



**INVITED ARTICLE ID 00188507**

Lian-Sheng Ma,  
President and Company  
Editor-in-Chief  
*World Journal of Clinical Cases*

Aug 8, 2017

Dear Editors and Reviewers,

Thank you for your invitation to submit a observational study for your journal. Also thank reviewers for a thorough review of our manuscript entitled “**Effect of *Helicobacter pylori* Eradication on Elder Cases: Observational Study in Community-based Medicine**” by Masaki Maruyama, et al. and myself.

The thoughtful comments from the reviewers are greatly appreciated. In preparing for revision, we have carefully studied reviewers’ comments and incorporated many of their suggestions into the revised manuscript. For your convenience, we have highlighted the changes made in blue. We hope this revised manuscript is now acceptable for publication in *World Journal of Clinical Cases*. **The provided ID for this invited Observational Study is (00188507).**

We declare that this work is original, the manuscript is not under consideration by other journals. All authors approved the contents submitted. We look forward to hearing from you at your earliest convenience.

Thank you for your consideration.  
Sincerely yours,

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Dear Reviewers:

Thank you very much for your thoughtful comments and suggestions. In preparing the revision, we have carefully studied your comments and incorporated many of your suggestions into the revised manuscript. The following are our point-by-point responses to your comments/concerns.

### **Reviewer #1**

*1 This is an interesting study. The authors concluded that H.P eradication prevented weight loss and subclinical IDA in elderly individuals.*

*1. 228 patients were diagnosed as having HP infected chronic gastritis and authors excluded the patients who had been diagnosed as gastric cancer, gastric ulcer, duodenal ulcer etc. So, finally 130 patients were included in this study. Do these 130 patients have to do HP eradication? (Subjects included in this study did not have a peptic ulcer or gastric cancer)*

**Response:** We are grateful to the reviewer for the positive comments, high scores, and for recognizing the significance of our work. In Japan, it is recommended to eradicate *H. pylori* if the patients are diagnosed with chronic gastritis.

*2. As the authors have noted, this study is an observational study, but the number of subjects included in the study is too small.*

*3. Since this study is an observational study anyway, in order to get this results, the authors had to compare groups with continuously HP infected chronic gastritis and groups with HP eradication.*

**Response:** As this is an observational study to obtain the preliminary data to bridge toward prospective study, although the number of cases is relatively smaller, it is agreeable and comparison to the control should be done in the coming prospective study.

### **Reviewer #2**

*This study investigated the effect of H. pylori eradication therapy on the extra-gastrointestinal factors in elderly patients. The authors observed that H. pylori eradication therapy for elderly patients with chronic gastritis increased BMI and MCV. **The study is interesting, and the manuscript is well-written.** My only concern is that the patients who failed H. pylori eradication should be included as a control group.*

**Response:** We are grateful to the reviewer for the positive comments, high scores, and for recognizing the significance of our work. Yes, the control group should be carefully monitored in the coming prospective study.

### **Reviewer #3**

*This manuscript provides the data on the effect of Hp eradication on the health of elderly (about 70 and over) patients. The study conducted over two year period with 130 elderly patients revealed that Hp eradication therapy exerted beneficial effect (increase) on the patient body weight loss and the iron deficiency anemia. ....**the presentation is quite focused on the topic. Although, the area of Hp effects is of highly interest to the readership.***

**Response:** We are grateful to the reviewer for thorough review. Yes, we believe that this observational study can contribute to the better management of cases.

### **Reviewer #4**

*A minor polish for the english is the only requirement*

**Response:** We are grateful to the reviewer for thorough review. We have carefully corrected the English and the draft has been edited by the native English speaker. The certificate is attached.

From: bpgmanuscriptinviting@wjgnet.com  
Sent: Wednesday, October 12, 2016 10:50 AM  
To: kenya-k@med.niigata-u.ac.jp  
Subject: Number ID: 00188507 Acceptance of invitation to contributemanuscripts to the World Journal of Gastroenterology

Dear Dr. Kamimura,

Thank you very much for accepting our invitation for contribution of high quality manuscripts to the World Journal of Gastroenterology. The columns in which your submitted manuscript can be published are as follows:

Number ID: 00188507

Publication Name: World Journal of Gastroenterology

Author: Kamimura, K

Title: Extra-gastrointestinal effect of Helicobacter pylori eradication therapy for chronic gastritis patients on elderly individuals; Two years observational before-after study in rural Japan

Manuscript Type: Observational Study

Title Accepted Date: 2016-10-12 09:50

Title Submit Date: 2016-10-12 07:21

The World Journal of Gastroenterology requirements for full standard manuscript format and steps to submit manuscripts in the attachment.

There is no restriction on number of words, figures, tables or references. Your paper will be published free of charge after peer review. In addition, guidelines for manuscript preparation, submission, and manuscript format, see attached.

Best regards,

Lian-Sheng Ma, President and Company Editor-in-Chief

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**Invited Article (Author ID 00188507)**



**Name of Journal: *World Journal of Clinical Cases***

**Manuscript Type: OBSERVATIONAL STUDY**

**Effect of *Helicobacter pylori* Eradication on Elder Cases: Observational Study in  
Community-based Medicine**

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**Running title: *Helicobacter pylori* eradication therapy for elderly patients**

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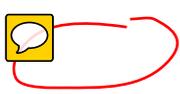
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**Disclosure**

The authors declare that they do not have a current financial arrangement or affiliation with any organisation that may have a direct interest in their work.



**Statement of No Conflicts:** The authors declare that they have no current financial arrangement or affiliation with any organization that may have a direct influence on their work.



## **ABSTRACT**

**AIM:** To examine the effect of *Helicobacter pylori* eradication therapy on the extra-gastrointestinal factors in elderly patients by a before–after observational study in community medicine.

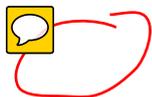
**METHODS:** Medical records (1 May 2013–31 January 2014) of 130 patients who underwent *H. pylori* eradication therapy with 2-year after-eradication observation in our institute were reviewed. Data on sex; age; body weight; body mass index; mean corpuscular volume; total protein; low-density lipoprotein cholesterol, triglyceride, haemoglobin A1c and haemoglobin levels and gastric hyperplastic polyps at eradication was extracted. Two-year after-eradication change in data was analysed by paired-sample t-test; relationship between gastric hyperplastic polyps and subclinical iron deficiency anaemia improvement was evaluated.

**RESULTS:** The mean patient age (median, interquartile range) at eradication was 69.6 (71.5, 64–77) years. Paired-sample t-tests showed that body weight, body mass index and mean corpuscular volume increased by 0.52 kg ( $P = 0.018$ ),  $0.25 \text{ kg/m}^2$  ( $P = 0.006$ ) and 0.83 fL ( $P < 0.001$ ), respectively. The nonparametric Mann–Whitney test showed no significant difference in the change rate of mean corpuscular volume after eradication between the groups with and without gastric hyperplastic polyps ( $P = 0.892$ ).

**CONCLUSION:** *H. pylori* eradication therapy prevented weight loss and subclinical iron deficiency anaemia in elderly individuals. Gastric hyperplastic polyps were not associated with subclinical iron deficiency anaemia.

**Key words:** *Helicobacter pylori*; Iron deficiency anaemia; Body weight; Elderly; Polyp

**Core tip:** The effect of *Helicobacter pylori* eradication therapy on the extra-gastrointestinal factors in elderly patients was focused in this study. *H. pylori* eradication therapy prevented weight loss and subclinical iron deficiency anaemia in elderly individuals. Gastric hyperplastic polyps were not associated with subclinical iron deficiency anaemia. The results obtained in this study will help physician to treat elderly patients in community-based medicine.



## Introduction

*Helicobacter pylori* infection affects many extra-gastrointestinal symptoms and diseases, including iron deficiency anaemia (IDA), obesity, diabetes mellitus and hyperlipidemia<sup>[1,2]</sup>. Although major population surveys and meta-analysis have revealed an increased risk for IDA in addition to a strong evidence for the efficacy of *H. pylori* eradication for the treatment of unexplained IDA, the relationship between *H. pylori* infection and prevalence of other extra-gastrointestinal tract diseases is unclear. The influence of *H. pylori* pathogenicity is currently unknown, particularly in elderly individuals<sup>[1,3-6]</sup>. In addition, the underlying mechanism of *H. pylori*-related IDA is still unclear<sup>[7,8]</sup>.

*H. pylori* eradication therapy for patients with peptic ulcer is associated with gain of body weight<sup>[9,10]</sup>. The relationship between *H. pylori* infection and overweight is unclear, even in large-scale epidemiological studies<sup>[11-14]</sup>. However, this increase might related to the recovery of peptic ulcer and chronic inflammation. On the other hand, because of previously reported inconsistent results, the cause-and-effect relationship between *H. pylori* infection and metabolic disease is also ambiguous, and there are few reports on elderly individuals<sup>[2,15-19]</sup>. Because the development of an aging society may be

upcoming event in the near future, the effect of *H. pylori* eradication therapy on the extra-gastrointestinal organs in elderly individuals should be investigated.

Therefore, the purpose of this observational study was to examine the effects of *H. pylori* eradication in elderly individuals on systemic conditions including body weight, biochemical results, and manifestations of clinical or subclinical anaemia comparing data between before-eradication and 2 years after *H. pylori* eradication. We have also compared rates of IDA improvement in chronic gastritis with and without gastric hyperplastic polyp (GHP) to investigate the relationship between GHP and *H. pylori*-related IDA.

## **Materials and methods**

This was an observational before–after study in which the case group included 130 individuals who were continuously treated with medications for chronic diseases, such as essential hypertension, hyperlipidemia and/or diabetes mellitus. They were all diagnosed with *H. pylori*-infected chronic gastritis by routine esophagogastroduodenoscopy (EGD) and the rapid urease test at Kashiwazaki Central Hospital between 1 May 2013 and 31 January 2014.

The patient was considered to be eligible when fulfilled the following inclusion criteria:

(1) *H. pylori* eradication therapy was successful and was followed by the urea breath test and (2) the patient had been measured/tested for body weight; body mass index (BMI); mean corpuscular volume (MCV); total protein (TP) and low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), haemoglobin (Hb) and haemoglobin A1c (HbA1c) levels at two time points: before and 2 years after *H. pylori* eradication therapy was completed. However, we included patients with some missing measurement values and as elderly if older than 65 years old. We excluded patients with mucosal breaking lesions, such as gastric cancer or peptic ulcers, history of gastrointestinal surgery, and the other diseases might cause anemia. This study was approved by the institutional review board of Kashiwazaki Central Hospital. Written informed consent was obtained from all patients, and the study was conducted in accordance with the ethical guidance of the 1975 Declaration of Helsinki.

To identify differences in a patient between two time points, a paired-sample t-test was performed. When there were  $\leq 30$  cases, a Wilcoxon signed test was performed. For continuous variables, two-group comparisons, such as Hb and MCV, were performed

using the nonparametric Mann–Whitney test because assumptions of normality of the distribution were not verified. We excluded the patients with missing data in each group before analysis. The threshold for significance was  $P < 0.05$ . In all statistical analysis, we used EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics<sup>[20]</sup>. The results for changes in variable before and after *H. pylori* eradication are presented as the mean  $\pm$  standard deviation (SD).

## **Results**

### ***Patient characteristics***

Between 1 May 2013 and 31 January 2014, 228 patients were diagnosed as having *H. pylori*-infected chronic gastritis by EGD and the rapid urease test were included. The patients who had been diagnosed as having gastric cancer ( $n = 3$ ), gastric ulcer ( $n = 16$ ), duodenal ulcer ( $n = 20$ ) and gastro-duodenal ulcer ( $n = 7$ ) who could not be followed up for 2 years after *H. pylori* eradication ( $n = 52$ ), a total of 98 patients, were excluded from the initial 228 patients with *H. pylori*-infected chronic gastritis. Finally, a total of

130 patients [mean age, 69.6 years; median age, 71.5 (interquartile range, 64–77 years); 52 (40%) males] were analysed in the study.

### ***Effect of *H. pylori* eradication on various factors***

The effect of *H. pylori* eradication therapy on various physiological factors was carefully examined comparing the value before and after the therapy in all 130 elderly patients with the interval of 2 years for each (Table 1). The Body weight increased from a mean  $\pm$  SD of  $57.3 \pm 10.4$  kg before *H. pylori* eradication to  $58.2 \pm 10.3$  kg 2 years after *H. pylori* eradication ( $P = 0.018$ ). In addition, BMI increased from  $23.4 \pm 3.1$  before *H. pylori* eradication to  $23.7 \pm 3.0$  2 years after *H. pylori* eradication ( $P = 0.006$ ). MCV increased from  $89.2 \pm 4.9$  fL before *H. pylori* eradication to  $90.0 \pm 4.4$  fL 2 years after *H. pylori* eradication ( $P < 0.001$ ) whereas no significant changes were seen in the value of Hb ( $P = 0.84$ ). The paired-sample t-test showed no significant differences in other measurements including Total protein (TP), low-density lipoprotein cholesterol (LDL-C), Triglyceride (TG), and haemoglobin A1c (HbA1c), before and 2 years after *H. pylori* eradication (Table 1).

### ***Subgroup analysis of factors in elderly patients***

The patients older than 65 years old were considered to be elderly and the factors affected by the *H. pylori* eradication treatment have been carefully assessed by the subgroup analyses (Table 2). In the group of patients  $\geq 65$  years ( $n = 97$ ), BMI increased from  $23.6 \pm 3.0$  before *H. pylori* eradication to  $23.8 \pm 3.1$  2 years after *H. pylori* eradication ( $P = 0.045$ ). MCV increased from  $89.2 \pm 5.3$  fL before *H. pylori* eradication to  $90.1 \pm 4.7$  fL 2 years after *H. pylori* eradication ( $P = 0.0017$ ) whereas no significant changes were seen in the value of Hb ( $P = 0.84$ ). There were no significant differences in other measurements in the group of patients  $\geq 65$  years (Table 2).

These results suggest that the *H. pylori* eradication contribute to maintain the BMI avoiding the loss of body weight, and to recovery from subclinical IDA caused by the chronic inflammation in the stomach. In addition, even with the 2 years period of the study, no significant changes were seen in the various nutritional factors, indicating that the better digestion, absorption, after the eradication therapy.

### ***Effect of eradication and the level of haemoglobin***

To determine the effect of eradication on anaemia, level of Hb was carefully assessed in the patients (Table 3).

Although the patients with Hb levels  $< 12.5$  g/dL before *H. pylori* eradication increased from  $11.5 \pm 0.86$  g/dL to  $12.3 \pm 0.99$  g/dL at 2 years after *H. pylori* eradication ( $P = 0.017$ ), paired-sample t-tests showed no significant difference in Hb levels before and 2 years after *H. pylori* eradication in the group with Hb  $\geq 12.5$  g/dL (Table 3). In addition, to examine whether the rates of IDA improvement in chronic gastritis is related to the existence of GHP, the level of improvement of Hb and MCV values before and after the eradication were compared (Figure 1). The nonparametric Mann–Whitney test showed no significant increase in Hb levels and MCV ( $P = 0.89$ ) from before to 2 years after *H. pylori* eradication ( $P = 0.19$ ) between the groups with and without GHP (Figure 1) and its size. These results indicate that the improving tendency of anaemia after *H. pylori* eradication did not correlate with the presence of GHP or its size.

## **Discussion**

Our study showed that *H. pylori* eradication therapy for elderly patients with chronic gastritis increased BMI and MCV, 2 years as a result of successful *H. pylori* eradication. The level of MCV has been considered as one of the marker of subclinical IDA and its recovery reflect the improvement of IDA <sup>[21]</sup>. Previous studies have shown similar results in patients with anaemia whose Hb significantly improved after *H. pylori*

eradication<sup>[1,3-6]</sup>. There was no difference in the rate of increase in MCV (improvement in IDA) between groups with and without GHP. This finding suggests that GHP is not involved in an anaemic improvement pathway after *H. pylori* eradication.

It is known that the proportion of individuals with BMI > 30 generally increases up to the age of 60 years, and BMI tends to decrease after the age of 61 years<sup>[22]</sup>. In addition, the body weight loss in elderly individuals is a predictive factor for death, mildly obese individuals have the lowest mortality rate<sup>[23,24]</sup>. It might be related to the recently established concept of 'Frailty', a risk factor for falls, disability, hospitalization and mortality during old age. It is defined by the following criteria: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity<sup>[25]</sup> and energy & protein support is recommended to treat the condition<sup>[26]</sup>. Interestingly, in our study, we found that elderly patients gained weight after *H. pylori* eradication. This result was inconsistent with the general tendency towards body weight loss in the elderly population and suggested that the effect of *H. pylori* eradication on preventing body weight loss or increase. The mechanisms might include, improvement of gastro-duodenal inflammation, ulcerative lesions, etc. as well as decrease of serum level of leptin which plays a crucial role to regulate food intake

and energy expenditure.<sup>[11, 27]</sup> Thus, we infer that *H. pylori* eradication therapy for elderly patients with *H. pylori*-infected chronic gastritis may be an effective therapy for prevention of weight loss in elderly individuals.

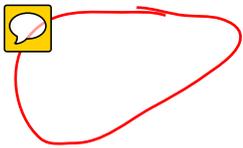
Our results are consistent with those of previous studies showing improvement of anaemia after *H. pylori* eradication therapy in elderly individuals<sup>[1,3-6]</sup>. Our study also showed that MCV increased after *H. pylori* eradication in the total study population as well as in the elderly patient group. However, presence of GHP was not related to the increase in the MCV rate. An important finding from previous study is that 80% of GHP disappeared after *H. pylori* eradication therapy within an average of 7.1 months<sup>[28]</sup>. A recent report suggested that *H. pylori*-related IDA was associated with several factors in patients with GHP and nodular gastritis<sup>[29]</sup>. Bleeding from GHP is assumed to be the cause of *H. pylori*-related IDA. However, a previous study showed that even faecal occult blood-negative patients may be anaemic<sup>[30]</sup>. In addition, the mechanism might not be applicable to nodular gastritis. A recent study suggested that the cause of anaemia in patients with GHP is not bleeding from GHP but rather a decrease in iron absorption caused by a low-acid state<sup>[26]</sup>. Therefore, our results provide some support for the hypothesis that the improvement of *H. pylori*-related IDA is caused by an underlying

mechanism other than GHP deletion.

One plausible reason for the finding of no significant changes in TP, TG, LDL-C and HbA1c levels is the presumed administration of statins and/or antidiabetic drugs to the patients. A previous report showed that serum total cholesterol levels did not change after *H. pylori* eradication<sup>[11]</sup>. Therefore, our results may be consistent with these previous findings.

A limitation of our study, however, is that although previous studies have shown that diabetes was exacerbated by *H. pylori* infection<sup>[17-19]</sup>, our findings suggest no exacerbation or improvement of diabetes by eradication was because of strict management by a diabetologist in our hospital. In addition, the power of this study was limited because of the small number of participants and patients with subclinical IDA, of the single-centre analysis and of the retrospective-observational study design. Therefore, future larger prospective studies are essential to confirm the effect of *H. pylori* eradication on systemic conditions by monitoring symptoms, medical history, and laboratory exams comparing with cases failed for the eradication.

In conclusion, our findings suggest that an increase in MCV is associated with body weight gain and improvement of subclinical IDA after *H. pylori* eradication in elderly patients with chronic gastritis. The tendency for subclinical IDA to improve after *H. pylori* eradication did not correlate with the presence of GHP. In addition, even with the 2 years period of the study, no significant changes were seen in the various nutritional factors, indicating that the better digestion, absorption, after the eradication therapy. Because the development of an aging society may be upcoming event in the near future, *H. pylori* eradication therapy may be a useful approach for preventing weight loss and frailty in elderly individuals.





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## **Table and Figure legends**

### **Table 1 Comparison of various factors before and after *H. pylori* eradication therapy in all subjects (n = 130)**

BMI: Body mass index; Hb: Haemoglobin; MCV: Mean corpuscular volume; TP: Total protein; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; HbA1c: Haemoglobin A1c.

### **Table 2 Subgroup analysis of various factors before and after *H. pylori* eradication therapy in the group of patients > 65 years (n = 97)**

BMI: Body mass index; Hb: Haemoglobin; MCV: Mean corpuscular volume; TP: Total protein; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; HbA1c: Haemoglobin A1c.

### **Table 3 Differences in the eradication effect on the rate of increase in haemoglobin level between groups of patients with < Hb 12.5 g/dL (n = 20) and patients with ≥**

**Hb 12.5 g/dL (n = 96)** Hb: Haemoglobin.

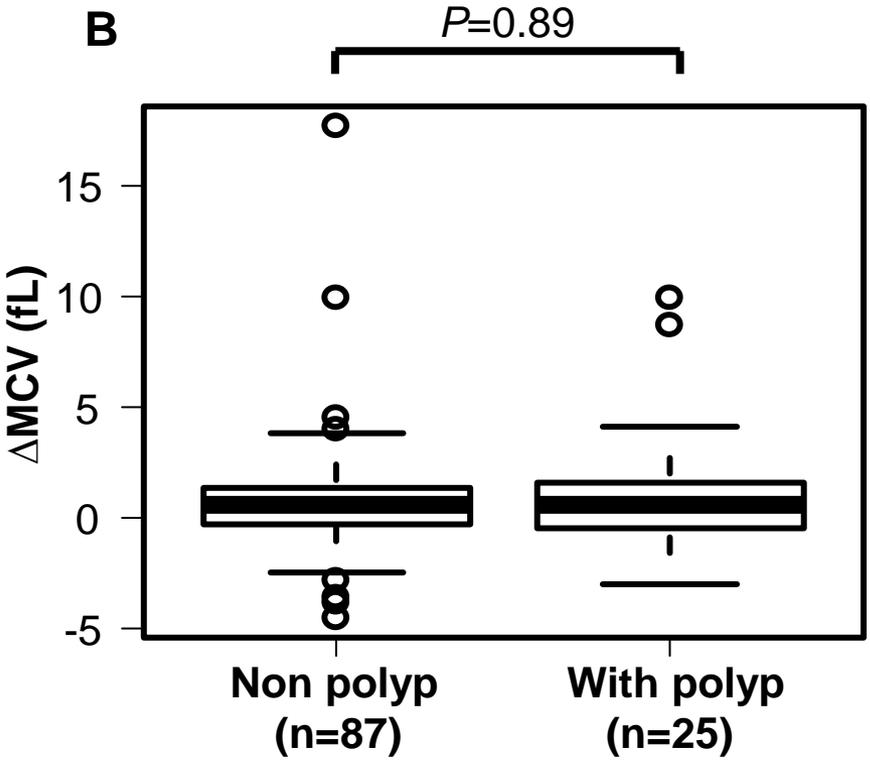
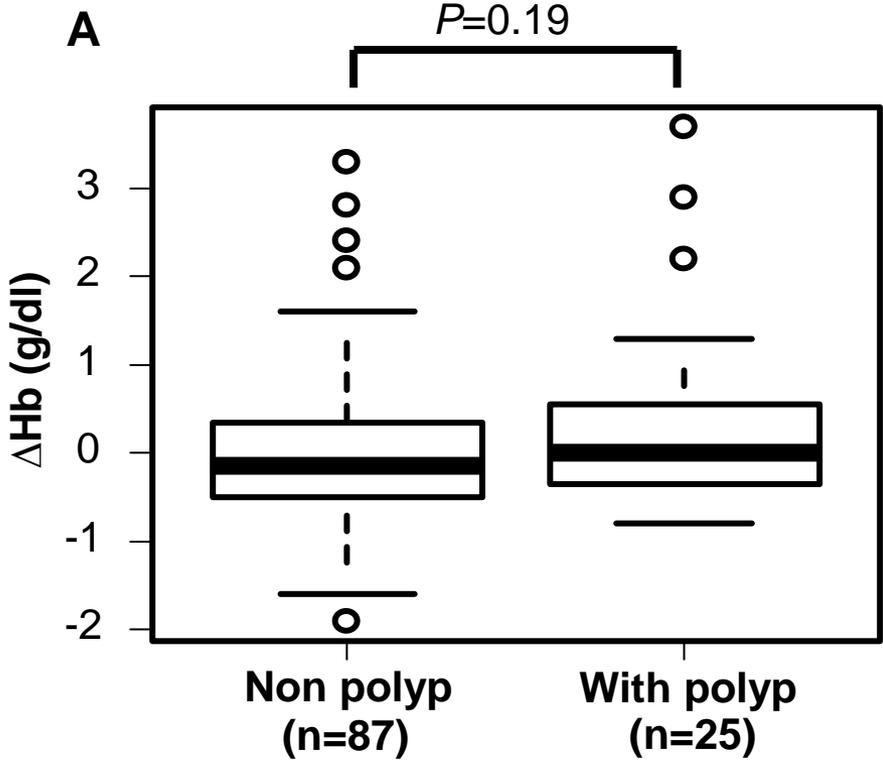
### **Figure 1 Comparison of haemoglobin and mean corpuscular volume levels before**

**and after *H. pylori* eradication therapy in patients with or without gastric hyperplastic polyps**

A: Change in the haemoglobin level; B: Mean corpuscular volume level; Hb:

Haemoglobin; MCV: Mean corpuscular volume.

**Figure 1**



**Table 1**

Variable	Pre-eradication		Post-eradication		Mean difference	95% CI	P value	
	Subjects	Missing	Mean (SD)	Mean (SD)				
Body weight (kg)	124	6	57.3 (10.4)	58.2 (10.3)	0.52	0.09-0.94	0.018	*
BMI (kg/m <sup>2</sup> )	121	9	23.4 (3.1)	23.7 (3.0)	0.25	0.074-0.42	0.006	**
Hb (g/dl)	115	15	13.8 (1.4)	13.8 (1.3)	0.018	-0.16-0.19	0.84	
MCV (fL)	113	17	89.2 (4.9)	90 (4.4)	0.83	0.32-1.34	< 0.001	**
TP (g/dl)	90	40	7.4 (0.5)	7.5 (0.4)	0.024	-0.058-0.11	0.56	
LDL-C (mg/dl)	107	23	114.3 (23.9)	116.2 (25.0)	1.2	-2.82-5.30	0.55	
TG (mg/dl)	107	23	122 (70.5)	126.6 (77.1)	6.81	-4.48-18.11	0.23	
HbA1c (%)	42	88	6.2 (0.81)	6.3 (0.75)	0.057	-0.21-0.095	0.45	

**Table 2**

Variable	Subjects	Missing	Pre-eradication	Post-eradication	Mean difference	95% CI	P value	
			Mean (SD)	Mean (SD)				
Body weight (kg)	92	5	57.1 (10.4)	57.8 (10.3)	0.41	-0.92-0.097	0.12	
BMI (kg/m <sup>2</sup> )	90	7	23.6 (3.0)	23.8 (3.1)	0.21	-0.42--0.0041	0.045	*
Hb (g/dl)	85	12	13.7 (1.5)	13.7 (1.3)	-0.02	-0.18-0.22	0.84	
MCV (fL)	85	12	89.2 (5.3)	90.1 (4.7)	0.95	-1.54--0.37	0.0017	**
TP (g/dl)	66	31	7.5 (0.5)	7.5 (0.4)	0.011	-0.096-0.12	0.84	
LDL-C (mg/dl)	77	20	111.9 (21.2)	114.2 (24.8)	1.25	-6.07-3.58	0.61	
TG (mg/dl)	77	20	116.7 (56.2)	112.6 (44.8)	-1.68	-8.50-11.85	0.74	
HbA1c (%)	30	67	6.4 (0.8)	6.4 (0.7)	0.013	-0.16-0.19	0.88	

**Table 3**

<b>Variable</b>	<b>Subjects</b>	<b>Missing</b>	<b>Pre-eradication</b>	<b>Post-eradication</b>	<b>Mean difference</b>	<b>95% CI</b>	<b>P value</b>
			<b>Mean (SD)</b>	<b>Mean (SD)</b>			
Less than Hb 12.5 g/dl	19	1	11.5 (0.7)	12.3 (1.0)	0.85	0.22-1.48	0.017 *
More over Hb 12.5 g/dl	96	11	14.2 (1.1)	14.1 (1.2)	-0.15	-0.15-0.0092	0.064