In contrast to smokers, among patients with peptic ulcers, non-smokers with *H. pylori* infection showed no difference in IgG, IgA, or IgM levels.

3.2.3 The results of study 3

Table 7 presents the results of study 3, the control for study 2, examining the effects of *H. pylori* infection on serum levels of immunoglobulins in non-ulcer gastritis patients. As to the effect of *H. pylori* infection, patients with non-ulcer gastritis showed a phenomenon opposite to that in peptic ulcer patients, except for IgA in smokers. Patients with *H. pylori* infection had increased serum IgG, IgA, and IgM levels regardless of smoking status, although only the IgG difference in non-smokers (p<.0001) and the IgM difference in smokers (p=.0288) were statistically significant. Compared to patients with peptic ulcer, *H. pylori* infection, at minimum, did not suppress serum immunoglobulin levels regatdless of smoking status. *H. pylori* infection appeared to up-regulate serum immunoglobulin levels in non-ulcer patients with gastritis.

Table 7. Effect of *H. pylori* infection on serum immunoglobulin levels in patients with non-ulcer gastritis

H. pylori	Positive	Negative	P
N	93	57	
IgG	1234.5+/-264.3	1205.5+/-278.6	NS
IgA	236.6+/-97.0	254.7+/-111.8	NS
IgM	104.7+/-58.6	83.4+/42.9	.0288

Table 7a. Serum immunoglobulin levels in smokers

H. pylori	Positive	Negative	P
N	325	247	
IgG	1392.1+/-288.7	1295.0+/-237.7	<.0001
IgA	264.0+/-112.7	251.0+/-89.7	NS
IgM	112.4+/-63.5	104.8+/69.0	NS

IgG: Immunoglobulin G (mg/dl)
IgA: Immunoglobulin A (mg/dl)
IgM: Immunoglobulin M (mg/dl)
N: Number of patients
NS: Not significant
P: Probability

Table 7b. Serum immunoglobulin levels in non-smokers

4. Discussion

We initially showed definite suppression of serum immunoglobulin levels in current smokers with *H. pylori*-associated peptic ulcer (Tables 4a), and this suppression was observed even in patients without *H. pylori* infection, although the difference did not reach statistical significance possibly due to our small sample size (Table 4b). In contrast to patients with peptic ulcer, those with non-ulcer gastritis showed suppressed levels of serum immunoglobulins, regardless of *H. pylori* status. These observations support the notion that smoking causes a skewed Th1 response in current smokers, regardless of whether or not *H. pylori* infection or peptic ulceration is present. As to the Th skew in smokers, there are conflicting reports, with some reporting a Th2 skew in smokers [Hagiwara *et al.,* 2001; Zeidel *et al.,* 2002; Cozen *et al.,* 2004]. However, two noteworthy studies conducted recently have challenged this concept. Whetzel *et al*. reported elevated peripheral IFN-γ levels, especially in female smokers, and in surgically resected specimens from the colon of smokers [Whetzel *et al.,* 2007], and Kikuchi *et al*. showed that nicotine exerted a Th1-dominant effect via nicotinic acetylcholine receptors in the intestine [Kikuchi *et al.,* 2008].

As stated in the introduction, *H. pylori* infection is known to skew T helper differentiation toward type 1 (Th1) properties (production of IL-2, IFN- γ, and TNF)- thereby counteracting Th2-dependent processes. Th1 differentiation may reduce humoral immunity by down-regulating immunoglobulin production resulting in suppressions of serum IgG, IgA, and IgM levels. *H. pylori*, therefore, is presumed to down-regulate serum immunoglobulin levels in infected individuals. On the contrary, extracellular bacterial infections usually up-regulate IgM initially, and then IgG. Because *H. pylori* extracellularly colonizes the gastric mucosa, it should induce a Th2 response because such ubiquitous bacterium would be expected to colonize the mucosa (Table 1b). In accordance with this theory, Mohammadi *et al.* reported the presence of a Th2 response to effectively reduce the bacterial load in a mouse model of *H. pylori* infection: Th1 cells enhance gastritis and Th2 cells reduce bacterial load [Mohammadi *et al.,* 1997]. The current data from the control group in study 3 are also in accordance with this theory, i.e., *H. pylori* infection raises levels of serum immunoglobulins in both smokers (IgM) and non-smokers (IgG) with non-ulcer gastritis. This differs from the situation in patients with peptic ulcer, in whom *H. pylori* infection did not suppress serum immunoglobulin levels, of non-ulcer patients suggesting the unique phenomenon of Th1 skew seen only in patients with peptic ulcer (Table 7). Taking our current observations together, suppression, i.e., a lack of upregulation of serum immunoglobulins appears to be a unique feature of smokers with both peptic ulcer and *H. pylori* infection. Th1 skew observed in *H. pylori*-infected patients with peptic ulcer appeared to exceed the expected Th2 skew in patients infected with extracellular bacteria such as *H. pylori* itself, especially in smokers. In addition, vast majority of gastric T cells may be already polarized to produce Th1 cytokine even in the absence of *H. pylori* infection [Itoh, et al., 1999]. We therefore stress that the Th1 skew induced by *H. pylori*, smoking, and the presence of peptic ulceration may synergistically exert a Th1 response which prevails over the expected Th2 skew, i.e., up-regulation of serum immunoglobulin levels induced by the presence of extracellular bacterial infection by *H. pylori* itself.

The Th1 skew observed in patients with *H. pylori* infection indicated a Th1-polarized response to be associated with mucosal damage that can induce peptic ulcer, while a mixed Th1 and IL-4-drived Th2 polarized response appeared to be associated with a low degree of gastric inflammation and reduced bacterial load resulting in the prevention of ulcer

formation [D'Elios *et al.,* 1997, 2003, 2005; Mohammadi *et al.,* 1997; Holck *et al*., 2003]. Th2 drive therefore may be preferable to hasten ulcer healing in such patients. However, mixed or dysregulated Th responses may trigger T cell-dependent B cell activation involved in the development of low grade B cell lymphoma associated with *H. pylori* [D'Elios *et al.,* 2003, 2005].

5. Conclusion

As shown herein, current smoking is consitently associated with suppressed serum immunoglobulin levels (study 1), and *H. pylori* infection definitely reduced these levels in smokers with peptic ulcer (study 2). Furthermore *H. pylori* infection up-regulated IgG, IgA, and IgM in the absence of peptic ulcer. Current smoking, *H. pylori* infection, and the presence of peptic ulceration may interact to suppress the levels of serum immunoglobulins as a result of a Th1 shift which overwhelms the Th2 shift expected with extracellular bacterial infection.

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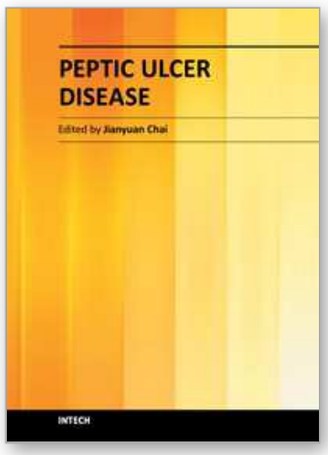

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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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