Changes in Gastric Mucosal Glycosylation Before and After Helicobacter pylori Eradication Using Lectin Microarray Analysis

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Cite this article as: Ogawa R, Okimoto T, Kodama M, et al. Changes in gastric mucosal glycosylation before and after *Helicobacter pylori* eradication using lectin microarray analysis. *Turk J Gastroenterol.* 2022;33(2):88-94.

ABSTRACT

Background: *Glycosylation is a common post-translational modification, and it has been reported that alterations in the glycosylation patterns on cells are related to cell proliferation, differentiation, tissue adhesion, and carcinogenesis. This study aimed to investigate the relationship between Helicobacter pylori infection and gastric mucosal glycosylation using a lectin microarray system.*

Methods: *Gastric mucosal samples were obtained from 10 Helicobacter pylori-non-infected patients, 10 H. pylori-infected patients, and 10 after H. pylori-eradicated patients who underwent gastric mucosal biopsy by endoscopy in our institute. The gastric gland cells which were isolated from formalin-fixed, paraffin-embedded gastric mucosal biopsy samples using laser capture microdissection were used for lectin microarray to obtain lectin–glycan interaction values.*

Results: *Comparison of the lectin–glycan interaction values before and after eradication in the same patients showed significant increases for* Ricinus communis *agglutinin 120,* Trichosanthes japonica *agglutinin II,* Euonymus europaeus *lectin, jacalin,* Amaranthus caudatus *agglutinin, and Maclura pomifera agglutinin and significant decreases for* Urtica dioica *agglutinin,* Lycopersicon esculentum *lectin,* Ulex europaeus *agglutinin,* Sambucus nigra *agglutinin,* Sambucus sieboldiana *agglutinin, and* Trichosanthes japonica *agglutinin* I. *Furthermore, jacalin and MPA in the gastric antrum were significantly decreased with H. pylori infection compared with the without infection group and improved to the levels seen without infection as a result of eradication.* Lycopersicon esculentum *lectin,* Sambucus nigra *agglutinin,* Sambucus sieboldiana *agglutinin, and* Trichosanthes japonica *agglutinin I in the gastric body were significantly increased with H. pylori infection and improved to the level seen without infection as a result of eradication.*

Conclusion: *H. pylori infection changes the lectin binding state which is related to various cancers on the gastric mucosal cell. Furthermore, those changes are reversible by H. pylori eradication.*

Keywords: *Glycosylation, Helicobacter pylori, lectins, microarray analysis*

INTRODUCTION

Helicobacter pylori is a gram-negative bacterium that can live in the stomach, and it is known that *H. pylori* infection causes various upper gastrointestinal diseases, including atrophic gastritis, gastroduodenal ulcer, mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[1-3] Some studies have provided a human model of gastric carcinogenesis with the following sequential stages: chronic gastritis, atrophy, intestinal metaplasia, and dysplasia.[4] It is well known that severe atrophy and intestinal metaplasia are risk factors for gastroduodenal ulcers and gastric cancers.[5] To date, several reports have shown that *H. pylori* eradication therapy reduced the risk of developing gastric cancer and metachronous gastric cancers after endoscopic resection.[6-8] In recent years, *H. pylori* infection and methylation, an epigenetic change, have been reported as a newly discovered mechanism of gastric carcinogenesis.[9,10] It also has been reported that not only does *H. pylori* infection cause DNA methylation in the gastric mucosa but also that the methylation level decreases to certain levels following *H. pylori* eradication, suggesting a relationship with inflammation.[11] However, studies of the factors that can predict a reduced gastric cancer risk after *H. pylori* eradication are still insufficient.

Glycosylation is a common post-translational modification,[12] and it has been reported that alterations in the glycosylation patterns on cells and specific glycotransferases are related to cell proliferation, differentiation,

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Received: ***January 29, 2021*** *Accepted:* ***May 3, 2021*** *Available Online Date:* ***December 24, 2021***

DOI: ***10.5152/tjg.2021.201116***

tissue adhesion, and carcinogenesis.[13] Recently, a lectin microarray system has been developed to comprehensively analyze glycan profiles using lectins that specifically recognize various sugar moieties.[14-16] To date, there has been no report of the changes in the glycosylation patterns after *H. pylori* eradication.

Thus, in this study, a lectin microarray system was used to identify glycosylation patterns by comparing the glycosylation patterns on cells before and after *H. pylori* eradication.

MATERIALS AND METHODS

Patients and Clinical Samples

After providing informed consent, the samples from patients who underwent esophagogastroduodenography at our institute underwent histological examination, culture testing, and the rapid urease test (RUT) to identify the infection of *H. pylori*. A positive result on any one of these tests was considered active *H. pylori* infection. Those who were found negative on all tests, who presented with no atrophy on endoscopy, and had no clear history of *H. pylori* eradication were included in the *H. pylori* without infection group.

Patients with *H. pylori* infection received proton pump inhibitor-based combination therapy. Four to 8 weeks after completing the eradication therapy, the urea breath was performed to assess the success of eradication therapy. One year after eradication therapy, biopsies for RUT, culture, and histological examination were performed by endoscopic examination.

Biopsy specimens were taken from 2 points of the stomach: the greater curvature of the antrum and the greater curvature of the upper body. The biopsy samples for histopathology were fixed in 10% neutral formalin for 24 hours and subsequently embedded in paraffin. Gastric mucosal samples were evaluated according to the updated Sydney system.[17] Gastritis grade was also evaluated using the operative link of gastric atrophy (OLGA) staging system[18] and operative link of gastric intestinal metaplasia (OLGIM) staging system.[19] The OLGA staging system classifies gastritis as grades 0-IV based on a combination of the degree of the antrum and corpus atrophy. The OLGIM staging system classifies gastritis as grades 0-IV based on a combination of the degree of the antrum and corpus intestinal metaplasia. The ratio of grade 0-II/III, IV was evaluated. Endoscopic findings of gastric mucosal atrophy were assessed according to the Kimura-Takemoto classification.[20] In this study, 10 *H. pylori*-infected patients who were judged to have mild atrophy (C1 and C2) and 10 *H. pylori*-non-infected patients were selected. The study protocols were approved by the ethics committee of our institute.

Sample Preparation and Lectin Microarray

Formalin-fixed, paraffin-embedded sections (10 μm for lectin microarray) of gastric mucosal biopsy tissues were placed on glass slides and deparaffinized. In this study, laser capture microdissection (LCM) (Arcturus Engineering, Mountain View, Calif, USA) was used for the isolation of gastric gland cells to prevent effects due to inflammatory cells. Only gastric gland cells were marked and scratched from the glass slide using LCM.

The lectin microarray was performed as described previously.[21-23] Fluorescent images of the lectin arrays were obtained using an evanescent-field fluorescence scanner (GlycoStation Reader 1200; GlycoTechnica Ltd.), and the data were analyzed using GlycoStation Tool Pro Suite 1.5 (GlycoTechnica Ltd.).

Statistical Analysis

Statistical analyses were performed using SPSS software (PASW Statistics 18, SPSS Japan), and data are expressed as means ± SD. The Student's *t*-test was used to compare updated Sydney system scores and lectin signal intensity results. A *P*-value less than .05 was considered significant.

RESULTS

Baseline Characteristics

The baseline characteristic data are shown in Table 1. Ten patients each were examined before *H. pylori* eradication, 1 year after *H. pylori* eradication, and without *H. pylori* infection. The patients in the before and after eradication groups were the same patients. No significant difference in the histological atrophy score for the gastric antrum was seen between the before and after eradication groups or between the after eradication and without infection groups. The score was significantly higher in the before eradication group than in the without infection group ($P < .001$). The histological atrophy score for the gastric body was significantly lower in the after eradication and without infection groups than in the before eradication group ($P < .001$). The inflammation scores for the gastric antrum and body were significantly lower in the after eradication and without infection groups than in the before eradication group ($P < .001$). As in the case of the inflammation scores, the activity scores for the gastric antrum and body were

Table 1. Baseline Characteristics and Histological Scores

	Without Infection	Before Eradication	After Eradication	*P*
Number of patients	10	10	10	
Gender (male)	5	5	5	
Age (years)	60 ± 13.06	56.3 ± 12.72	57.4 ± 12.71	*.265, ***.329
Endoscopic findings				
Reflux esophagitis	2	0	0	
Chronic gastritis	4	10	10	
Gastric ulcer, duodenal ulcer	0	0	0	
Gastric cancer	0	0	0	
Histological atrophy score				
Antrum	0.4 ± 0.490	1.3 ± 0.458	0.9 ± 0.700	*<.001, **.169, ***.096
Body	0	0.8 ± 0.600	0	*<.001, **<.001
Inflammation score				
Antrum	1.0	2.7 ± 0.458	1.8 ± 0.400	*<.001, **<.001, ***<.001
Body	1.0	2.5 ± 0.671	1.4 ± 0.490	*<.001, **<.001, ***.025
Activity score				
Antrum	0.1 ± 0.30	1.6 ± 0.663	0	*<.001, **<.001, ***.331
Body	0	1.4 ± 0.800	0.1 ± 0.3	*<.001, **<.001, ***.331
OLGA staging system				
0-II/III, IV	10/0	10/0	10/0	

Results are expressed as mean ± SD, and number. Histological scores were evaluated according to the updated Sydney system.
*Comparison between without infection and before eradication;**Comparison between before eradication and after eradication;***Comparison between without infection and after eradication.

significantly lower in the after eradication and without infection groups than in the before eradication group ($P < .001$). There were no differences in the ratio of OLGA staging (0-II/III, IV) between the without infection group, before eradication group, and after eradication group (Table 1). All cases were stage 0 evaluated by the OLGIM staging system.

Lectin Microarray Profiles of Gastric Mucosa

Table 2 shows the differential glycan analysis results for 45 lectins (LGI values) expressed by the before eradication group and the after eradication group. Comparison of the lectin–glycan interaction (LGI) values for the gastric antrum before and after eradication in the same patients showed significant increases for RCA120, TJA-II, EEL, jacalin, ACA, and MPA and a significant decrease for UDA. In the gastric body, significant decreases were seen for 5 lectins after eradication: LTL, UEA, SNA, SSA, and TJA-I.

Comparing the above changes in lectin expression, jacalin and MPA in the gastric antrum were significantly decreased with *H. pylori* infection compared with the without infection group and improved to the level seen without infection as a result of eradication (Figure 1).

In the gastric body, LTL, SNA, SSA, and TJA-I were significantly increased with *H. pylori* infection and improved to the level seen without infection as a result of eradication (Figure 2).

DISCUSSION

The lectin microarray system can comprehensively evaluate the expression status of glycoproteins using straightforward, basic technology. It enables 45 independent LGI values to be measured in formalin-fixed clinical samples.[21]

Previous studies have examined the glycosylation patterns of glycoproteins in human gastric juice before and after *H. pylori* eradication.[24] With the use of lectins and monoclonal antibodies, increases in MUC5AC and MUC1 after *H. pylori* eradication have been reported.

Table 2. Differential Glycan Profiling Between Before Eradication Group (*n* = 10) and After Eradication Group (*n* = 10) Using Data from 45 Lectins

	Antrum				Body		
Lectin	Before Eradication	After Eradication	*P*	Lectin	Before Eradication	After Eradication	*P*
Lotus tetragonolobus lectin (LTL)	33.3	32.5	N.S.	LTL	33.5	25.2	.025
Pisum sativum agglutinin (PSA)	82.1	71.9	N.S.	PSA	93.2	86.8	N.S.
Lens culinaris agglutinin (LCA)	94.7	81.6	N.S.	LCA	114.5	104.2	N.S.
Ulex europaeus agglutinin I (UEA_I)	76.5	75.6	N.S.	UEA_I	83.6	61.9	.009
Aspergillus oryzae lectin (AOL)	250.3	253.7	N.S.	AOL	247.7	209.6	N.S.
Aleuria aurantia lectin (AAL)	240.4	267.8	N.S.	AAL	266.4	257.2	N.S.
Maackia amurensis lectin I (MAL_I)	19.7	17.6	N.S.	MAL_I	14.6	12.9	N.S.
Sambucus nigra agglutinin (SNA)	89.6	85.2	N.S.	SNA	91.2	64.4	.014
Sambucus sieboldiana agglutinin (SSA)	96.6	100.0	N.S.	SSA	93.8	70.5	.023
Trichosanthes japonica agglutinin I (TJA-I)	112.8	109.9	N.S.	TJA-I	118.9	85.8	.015
Phaseolus vulgaris Leucoagglutinin (PHA(L))	15.0	11.9	N.S.	PHA(L)	14.8	8.5	N.S.
Erythrina cristagalli agglutinin (ECA)	17.2	16.8	N.S.	ECA	13.0	10.6	N.S.
Ricinus communis agglutinin 120 (RCA120)	120.6	138.7	.003	RCA120	100.3	104.8	N.S.
Phaseolus vulgaris Erythroagglutinin (PHA(E))	71.1	64.3	N.S.	PHA(E)	85.5	101.8	N.S.
Datura stramonium agglutinin (DSA)	230.6	246.0	N.S.	DSA	293.9	330.5	N.S.
Griffonia simplicufolia lectin II (GSL-II)	22.2	15.8	N.S.	GSL-II	17.4	2.8	N.S.
Narcissus pseudonarcissus agglutinin (NPA)	167.6	156.6	N.S.	NPA	175.2	221.9	N.S.
Canavalia ensiformis agglutinin (ConA)	94.0	87.6	N.S.	ConA	123.2	123.4	N.S.
Galanthus nivalis agglutinin (GNA)	95.2	76.7	N.S.	GNA	88.3	118.6	N.S.
Hippeastrum Hybrid lectin (HHL)	26.8	21.3	N.S.	HHL	31.4	43.9	N.S.
Agrocybe cylindracea (ACG)	122.9	116.3	N.S.	ACG	94.6	97.1	N.S.
Tulipa gesneriana I (TxLC_I)	40.7	30.8	N.S.	TxLC_I	61.8	65.3	N.S.
Bauhinia purpurea lectin (BPL)	87.9	94.5	N.S.	BPL	76.4	61.7	N.S.
Trichosanthes japonica agglutinin II (TJA-II)	106.5	122.4	.018	TJA-II	88.5	77.5	N.S.
Euonymus europaeus lectin (EEL)	37.6	51.5	.017	EEL	33.2	21.8	N.S.
Agaricus bisporus agglutinin (ABA)	174.6	178.8	N.S.	ABA	137.1	106.9	N.S.
Lycipersicon esculentum lectin (LEL)	248.8	253.8	N.S.	LEL	297.7	301.5	N.S.
Solanum tuberosum lectin (STL)	340.5	312.5	N.S.	STL	391.7	448.4	N.S.
Urtica dioica agglutinin (UDA)	186.0	159.7	.019	UDA	227.8	261.5	N.S.
Phytolacca americana (PWM)	49.7	40.7	N.S.	PWM	34.4	25.7	N.S.
Jacalin	132.5	154.9	.002	Jacalin	118.1	124.1	N.S.
Peanut Agglutinin Arachis hypogaea (PNA)	15.0	14.3	N.S.	PNA	6.8	7.8	N.S.
Wisteria floribunda agglutinin (WFA)	67.5	79.0	N.S.	WFA	44.3	42.7	N.S.
Amaranthus caudatus agglutinin (ACA)	133.9	160.5	.023	ACA	126.2	112.6	N.S.
Maclura pomifera agglutinin (MPA)	54.5	90.3	.001	MPA	38.7	39.6	N.S.
Helix pomatia agglutinin (HPA)	71.8	79.3	N.S.	HPA	62.1	59.0	N.S.
Vicia villosa agglutinin (VVA)	41.4	43.6	N.S.	VVA	19.5	21.9	N.S.

(*Continued*)

Table 2. Differential Glycan Profiling Between Before Eradication Group (*n* = 10) and After Eradication Group (*n* = 10) Using Data from 45 Lectins (*Continued*)

	Antrum				Body		
Lectin	Before Eradication	After Eradication	*P*	Lectin	Before Eradication	After Eradication	*P*
Dolichos biflorus agglutinin (DBA)	52.8	51.7	N.S.	DBA	25.8	19.8	N.S.
Soybean Agglutinin Glycine max (SBA)	53.0	58.3	N.S.	SBA	31.1	30.1	N.S.
Calsepa	204.0	165.2	N.S.	Calsepa	224.9	285.9	N.S.
Psophocarpus tetragonolobus lectin I (PTL_I)	21.1	25.8	N.S.	PTL_I	20.5	15.1	N.S.
Maackia amurensis (MAH)	24.9	19.4	N.S.	MAH	17.2	16.5	N.S.
WGA	208.5	195.0	N.S.	WGA	173.2	168.8	N.S.
Griffonia Simplicifolia lectin I A4 (GSL_I_A4)	45.5	47.9	N.S.	GSL_I_A4	32.3	26.3	N.S.
Griffonia Simplicifolia lectin I B4 (GSL_I_B4)	21.8	21.6	N.S.	GSL_I_B4	14.5	14.5	N.S.

Results are expressed as average.

N.S., not significant; LTL, *Lotus tetragonolobus* lectin; PSA, *Pisum sativum* agglutinin; LCA, *Lens culinaris* agglutinin; UEA_I, *Ulex europaeus* agglutinin I; AOL, *Aspergillus oryzae* lectin; AAL, *Aleuria aurantia* lectin; MAL_I, *Maackia amurensis* lectin I; SNA, *Sambucus nigra* agglutinin; SSA, *Sambucus sieboldiana* agglutinin; TJA-I, *Trichosanthes japonica* agglutinin I; PHA(L) , *Phaseolus vulgaris* leucoagglutinin; ECA, *Erythrina cristagalli* agglutinin; RCA120, *Ricinus communis* agglutinin 120; PHA(E), *Phaseolus vulgaris* erythroagglutinin; DSA, *Datura stramonium* agglutinin; GSL-II , *Griffonia simplicifolia* lectin II; NPA, *Narcissus pseudonarcissus* agglutinin; ConA, *Canavalia ensiformis* agglutinin; GNA, *Galanthus nivalis* agglutinin; HHL, *Hippeastrum* Hybrid lectin; ACG, *Agrocybe cylindracea*; TxLC_I, *Tulipa gesneriana* I; BPL, *Bauhinia purpurea* lectin; TJA-II, *Trichosanthes japonica* agglutinin II; EEL, *Euonymus europaeus* lectin; ABA, *Agaricus bisporus* agglutinin; LEL, *Lycopersicon esculentum* lectin; STL, *Solanum tuberosum* lectin; UDA, *Urtica dioica* agglutinin; PWM, *Phytolacca Americana*; PNA, *Peanut* agglutinin *Arachis hypogaea*; WFA, *Wisteria floribunda* agglutinin; ACA: Amaranthus caudatus agglutinin; MPA, *Maclura pomifera* agglutinin; HPA, *Helix pomatia* agglutinin; VVA, *Vicia villosa* agglutinin; DBA, *Dolichos biflorus* agglutinin; SBA, Soybean agglutinin glycine max; PTL_I, *Psophocarpus tetragonolobus* lectin I; MAH, *Maackia amurensis*; GSL_I_A4, *Griffonia Simplicifolia* lectin I A4; GSL_I_B4, *Griffonia Simplicifolia* lectin I B4.

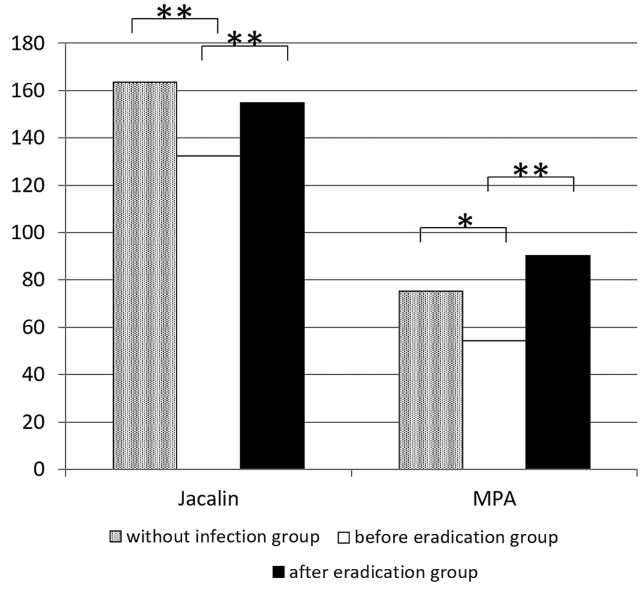

Figure 1. Lectin binding results according to the *H. pylori* infection state in gastric antrum. There were 10 cases in each group. Jacalin and MPA were significantly higher after eradication than in before eradication group, were higher without infection group as well. **P* < .05. ***P* < .01.

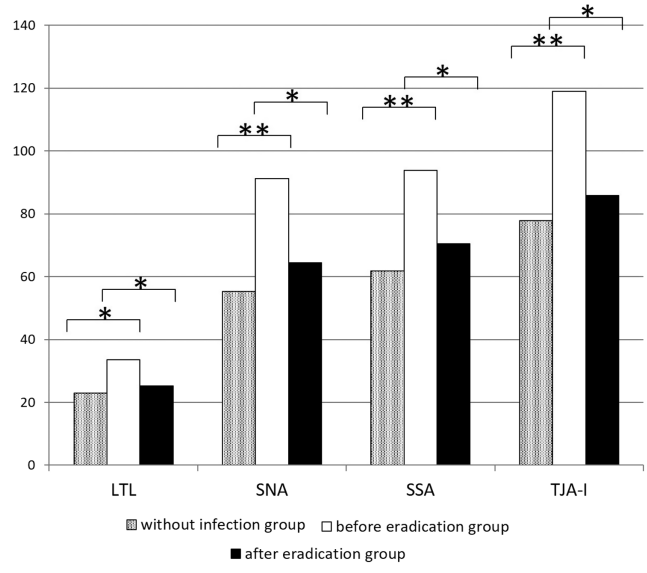

Figure 2. Lectin binding results according to the *H. pylori* infection state in gastric body. There were 10 cases in each group. LTL, SNA, SSA, and TJA-I were significantly lower after eradication than in before eradication group, were lower without infection group as well. **P* < .05. ***P* < .01.

However, there have been no reports of glycosylation patterns in the gastric mucosa with *H. pylori* infection and after its eradication.

In this study, to evaluate the change in glycan expression on the surface of gastric mucosal cells as a result of *H. pylori* infection, the lectin microarray system was used to evaluate such expression before and after *H. pylori* eradication. Comparison of 45 lectins before and 1 year after *H. pylori* eradication showed that changes in the binding signals for jacalin and MPA in the gastric antrum and for LTL, SNA, SSA, and TJA-I in the gastric body were affected by *H. pylori* infection. This study is the first to examine glycan expression on the surface of human gastric mucosal cells and the changes in expression that occur with *H. pylori* infection and eradication.

To minimize the effects of glycans on the surface of inflammatory cells, LCM was used in this study to collect gastric epithelial cells. It was found that the jacalin and MPA signals in the gastric antrum were significantly lower in the *H. pylori* infection group than in the gastric mucosa of the group without *H. pylori* infection, and that, 1 year after eradication, the signals returned to the levels seen without infection. Moreover, the LTL, SNA, SSA, and TJA-I signals in the gastric body were significantly increased in the *H. pylori* infection group and returned to the levels seen without infection 1 year after eradication. These changes were similar to those seen in *H. pylori* status as indicated by the inflammation and activity scores, suggesting that the changes resulting from *H. pylori* infection are reversible.

LTL has been reported to be a marker for cancer progression in bladder cancer cell lines. SNA has been reported to be a marker for the diagnosis, metastasis, and prognosis of colorectal and pancreatic cancers and hepatocellular carcinoma. SNA has also been reported to be a diagnostic marker for pneumonia. SSA has been described as being a predictive marker for diabetic nephropathy progression, and SSA, SNA, and TJA have been reported to be markers for the diagnosis and monitoring of major depressive disorder.[25] Jacalin is a 66-kDa protein isolated from the seeds of jackfruit.[26] It binds to various glycans, including galactose, *N*-acetylgalactosamine, mannose, *N*-acetylmuramic acid, and *N*-acetylneuraminic acid.[27] In particular, jacalin specifically recognizes the tumor-associated Thomsen–Friedenreich (TF) antigen and has antiproliferative effects on human colon cancer cells, highlighting its potential antitumor activity.[28] TF-antigen expression in the epithelium has been reported in cancer and precancerous conditions in humans.[29,30] Shamsuddin et al[30] reported TF-antigen expression rates of 100% (12/12) in lung cancer, 100% (19/19) in breast cancer, 100% (15/15) in ovarian cancer, 91.7% (11/12) in uterine cancer, 100% (6/6) in pancreatic cancer, 94.1% (16/17) in gastric cancer, and 100% (6/6) in liver cancer. Intriguingly, although the TF-antigen expression rate in normal gastric mucosal tissue was 100% (15/15), no TM antigen whatsoever was seen in normal non-gastric tissue. However, the normal gastric mucosa in this investigation was in a state of chronic gastritis and, therefore, not entirely normal tissue. Consequently, the effects of *H. pylori* could not be evaluated. MPA is a tetrameric plant seed lectin with a high affinity for the tumor-associated TF-antigen disaccharide, Galβ1, 3GalNAcα.[31] There have been no concrete reports about MPA so far. However, MPA and jacalin are 85% homologous,[32] and the 2 lectins have particularly high specificity for the TF-antigen[29] that is expressed in more than 85% of human carcinomas.[33] Therefore, it is possible that MPA is associated with carcinogenesis.

The results of this study showed that the signal levels for lectin binding to glycans resulting from *H. pylori* infection returned to the levels seen without infection as a result of *H. pylori* eradication. Thus, the data are intriguing in that they indicate that glycosylation is reversible.

There were limitations of this study. First, the sample size was small. However, as before the eradication group which this study applied to was matched age, sex, and atrophic degree, the number of patients was sufficient for analysis. Second, because glycans were not directly evaluated in tissue, it was not possible to examine what was recognized by the lectins evaluated in this study.

This study is the first report to examine lectin binding to gastric mucosal glycoproteins after *H. pylori* eradication in the same patients examined when infected with *H. pylori*. The findings are therefore important for areas where *H. pylori* infection and gastric carcinogenesis are closely related.

Ethics Committee Approval: The study was approved by the medical ethics committee of Oita University (No: 987).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Consept – R.O., T.O.; Design – R.O., T.O.; Supervision – T.O., M.K., K.M.U.; Materials – R.O., K.T., K.F., K.O., K.M.I.;

Data Collection and/or Processing – R.O.; Analysis and/or Interpretation – R.O., T.O.; Literature Search – R.O.; Writing Manuscript – R.O.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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