ORIGINAL RESEARCH PAPER

Gastroneology

KEY WORDS: Gastric premalignant lesion, malondialdehyde, gastritis

DIFFERENCES OF SERUM MALONDIALDEHYDE LEVELS IN GASTRITIS PATIENTS WITH AND WITHOUT GASTRIC PREMALIGNANT LESION

Taufik Sungkar Division of Gastroentero-Hepatology, Department of Internal Medicine, Universitas Sumatera Utara, Haji Adam Malik General Hospital, Medan, Indonesia

Masrul Lubis Division of Gastroentero-Hepatology, Department of Internal Medicine, Universitas Sumatera Utara, Haji Adam Malik General Hospital, Medan, Indonesia

Gontar Alamsyah Siregar* Division of Gastroentero-Hepatology, Department of Internal Medicine, Universitas Sumatera Utara, Haji Adam Malik General Hospital, Medan, Indonesia *Corresponding Author

Ginanda Putra Siregar Division of Urology, Department of Surgery, Universitas Sumatera Utara, Haji Adam Malik General Hospital, Medan, Indonesia

ABSTRACT

The main pathogenesis of gastritis and gastric cancer are inflammation process and the role of free radicals. Chronic inflammation can lead a gastric mucosa to be atrophy that can develop into intestinal metaplasia and dysplasia, and finally develop into gastric cancer. Malondialdehyde (MDA) is a free radical biomarker and found increased on both gastritis and gastric cancer. The purpose of this study was to determine differences of serum MDA levels in gastritis patients with and without gastric premalignant lesion. This cross sectional study was conducted in endoscopic unit of Adam Malik General Hospital Medan from April to June 2018. Gastric premalignant lesion diagnosis was made when one or more of the following were present: chronic atrophic gastritis, intestinal metaplasia, or dysplasia. A plasma MDA examination was performed using an HPLC MDA kit. Data were statistically analyzed. There were significant differences MDA levels in gastritis between with and without gastric premalignant lesion ($p = 0.024$). MDA levels in gastritis patients with gastric premalignant lesion were higher than without premalignant gastric lesion.

INTRODUCTION

Gastritis is an inflammatory process in the gastric mucosa and submucosa as response to acute or chronic injuries.[1] Latent mucosal inflammation can lead gastric mucosa to atrophy which can develop into intestinal metaplasia and dysplasia, and eventually can develop into invasive cancer. The natural course of gastric cancer is known as the Correa cascade.[2,3]

Helicobacter pylori infection has been generally accepted as a initiator of the Correa cascade and from epidemiological studies data, this infection play a role as a major risk factor for gastric cancer.[3,4]There has been reported about increasing the prevalence of chronic inflammation, inflammatory activity, glandular atrophy and intestinal metaplasia in cases of superficial gastritis, erosive gastritis, gastric ulcers, and early gastric cancer both in cases accompanied by *H. pylori* infection or not. The extent and severity of gastritis objectively can be seen through the histopathologic examination by the Updated Sydney System (USS) that assessing lymphocyte infiltration, neutrophil activity, atrophic gastritis, intestinal metaplasia, and dysplasia where atrophic gastritis, intestinal metaplasia, and dysplasia are classified as gastric premalignant lesion.[5]

Data about absolute risk associated with gastric premalignant lesion are inconsistent. The mean risk of stomach cancer reported in Europe in patients with dysplasia varied from 0% to 73%.[6] Study by Song et al reported 1 in 50 with atrophic gastritis, 1 in 39 with intestinal metaplasia, and 1 of 19 with dysplasia will become gastric cancer within 20 years.[3]

The main pathogenesis of gastritis and gastric cancer are inflammation process and the role of free radicals. Free radicals cause mucosal damage by degrading of the basalis epithelial membrane, disrupting cell metabolism, and damaging DNA.[7] Anion superoxide radicals (O_2^-) are generated by neutrophil infiltration reactions to cellular lipid membranes that lead to lipid peroxidation and metabolized into malondialdehyde (MDA). MDA is cytotoxic that was reported to play a role in tumorigenesis and carcinogenic.[8] Free radicals have very short half-lives that are difficult to measure in the laboratory. Damage to lipid tissue due to free radicals can be checked by measuring the MDA which is a lipid peroxidation product. The production of free radicals is indirectly assessed with lipid peroxidation levels.[9] This study aimed to determine the differences serum MDA levels in gastritis with and without gastric premalignant lesion.

METHODS

Patient Selection

This study was a cross-sectional study design on eighty consecutive gastritis patients that were admitted to endoscopic unit in General Hospital Haji Adam Malik Medan from April - June 2018. Inclusion criteria were male or female > 18 years old, patients diagnosed gastritis by endoscopic and histopathologic examination and cooperative patients. While for exclusion criteria are patients who have received *H.pylori* eradication therapy in the last 6 months, suffering from systemic diseases such as diabetes mellitus, hypertension, kidney failure, hepatitis, liver cirrhosis, pancreatitis, chronic heart failure and malignant disease. This study was approved by local ethics committee and all patients have been given informed consent.

Histopathologic Examination

Diagnosis of gastritis was performed by histopathologic examination. The procedure was performed by taking biopsies from antrum and corpus gaster, staining by Hematoxylin-Eosin.[10] All specimens were examined in the anatomical pathology laboratory at the Universitas Sumatra Utara. Gastric premalignant lesion diagnosis was made when one or more of the following were present: chronic atrophic gastritis, intestinal metaplasia, or dysplasia.

Measurement of MDA

High performance liquid chromatographic (HPLC) analysis was performed by isocratic method using HPLC Agilent 1200 (San Jose, CA, USA) system with commercial MDA kit (Immundiagnostik AG, Bensheim, Germany). The first step in determining the MDA is sample preparation with a derivatization reagent that converts MDA into a flurosent product. Thereafter, the pH was optimized and the reaction mixture (20 ml) was chromatographed in reversed phase C18 column (18.5 mm, 125 × 4 mm) at 30 °C. The flow rate was 0.8 ml/min. Fluorometric detection was performed with excitation at 515 nm and emissions at 553 nm. The detection limit is 0.15 µmol/L.[11]

STATISTICAL METHODS

Data analysis was performed through univariate and bivariate

analyses using the SPSS 22nd version (SPSS Inc., Chicago) with a 95% confidence interval. Bivariate analysis was performed using Mann-Whitney U test with significance p<0.05.

RESULT

This study was followed by 80 gastritis patients with male was 44 people (55%). The mean age in this study was 54.4 ± 10.1 years and the mean BMI was 22.7 ± 3.8 kg/m2. The majority of subjects was Bataknese (67.5%) and the most frequent employment was housewives (38.8%) followed by private employees (36.3%) (Table 1).

Tabel 1. Basic characteristics of subjects

Characteristics	n = 80
Sex Men Women	44 (55%) [a] 36 (45%)
Age, years	54.4 + 10.1 [b]
BMI, kg/m^2	22.7 + 3.8 [b]
Ethnic Bataknese Javanese Acehnese	54 (67.5%) [a] 20 (25%) 6 (7.5%)
Occupation Private employees Housewives Entrepreneur Student Others	29 (36.3%) [a] 31 (38.8%) 14 (17.5%) 4 (5%) 2 (2.5%)
Education Elementary School Junior High School Senior High School University	7 (8.8%) [a] 11 (13.8%) 53 (66.3%) 9 (11.3%)

[a]categorical data : n (%)
[b]numeric data, mean + SD

From histopathologic results of gastric mucosal biopsy, we obtained gastric premalignant lesion were 18 patients (22.5%). MDA levels in patients with gastric premalignant lesion were higher than patients without gastric premalignant lesion. Median MDA levels in gastritis with and without gastric premalignant lesion were 1.67 (0.93 - 2.91) µmol/L and 1.22 (0.78 - 2.24) µmol/L (Table 2).

Tabel 2. Comparison of MDA levels in gastritis patients with and without gastric premalignant lesion

Diagnosis	MDA	p
Gastric premalignant lesion Yes No	 1.67 (0.93 – 2.91) 1.22 (0.78 – 2.24)	 0.024*

*p<0,05

In this study, the Mann-Whitney test showed a significant differences of MDA levels in gastritis patients between with and without gastric premalignant lesion (p = 0.024).

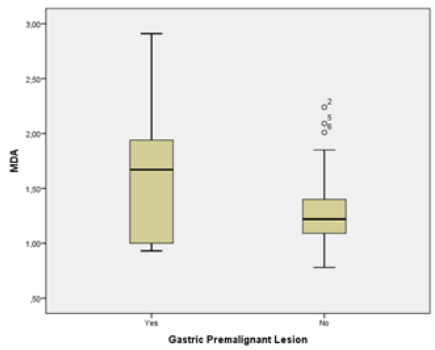

Figure 1. Boxplot serum MDA levels in gastritis patients with and without gastric premalignant lesion

DISSCUSSION

In this study, male more diagnosed with gastritis than female (55% vs 45%). This result was consistent with previous studies conducted by Elsawaf et al that majority chronic gastritis in Saudi Arabia was male (54.1%).[12] Takeo et al reported that the majority of chronic gastritis in Japan were male (62.7%).[13] Another similar study reported that majority chronic gastritis were male in India, Sweden, and Indonesia (65%, 51,3% and 51,25% respectively).[3,14,15]

The mean age of chronic gastritis patient in this study was 54.4 years. The mean age in this study was also similar to previous studies. Studies by Song et al in Sweden, Elsawaf et al in Saudi Arabia, Takao et al in Japan, Choudhury et al in India and Darmadi et al in Medan reported the mean age of chronic gastritis patients was 56 years, 43 years, 56.5 year, 54.17 years, 49.3 years respectively.[3,12-15]

Under normal circumstances, free radicals will form in small amounts. However, it is not pathological because the amount of free radicals will be balance by increased endogenous antioxidants (glutathione, superoxide dismutase, and catalase) as a compensatory mechanism to prevent tissue damage. The presence of phagocyte cells in gastritis patients will lead increasing free radicals. Anion superoxide radicals (O_2^-) are generated by neutrophil infiltration reactions in cellular lipid membrane that lead to lipid peroxidation formation and metabolized to MDA.[16] These lipid peroxidation reactions will damage cell membranes and release of intracellular components such as lysosomal enzymes that cause tissue damage, degradation of the epithelial basal membrane, interfere cell metabolism, and mutagenic MDA deoxyguanosine (Mi-dG).[17,18]

In this study, MDA levels were significantly higher in gastric premalignant lesion compared to gastritis patients without gastric premalignant lesion (p = 0.024). This results was consistent with previous research, Bitla et al (2011) conducted a study of 22 patients showing that MDA levels were increased significantly in patients with gastric carcinoma (p = 0.027).[19] Another study of 40 gastritis patients in Medan stated a significant association between elevated MDA levels with chronic atrophic gastritis (p = 0,002) and intestinal metaplasia (p = 0,001),[20] in which chronic atrophic gastritis and intestinal metaplasia are classified as gastric premalignant lesion.

Our study showed an increased in MDA levels in gastritis with gastric premalignant lesion significantly. Elevated levels of MDA can be used as a parameters to detect severe tissue damage and it has been reported from previous studies that MDA levels are associated with mutagenesis and carcinogenesis.[19]

CONCLUSION

MDA levels were significantly higher in gastric premalignant lesion compared to gastritis patients without gastric premalignant lesion.

ACKNOWLEDGMENTS.

We would like to express our gratitude to Research Institute Universitas Sumatera Utara (No: 69/UN5.2.3.1/PPM-KP-TALENTA USU/2018) as our source of research funding.

Conflict of interest.

The author stated that there are no conflict of interest regarding the publication of this article.

REFERENCES

[1] El-Zimaity HMT. Recent advances in the histopathology of gastritis. Curr Diagn Pathol. 2007;13:340-8.
[2] Ohata H, et al. Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. Int J Cancer. 2004;109(1):138-43.
[3] Song H, et al. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. BMJ. 2015: 351 3867.
[4] Sipponen P, Maaroos HI. Chronic gastritis. Scand J Gastroenterol. 2015;50:657-67
[5] Zhang C, Yamada N, Wu Y. Helicobacter pylori infection, glandular atrophy and intestinal metaplasia in superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer and early gastric cancer. World J Gastroenterol. 2005;11:791-6.
[6] Dinis-Ribeiro M, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society

of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy. 2012;44:74-94.
[7] Demir S, et al. Role of free radicals in peptic ulcer and gastritis. Turk J Gastroenterol. 2003;14:39-43.
[8] Tiwari SK, et al. Relevance of Helicobacter pylori genotypes in gastric pathology and its association with plasma malondialdehyde and nitric oxide levels. Inflammopharmacol. 2010;18:59-64.
[9] Arkhaesi N. Kadar malondialdehyde serum sebagai indikator prognosis keluaran pada sepsis neonatorum. Semarang: Departemen Ilmu Kesehatan Anak FK Undip;2008. p 12-22.
[10] Rugge M, et al. Gastritis: the histology report. Dig Liver Dis. 2011;43S:373–84.
[11] Immundiagnostik AG. Malondialdehyde HPLC Kit. 2010 [cited 10 Desember2016]. Available from: http://immundiagnostik.com/fileadmin/pdf/ Malondialdehyd_ KC1900.pdf
[12] Elsawaf ZM, Albasri AM, Hussainy AS. Histopathological pattern of benign endoscopic gastric biopsies in Western Saudi Arabia: a review of 1236 cases. J Pak Med Assoc. 2017;67:252-5.
[13] Takao T, et al. Multifaceted assessment of chronic gastritis: a study of correlations between serological, endoscopic, and histological diagnostics. Gastroenterol Res Pract. 2011: Article Id631461.
[14] Choudhury S, Laishram RS, Punyabati P. Histopathological study of gastric mucosal biopsies in chronic gastritis patients with special correlation to Helicobacter pylori infection at Rims Hospital. J Evid Based Med Health. 2016;3:2829-35.
[15] Siregar GA, Halim S, Sitepu RR. Serum TNF- , IL-8, VEGF levels in Helicobacter pylori infection and their association with degree of gastritis. Acta Med Indones. 2015;47: 120-6.
[16] Li J, et al. Malondialdehyde and SOD-induced changes of gastric tissues in acute gastric mucosal injury under positive acceleration. Genetics and Molecular Research. 2015;14:4361-8.
[17] Joseph RM, Varela V, Kanji VK. Protective effects of zinc in indomethacin-induced gastric mucosal injury: evidence for a dual mechanism involving lipid peroxidation and nitric oxide. Aliment Pharmacol Ther. 1999;13:203-8.
[18] Santra A, Chowdhury A, Chaudhuri S. Oxidative stress in gastric mucosa in Helicobacter pylori infection. Indian J Gastroenterol. 2000;19:21-3.
[19] Bitla AR, Reddy EP, Sambasivaih K. Evaluation of plasma malondialdehyde as a biomarker in patients with carcinoma of stomach. Biomed Res. 2011;22:63-8.
[20] Darmadi, Siregar GA, Dairi LB. Association between degree of Gastritis and Malondialdehyde level of Gastritis patients at Adam Malik General Hospital Medan. Indones J Gastroenterol Hepatol Dig Endosc. 2017;18(2):80-6.