**Name of journal:** **World Journal of Gastroenterology**

**ESPS Manuscript NO: 5413**

**Columns: BRIEF ARTICLES**

**Risk factors associated with Barrett’s epithelial dysplasia**

Fujita M *et al*. Risk factors for Barrett’s epithelial dysplasia

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**Received:** September 5, 2013 **Revised:** October 27, 2013

**Accepted:** November 18, 2013

**Published online:**

**Abstract**

**AIM:** to elucidate risk factors associated with dysplasia of short segment Barrett’s esophagus.

**METHODS:** A total of 151 Barrett’s esophagus (BE) patients who underwent endoscopic examination from 2004 to 2008 in Aoyama Hospital, Tokyo Women’s Medical University and whose diagnosis were confirmed from biopsy specimen were enrolled in the study. BE was diagnosed based on endoscopic findings of gastric-appearing mucosa or apparent columnar lined esophagus proximal to the esophagogastric junction. Dysplasia was classified into 3 grades - mild, moderate and severe - according to the guidelines of the Vienna classification system for gastrointestinal epithelial neoplasia. Anthropometric and biochemical data were analyzed to identify risk factors for BE dysplasia. The prevalence of *Helicobacter pylori* (*H. pylori*) infection and the expression of *p53* by immuno-histological staining were also investigated.

**RESULTS:** Histological examination classified patients into 3 types, a specialized columnar epithelium (SCE) type (*n* = 65), a junctional type (*n* = 38) and a gastric fundic type (*n* = 48). The incidence of dysplasia or adenocarcinoma from BE of the SCE type was significantly higher than that of the other 2 types (*p* < 0.01). The univariate analysis revealed that gender, *H. pylori* infection, body weight, *p53* overexpression**,** and low diastolic blood pressure (BP) were associated with BE dysplasia. In contrast, body mass index, waist circumference, metabolic syndrome complications, and variables related to glucose or lipid metabolism were not associated with dysplasia. Multivariate logistic analysis showed that overexpression of *p53* [odds ratio (OR) =13.1, *p* = 0.004], *H. pylori* infection (OR=0.19, *p* = 0.066), and diastolic BP (OR=0.87, *p* = 0.021) were independent risk factors for epithelial dysplasia in BE patients with the SCE type.

**CONCLUSION:** Overexpression of *p53* is a risk factor associated with dysplasia of BE, however, *H. pylori* infection and diastolic BP inversely associated with dysplasia of BE might be protective to BE dysplasia.

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**Key words:** Barrett’s esophagus; dysplasia; *Helicobacter pylori*; *p53*; risk factors

**Core tip:** Since Barrett’s esophagus (BE), known as a precancerous state of adenocarcinoma, will be common in Asian countries it is important to establish a high risk group or a strategy for screening or follow-up of BE. We present here the results of univariate and multivariate analysis to identify variables associated with dysplasia of BE. The *p53* expression in immunohistochemistry was associated with dysplasia, and *Helicobacter pylori* infection and high diastolic blood pressure may act as a protective factor to dysplastic change of BE. These three factors may be candidates to establish a high risk group of adenocarcinoma of esophagus.

Fujita M, Nakamura Y, Kasashima S, Misaka R, Nagahara H. Risk factors associated with Barrett’s epithelial dysplasia. *World J Gastroenterol* 2013;

**Available from:** URL: http://www.wjgnet.com/1007-9327/

**DOI:** http://dx.doi.org/10.3748/wjg.

**INTRODUCTION**

Barrett’s esophagus (BE) is defined as a condition in which normal squamous mucosa is replaced by columnar epithelium. This intestinal metaplasia of the distal esophagus is considered to bea pre-malignant condition where metaplasia may progress to dysplasia and subsequently to adenocarcinoma[1-6]. BE is generally regarded as a complication of chronic and severe gastroesophageal reflux disease (GERD). Elevation of the intra-abdominal pressure by obesity is a factor contributing to GERD, suggesting that obesity is a risk factor for BE[7-10]. GERD and BE appear to be metabolic syndrome (MS)-related complications, given that waist circumference, obesity, and body mass index (BMI) are associated with GERD[11-16].

Moreover, *Helicobacter pylori* (*H. pylori*) infection may play a key role in suppression of BE. Two main inhibiting roles for development of BE have been postulated in *H. pylori* infection; *H. pylori-*induced atrophic gastritis resulting in less gastric acid secretion and neutralization of the gastric acid by ammonia produced by *H. pylori* independently of gastric atrophy[17-23]. Cag-A positive *H. pylori* infection is strongly associated with a reduced risk of esophageal adenocarcinoma, and the association is independent of gastric atrophy, suggesting the involvement of a mechanism other than reduced acidic gastric reflux[24-26]. In Japan, the prevalence of *H. pylori* is declining and it can be easily eradicated; however, it remains uncertain whether the incidence of BE will increase or decrease as a consequence of the low prevalence of *H. pylori* infection[27,28].

BE is characterized by 3 types of columnar epithelium, namely cardiac type (junctional type), fundic type, and intestinal metaplasia type [specialized columnar epithelium type (SCE) type]. It has been shown that there is an extremely high incidence of adenocarcinoma in the distal esophagus arising from SCE in patients with BE[29,30].

BE is classified as either long segment type (length ≥ 3 cm) or short segment type (length ＜ 3 cm). In Western countries, long segment Barrett’s esophagus (LSBE) is most prevalent, while short segment Barrett’s esophagus (SSBE) is most common and the incidence of adenocarcinoma arising SSBE are steadily increasing in Japan[27,28,31-33].

A number of studies have shown that most patients with BE do not progress to cancer, although some do[1-3,29,30]. Thus, it is important to determine how BE progresses to dysplasia and adenocarcinoma and to identify the type of BE patients who may have a possibility of malignant transformation in SCE. It has been reported that central adiposity, metabolic syndrome, and high BMI are associated with BE and adenocarcinoma[10-16]. In this paper, we present risk factors associated with BE dysplasia.

**MATERIALS AND METHODS**

***Study population***

A total of 151 patients (105 male, 46 female) with histologically-diagnosed BE were enrolled. All cases were incident case and enrolled in a consecutive series from April 2004 and March 2008. Patients who had received antibiotics, steroids, or non-steroidal anti-inflammatory drugswere excluded from the study. Patients were also excludedif they had peptic ulcer, underwent partial gastrectomy, consumed alcohol excessively, or had morbid diseases such as liver cirrhosis and uremia. Written informed consent was obtained from all patients.

***Endoscopic examination***

BE was diagnosed based on endoscopic findings of gastric-appearing mucosa or apparent columnar lined esophagus proximal to the esophagogastric junction. The esophagogastric junction was defined as the pinch at the end of the tubular esophagus coinciding with the proximal margin of the gastric folds of the hiatal hernia. BE was defined as columnar mucosa proximal to the distal ends of esophageal longitudinal palisading vessels according to the Japanese Society of Esophageal Disese[34,35]. These veins are visible endoscopically when a conscious patient takes a deep breath.

SSBE was defined as an epithelium length less than 3 cm and LSBE as an epithelium length greater than 3 cm, as described previously[1,2,29,30] The length of BE were measured by measuring forceps (Olympus, Tokyo, Japan).

When abnormal columnar mucosa characteristics such as erosions, red flares, elevated regions, or mucosal breaks were observed between the proximal limit of the gastric folds and squamous epithelium, we detected metaplastic change by chromoendoscopy and staining mucosa with crystal violet (Figure 1a, b). For chromoendoscopy 200000 units of pronase (Pronase MS; Kaken Pharmaceutical Co., Matsumoto, Japan) dissolved in 300 ml of warm water was sprayed around the esophagogastric junction area with a spray-tube, and then a 0.03% solution of crystal violet was applied on the same area. A few minutes later, the sprayed area was washed thoroughly with water. When the mucosa showed a tubular or villous pit pattern, which is typical of SCE in BE was observed in the esophagogastric junction, we performed a targeted biopsy in that area. BEwas confirmed by histological findings frombiopsy specimens in all patients.

***Histology***

All biopsy specimens were fixed in formalin, embedded in paraffin, sectioned, mounted on slides and then stained with hematoxylin and eosin using standard techniques. Dysplasia was classified into 3 grades-- mild, moderate and severe - according to the guidelines of the Vienna classification system for gastrointestinal epithelial neoplasia[17,36]. To perform immunohistological staining of p53, an anti-human p53 antibody (DO-7 mouse monoclonal antibody, IR616, Dako, Denmark) was used according to the manufacturer’s protocol. The expression level of p53 protein was determined and graded based on the intensity of nuclear staining in columnar cells as follows: no staining (-), positive nuclear staining in 5% to 10% of cells (+), and positive nuclear staining in more than 10% of cells (++), according to the work of Keswani *et al*[37] (Figure 2). All biopsy specimens were examined by an experienced gastrointestinal pathologist.

***H. pylori* infection**

The presence of gastric *H. pylori* was determined based on the results of Giemsa and/or Steiner’s silver staining in a minimum of 3 gastric surveillance biopsies (1 obtained from the antral greater curvature, 1 from the greater curvature of the mid to distal body, and 1 from the lesser curvature in the proximal body). *H. pylori* colonization was assessed by an experienced pathologist blinded to the clinical data. Patients who were not confirmed *H. pylori* infection by using above histological analysis were further retested by other methods. We confirmed *H. pylori* negative by combination of serum HP specific antibody test with 13C-urea breath testor *H. pylori* antigen test in the stool.

***Anthropometry and blood pressure***

The body weights of patients, while not wearing heavy outdoor clothing or shoes, was measured to the nearest 0.1 kg using a digital scale. Height (barefoot) was measured using a portable stadiometer. Waist circumference was measured to the nearest 0.1 cm using a plastic tape just above the umbilical portion with standing in a relaxed position after gentle expiration. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m2). Blood pressure was measured with a mercury sphygmomanometer on each arm after at least 10 min of rest.

***Definition of MS and biochemical analysis***

MS was diagnosed according to the criteria set out by the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome[38]: central obesity (waist circumference ≥ 85 cm Japanese males, ≥ 90 cm Japanese females) plus any 2 of the following; raised triglycerides≥ 150 mg/dl or specific treatment for this lipid abnormality; reduced high density lipoprotein (HDL)-cholesterol < 40 mg/dl in males and females; raised blood pressure **(**systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg**)** or treatment of hypertension; fasting glucose ≥ 110 mg/dl or previously diagnosed Type 2 diabetes mellitus.

After a 12-h overnight fast, venous blood samples were taken for the standard biochemical data.

***Statistical analysis***

Statistical analysis was performed using SPSS 17.0 computer software for Windows (SPSS Japan Inc.). Results forcontinuous variables were expressed as mean ± SD for each subject group. The statistical difference was determined by two-sided Student’s *t*-test (for equal variance cases) or Welch’s *t*-test (for not equal variance cases). Non-normally distributed variables were compared by the Mann-Whitney *U* test. Variables given as proportions were compared using the *2* test. The relationships between risk factors and dysplasia including adenocarcinoma of BE were examined by multivariate logistic regression analysis. A *p-*value < 0.05 was considered to be statistically significant. Differences in mean laboratory data and anthropometric data across 3categories were evaluated using 1 way analysis of variance.

**RESULTS**

***Endoscopic findings of BE by crystal violet staining***

Crystal violet staining was performed when we recognized BE during routine endoscopic examination. The intestinal metaplastic lesion was stained with a violet color resulting in easy recognition of the targeted biopsy (Figure 1a, b).

***Dysplasia in SCE type BE***

The average age of the 151 BE patients was 62.9 years (± 10.6 years) and the ratio of males (*n* = 105) to females (*n* = 46) was 2.3:1. The demographic characteristics of the patients according to pathological classification are shown in Table 1. BE patients were classified into 3 categories: SCE type (*n* = 65), junctional type (*n* = 38), and gastric fundic type (*n* = 48), and the incidence of dysplasia in these 3 groups was 30.8% (20/65), 7.9% (3/38) and 4.2% (2/48), respectively. The ratio of dysplasia in patients with SCE type BE was significantly higher than in patients with junctional- and gastric fundic-type BE (*p* = 0.02 and *p* = 0.002, respectively).

***Variables associated with dysplasia in SCE type BE***

We focused on the SCE type of BE because of the high rate of dysplastic change associated with this condition, as shown in Table 1. We compared variables between SCE type BE patients with and without dysplasia (Table 2). *H. pylori* infection, *p53* over expression (Figure 2), body weight, and diastolic BP were identified as risk factors strongly associated with dysplastic change. In contrast, BMI, waist circumference, MS complications, and variables related to glucose or lipid metabolism were not associated with dysplasia. We then conducted multivariate logistic analyse~~i~~s of those variables that’s showed low p-values in the univariate analysis shown in Table 2**;** namely, gender, *H. pylori* infection, body weight, *p53* overexpression**,** and low diastolic BP. Among these these variables, *p53* overexpression, *H. pylori* infection, and low diastolic BP were independent risk factors associated with dysplasia complicated in patients with BE of the SCE type (Table 3). The *p*-value of *H. pylori* infection was 0.066, not less than 0.05, but its odds ratio was 0.187 that seemed to give a relatively strong effect on the association with Barrett epithelial dysplasia. Thus, we included it in the Table 3.

***Risk factors associated with progression of SCE from non-dysplastic epithelium to low-grade and high-grade dysplasia***

We assesed lineality of the relationship between risk factors and progression. We classified dysplasia into 3 groups - no dysplasia (*n* = 45), low-grade dysplasia (*n* = 14), and high-grade dysplasia (*n* = 6) including adenocarcinoma (Table 4). Based on analysis of variance, 6 variables were significantly associated with alteration of SCE from non-dysplasia to high-grade dysplasia: length of BE, *H. pylori* infection, *p53* overexpression, body weight, GERD**,** and low diastolic BP. Only 2 of these 6 variables showed a linear correlation with alteration to high-grade dysplasia; *i.e.*, *H. pylori* infection, and *p53* overexpression (Table 4).

***Correlation between p53 expression and progression of SCE from non-dysplasia to low- and high-grade dysplasia***

Given the strong association observed between *p53* overexpression and dysplasia seen in the multivariate logistic analysis (Table 3), we analyzed the level of *p53* expression and its association with progression of non-dysplastic SCE to low**-** and high-grade dysplasia including adenocarcinoma. The expression of *p53* was categorized as no expression (-), moderate expression characterized by positive nuclear staining in 5% to 10% of cells (+), and high expression, characterized by positive nuclear staining in more than 10% of cells (++) (Figure 2). As shown in Table 5, only 10% of patients in the non-dysplastic SCE group expressed *p53* at a low level, whereas expression was high in the group with high-grade dysplasia (*p* < 0.01).

**DISCUSSION**

A number of reports, based on endoscopic, biochemical, and anthropometric data, have identified GERD, absence of *H. pylori* infection, MS, waist circumference, and body weight as risk factors associated with the presence of BE[7-16]. One of the most notable findings from epidemiological reports has been a strong inverse association between *H. pylori* infection and dysplasia of Barrett’s epithelium[17,18,21-26].

Esophageal adenocarcinoma derived from BE is not common in Japan as compared with Western countries, whereas gastric carcinoma is more prevalent in Japan. This inverse relationship may reflect the high prevalence of *H. pylori* infection in Japan and the low prevalence in Western countries[24,39,40].

Another notable epidemiological difference between these regions is the length of BE; *i.e.*, SSBE is common in Japan but LSBE is more prevalent prevailing in Western countries[27,28,30,31]. The underlying reasons for this difference are not currently known.

Herein, we have identified risk factors associated with presence of BE dysplasia by comparison of patients with non-dysplasia to those with low- to high-grade dysplasia including adenocarcinoma. In our cohort, 94% of BE cases were the SSBE type (Table 2). Overexpression of *p53* was most important risk factor associated with dysplasia and adenocarcinoma (Table 3), and the level of *p53* expression was strongly related to the grade of dysplasia (Table 5). A number of studies have shown that *p53* overexpression is increased in parallel with progression of histological changes from metaplasia to high-grade dysplasia and adenocarcinoma[41-44]. In specimens obtained from surgical resection, expression of *p53* has been observed in the region of adenocarcinoma as well as in adjacent dysplastic epithelia. In addition, in many cases, *p53* gene mutations are found at the specific position resulting in a change in a specific amino acid residue in both adenocarcinoma and adjacent dysplastic epithelia[41,42]. These results suggest that *p53* mutation, which is relatively uncommon in non-dysplastic BE, is an important step in the progression to adenocarcinoma. Galipeau *et al*[45] showed that inactivation of *p53* by mutation is strongly associated with progression to aneuploidy**,** possibly through the loss of *p53*-mediated apoptosis and cell cycle arrest. The accumulation of these aneuploid cell populations has been shown to increase the risk of developing adenocarcinoma [46].

The possible causal role of *p53* in tumorigenesis as well as tumor progression in BE has been postulated based on histological evidence showing that *p53* mutations are more frequent in advanced stages in histology. Thus, it is important to address the hypothesis that *p53* overexpression could predict progression of non-dysplastic Barrett’s esophagus to adenocarcinomas. Younes *et al*[47] studied *p53* accumulation *via* immunohistochemistry in 54 patients with Barrett’s metaplasia, dysplasia, or adenocarcinoma; *p53* accumulation increased in parallel with histological progression from metaplasia to adenocarcinoma. Follow-up biopsies were available in 23 out of 54 patients who had dysplasia in at least 1 biopsy specimen. They showed only 1 of 21 (4.8%) patients with all *p53***-**negative in multiple biopsieshad histological progression. In contrast, 2 of 3 (67%) patients with *p53***-**positive biopsies progressed to high-grade dysplasia or intramucosal carcinoma (1 patient was lost to follow up). These retrospective data suggest that *p53* accumulation increases the risk of progression from low- to high-grade dysplasia. These data are also consistent with our results showing that the level of *p53* expression was correlated with the grade of dysplasia (Table 5), suggesting that mutated *p53*, which is expressed at an early stage, may stimulate the tumor progression in the metaplasia-dysplasia-adenocarcinoma sequence of BE.

We found a strong inverse association between *H. pylori* infection and the dysplasia in BE(Table 2); the lowest prevalence of *H. pylori* was observed in the high-grade dysplasia group (Table 4). Many studies have reported that the absence of *H. pylori* colonization is associated with a greater likelihood of developing esophageal dysplasia and adenocarcinoma[18,20-23]. Hence, *H. pylori* infection appears to have a protective effect against the development of dysplasia and adenocarcinoma in BE. The mechanism through which the absence of *H. pylori* colonization is associated with dysplasia in BE is unknown, but there are several possibilities. First, *H. pylori* infection, in particular the more virulent Cag A-positive strain**,** may lead to gastric atrophy resuting in suppression of acid production; this may lower the risk of BEand esophageal adenocarcinoma[24,25].

We analyzed the degree of atrophy of stomach according to Kimura -Takemoto’s classification[48] to confirm the association of low acidity and BE dysplasia. We could not find any statistically significant difference in ratio of atropy and distribution of degree of atrophy in normal subjects and subjects with dysplasia (data not shown).

With regard~~s~~ to the possible outcome of *H. pylori* eradication in BE, only a few studies have reported that the SSBE developed at 24 mo after *H. pylori* eradication, suggesting induction of SSBE by the eradication[49]. In Japan, the prevalence of *H. pylori* infection has been decreasing recentlyand the use of *H. pylori* eradication therapy has flourished. For this reason, the incidence of BE and adenocarcinoma is likely to increase, and it is therefore important to determine risk factors for malignant changes associated with the development of dysplasia and adenocarcinoma in BE after *H. pylori* eradication.

In our multivariate logistic analysis, diastolic blood pressure was an independent risk factor associated with progression of BE from non-dysplastic to dysplastic epithelium (Table 3). When we evaluated user of anti-hypertensive drugs, especially Ca antagonist, in normal subjects and subjects with dysplasia, we could not find any statistically significant difference (data not shown). Although this is the first report of a relationship between diastolic blood pressure and dysplasia in BE, the underlying mechanisms are unclear.

When we analyzed the relationship variables among three categories such as patients with no dysplasia, low- or high- grade dysplasia by analysis of variance, we detected no difference in diastolic blood pressure (Table 4). We hypothesized the non-linear relationship of diastolic BP among three groups shown in Table 4 as follows: If the variables were associated with malignant potential of Barrett epithelia it may show the linear relationship among three groups, normal, low grade and high grade dysplasia. The diastolic BP, however, may be associated with the step such as columnar epithelial metaplasia relatively early step of transformation.

In our univariate analysis, body weight was extracted as a risk factor for dysplasia in BE, but BMI and waist circumference were not. In a Swedish study of 189 cases of newly diagnosed esophageal adenocarcinoma, a strong positive association was found between BMI and esophageal adenocarcinoma when controlling for GERD symptoms[11]. A study from the Veterans Association in the United States found subjects with a BMI > 30 had a 4-fold greater risk for BE as compared with controls with a BMI < 25[7]. More recently, several studies have revealed that waist circumference, but not BMI, has a modest independent association~~s~~ with the incidence BE, dysplasia and adenocarcinoma. Other studies have reported that a higher waist-to-hip ratio is associated with BE when data are adjusted for GERD symptoms and BMI[14,50]. In our multivariate logistic analysis, anthropometric variables were not extracted as risk factors.

In conclusion we demonstrated that *p53* overexpression, absence of *H. pylori* infection, and low diastolic blood pressure are independent risk factor for associated with dysplastic changes of BE. Future studies such as well-desighned prospective studies are needed to elucidate the mechanisms underlying the association of these risk with the sequence of progression of dysplasia to adenocarcinoma in BE and establish a high-rsk group progressing to adenocarcinoma.

**COMMENTS**

***Background***

Barrett’s esophagus (BE) is defined as a condition in which normal squamous mucosa is replaced by columnar epithelium. This intestinal metaplasia of the distal esophagus is considered to bea pre-malignant condition where metaplasia may progress to dysplasia and subsequently to adenocarcinoma. It has been reported that central adiposity, metabolic syndrome, and high body mass index (BMI) are associated with BE and adenocarcinoma.

***Research frontiers***

In order to identify variables associated with BE dysplasia, many variables taken from biochemical and anthropometric data, *p53* expression examined by immunostainig and *Helicobacter pylori* (*H. pylori*) infection were analyzed. Consequently we analyzed so different type of variables.

***Innovations and breakthroughs***

Only three variables were selected by multivariate analysis. *p53* stainig was positively associated dysplasia, on the other hand *H. pylori* infection and diastolic blood pressure were inversely associated with BE dysplasia.

***Applications***

Using these three variables, the prospective study to determine the high risk group of BE dysplasia or factors related to progression of dysplasia may be a next step of study.

***Terminology***

BE is defined as a intestinal metaplasia in which normal squamous mucosa is replaced by columnar epithelium. BE is characterized by 3 types of columnar epithelium, namely cardiac type (junctional type), fundic type, and intestinal metaplasia type [specialized columnar epithelium type (SCE) type]. In these three type of BE, SCE type is especially considered to be a precancerou lesion of adenocarcinoma of esophagus.

***Peer review***

The authors showed the risk factors associated with Barrett's epithelial dysplasia. They enrolled 151 patients with BE in a single arm hospital. This study was well-organized and well investigated. They clearly showed that *p53* expression, absence of *H. pylori* infection and low diastolic blood pressure are risk factors associated with dysplasia of BE.

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**P-Reviewer:** Goll R,Naito Y, Seow-Choen F **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Figure 1 Barrett’s esophagus stained by crystal violet.** A: Regular observation of Barrett’s esophagus; B: Staining with crystal violet in the same region.

**Figure 2 Immunostaining of *p53*.** The upper panel shows hematoxylin and eosin staining and the lower panel shows immunostaining of *p53* using the identical sample. A: (-), no *p53* expression; B: (+), moderate *p53* expression characterized by positive nuclear staining in 5% to 10% of cells; C: (++), high *p53* expression characterized by positive nuclear staining in more than 10% cells.

**Table 1 Characterization of the 3 types of Barrett’s esophagus**

|  |  |  |
| --- | --- | --- |
|  | specialized columnar |  |
|  | epithelium type | junctional type | gastric fundic type |  |
|  | (*n* = 65) | (*n* = 38) | (*n* = 48) | *p*-value |
| Gender | 52/13 | 10/28 | 25/23 | 0.005 |
| Age (yr) | 62.9 ±10.6 | 65.0 ± 8.2 | 58.8 ± 11.9 | 0.07 |
| Dysplasia | 20/65 (30.8%) | 3/38 (7.9%) | 2/48 (4.2%) | 0.003 |

**Table 2 Univariate analysis of variables associated with Barrett’s epithelial dysplasia**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Normal** | **Dysplasia** | ***p*-value** | **odds ratio** | **95%CI** |
| (*n* = 45) | (*n* = 20) |  |  |  |
| Gender (Male/Female) | 33/12 | 19/1 | 0.073 | 0.145 | 0.017-1.202 |
| Age (yr) | 65.0 ± 9.8 | 64.2 ± 11.3 | 0.730 | 0.991 | 0.940-1.044 |
| Length of BE (SSBE/LSBE) | 43/2 | 18/2 | 0.402 | 2.389 | 0.312-18.294 |
| *H. pylori* infection rate | 34/9 (2) | 7/12 (1) | 0.0021 | 0.154 | 0.047-0.506 |
| *p53* positive rate | 4/41 | 13/7 | < 0.0011 | 19.036 | 4.800-75.499 |
| Body weight (kg) | 61.0 ± 9.7 | 68.2 ± 10.6 | 0.0191 | 1.081 | 1.013-1.154 |
| BMI (kg/m2) | 23.1 ± 2.8 | 23.7 ± 3.2 | 0.451 | 1.074 | 0.891-1.295 |
| Waist circumference (cm) | 86.9 ± 7.9 | 88.4 ± 9.0 | 0.585 | 1.022 | 0.945-1.105 |
| GERD | 19/26 | 9/11 | 0.835 | 1.120 | 0.387-3.235 |
| Hypertension (BP > 130/85) | 29/14 (2) | 9/10 (1) | 0.094 | 0.395 | 0.133-1.172 |
| Systolic BP (mmHg) | 127 ± 16 | 121 ± 16 | 0.264 | 0.980 | 0.946-1.015 |
| Diastolic BP (mmHg) | 76 ± 10 | 69 ± 8 | 0.0091 | 0.907 | 0.843-0.976 |
| Diabetes | 14/25 (6) | 10/9 (1) | 0.188 | 2.071 | 0.701-6.124 |
| Fasting blood glucose (mg/dl) | 118 ± 32 | 111 ± 19 | 0.447 | 0.992 | 0.971-1.013 |
| HbA1c (%) | 5.6 ± 1.0 | 5.5 ± 0.7 | 0.804 | 0.919 | 0.470-1.798 |
| Dyslipidemia | 24/19 (2) | 11/8 (1) | 0.322 | 0.576 | 0.193-1.715 |
| TG (mg/dl) | 144 ± 58 | 139 ± 98 | 0.807 | 0.999 | 0.991-1.007 |
| TC (mg/dl) | 202 ± 30 | 189 ± 33 | 0.141 | 0.987 | 0.969-1.005 |
| HDL-C (mg/dl) | 55 ± 13 | 53 ± 9 | 0.850 | 0.996 | 0.950-1.043 |
| LDL-C (mg/dl) | 118 ± 26 | 107 ± 30 | 0.152 | 0.985 | 0.964-1.006 |
| Fatty liver | 17/13 (15) | 6/8 (6) | 0.395 | 0.574 | 0.159-2.066 |
| γ-GT (U/l) | 55 ± 48 | 59 ± 77 | 0.781 | 1.001 | 0.992-1.011 |
| AST (IU/l) | 24 ± 8 | 25 ± 10 | 0.769 | 1.009 | 0.948-1.075 |
| ALT (IU/l) | 24 ± 15 | 24 ± 12 | 0.906 | 0.998 | 0.958-1.039 |
| Hs-CRP(mg/dl) | 0.107 ± 0.142 | 0.101 ± 0.116 | 0.890 | 0.706 | 0.005-98.830 |
| Metabolic syndrome | 15/14 (16) | 6/8 (6) | 0.586 | 0.700 | 0.194-2.530 |

CI: confidence interval; BE: Barrett’s epithelial; SSBE: short segment Barrett’s esophagus; LSBE: long segment Barrett’s esophagus; *H. pylori*: *Helicobacter pylori*; BMI: body mass index; GERD: gastroesophageal reflux disease; BP: blood pressure; TG: triglyceride; TC: total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: Hemoglobin A1c; γ-GT: gamma-glutamyl transpeptidase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Hs-CRP: high sensitivity C - reactive protein.

**Table 3 Multivariate analysis of variables associated with Barrett’s epithelial dysplasia**

|  |  |  |  |
| --- | --- | --- | --- |
| risk factor | *p*-value | odds ratio | 95%CI |
| *p53* | 0.004 | 13.107 | 2.275-75.504 |
| *H. Pylori* | 0.066 | 0.187 | 0.031-1.116 |
| diastolic BP | 0.021 | 0.874 | 0.780-0.980 |

CI: confidence interval; *H. pylori*: *Helicobacter pylori*; BP: blood pressure.

**Table 4 Analysis of variance for the 3 categories of Barrett’s epithelial: Non-dysplasia, low-grade dysplasia, and high-grade dysplasia**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No dysplasia** | **Low grade** | **High grade** | ***p*-value** |
|  | (*n* = 45) | (*n* = 14) | (*n* = 6) |  |
| Gender (Male/Female) | 33/12 | 13/1 | 6/0 | 0.177 |
| Age (yr) | 65.0 ± 9.8 | 64.3 ± 12.4 | 63.8 ± 9.4 | 0.941 |
| Length of BE (SSBE/LSBE) | 43/2 | 14/0 | 4/2 | 0.044 |
| *H. pylori* infection rate | 34/9 | 6/7 | 1/5 | 0.002 |
| *p53* positive rate | 4/41 | 7/7 | 6/0 | < 0.001 |
| Body weight (kg) | 61.0 ± 9.7 | 69.5 ± 9.8 | 65.5 ± 12.5 | 0.033 |
| BMI (kg/m2) | 23.1 ± 2.8 | 24.0 ± 3.1 | 23.3 ± 3.7 | 0.689 |
| Waist circumference (cm) | 86.9 ± 7.9 | 88.1 ± 9.6 | 89.3 ± 8.4 | 0.848 |
| GERD | 19/26 | 9/5 | 0/6 | 0.020 |
| Hypertension (BP > 130/85) | 29/14 | 6/7 | 3/3 | 0.155 |
| Systolic BP (mmHg) | 127 ± 16 | 120 ± 19 | 125 ± 6 | 0.473 |
| Diastolic BP (mmHg) | 76 ± 10 | 69 ± 9 | 71 ± 6 | 0.016 |
| Diabetes | 14/25 | 7/6 | 3/3 | 0.425 |
| Fasting blood glucose (mg/dl) | 118 ± 32 | 113 ± 19 | 108 ± 20 | 0.712 |
| HbA1c (%) | 5.6 ± 1.0 | 5.5 ± 0.7 | 5.5 ± 0.8 | 0.971 |
| Dyslipidemia | 24/19 | 5/8 | 3/3 | 0.612 |
| TG (mg/dl) | 144 ± 58 | 118 ± 71 | 183 ± 137 | 0.190 |
| TC (mg/dl) | 202 ± 30 | 195 ± 36 | 174 ± 25 | 0.124 |
| HDL-C (mg/dl) | 55 ± 13 | 55 ± 9 | 48 ± 7 | 0.407 |
| LDL-C (mg/dl) | 118 ± 26 | 112 ± 33 | 97 ± 17 | 0.201 |
| Fatty liver | 17/13 | 5/7 | 1/1 | 0.744 |
| γ-GTP (U/l) | 55 ± 48 | 40 ± 31 | 101 ± 126 | 0.097 |
| AST (IU/l) | 24 ± 8 | 26 ± 10 | 24 ± 10 | 0.837 |
| ALT (IU/l) | 24 ± 15 | 25 ± 13 | 21 ± 10 | 0.803 |
| Hs-CRP (mg/dl) | 0.107 ± 0.142 | 0.104 ± 0.126 | 0.084 ± 0.029 | 0.973 |
| Metabolic syndrome | 15/14 | 4/7 | 2/1 | 0.604 |

BE: Barrett’s epithelial; SSBE: short segment Barrett’s esophagus; LSBE: long segment Barrett’s esophagus; *H. pylori*: *Helicobacter pylori*; BMI: body mass index; GERD: gastroesophageal reflux disease; BP: blood pressure; HbA1c: Hemoglobin A1c; TG: triglyceride; TC: total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; γ-GT: gamma-glutamyl transpeptidase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Hs-CRP: high sensitivity C - reactive protein.

**Table 5 Relationship between the level of *p53* expression and the grade of dysplasia**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Normal**  | **Low grade** | **High grade and Ca** |
|  | (*n* = 45) | (*n* = 14) | (*n* = 6) |
| *p53* (-) | 41 | 7 | 0 |
| *p53* (+) | 4 | 4 | 4 |
| *P53* (++) | 0 | 3 | 2 |

Pearson *2* test, *p* < 0.001.