Eradication of Helicobacter Pylori Infection in Patients with Morbid Obesity and its Effect on the Components of Metabolic Syndrome

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Abstract

Introduction: Many studies were done in the past few years to assess any relation between helicobacter pylori infection and metabolic syndrome-related morbidity including cardiovascular disease but most of these studies had reported conflicting results.

Aim of the Work: To evaluate the changes in the components of metabolic syndrome and inflammatory parameters after helicobacter pylori eradication in patients with morbid obesity.

Subjects and Methods: We conducted a prospective, open-label, longitudinal, single-center study included 136 consecutive patients suffering from morbid obesity fulfilling the criteria of metabolic syndrome and had helicobacter pylori infection between January 2010, and 30 December 2012. Patients were referred to the Gastroenterology Unit of Farwaniya Hospital (regional hospital in Kuwait) for endoscopic evaluation of the possibility of sleeve gastrectomy surgery. All patients received the current standard triple therapy for 2 weeks. The metabolic and inflammatory parameters were assessed before and 6 weeks after eradication.

Results: Helicobacter pylori eradication rates were 68.75% with per protocol analysis and 64.7% with intention-to-treat analysis. Among the 88 patients with successful eradication, there were no significant differences in all variables before and after eradication of helicobacter pylori infection. There is minor increase in the mean of weight after eradication of helicobacter pylori but with no significant difference.

Conclusion: Helicobacter pylori eradication has no effect on metabolic and inflammatory parameters including lipid profile, blood sugar, insulin resistance and C-reactive protein in patients with morbid obesity.

Key Words: Helicobacter pylori — Morbid obesity — Metabolic syndrome.

Introduction

OBESITY, which nowadays represents a disease with rising prevalence, is the main factor leading to metabolic syndrome (MetS), which is characterized by a constellation of insulin resistance and cardiovascular risk factors, including atherogenic dyslipidemia, abnormal glucose tolerance, hypertension and visceral obesity. In addition, various other abnormalities of inflammation, hemostasis and fibrinolysis are often considered a part of this syndrome. Accumulation of these symptoms was reported to unequivocally increase the risk of cardiovascular morbidity and mortality. The body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) is the most commonly accepted measurement for obesity. A BMI exceeding 25 is considered overweight, while obesity is defined as a BMI of 30 or more. A BMI of 35 or more with serious comorbidity or a BMI of 40 or more is considered morbid obesity.

Helicobacter pylori (HP) is a gram-negative microaerophilic gastric pathogen that infects approximately one-half of the human population. Persistent colonization is associated with chronic inflammation processes, gastric atrophy, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma. This organism is also seen in other diseases such as primary biliary cirrhosis, functional vascular disorders (primary migraine and primary Reynaud's phenomenon), and ischaemic heart disease and immune thrombocytopenic purpura. Recently, the spectrum of HP related diseases has expanded to include gastroesophageal reflux disease and obesity. Several studies have shown that HP is associated with insulin resistance and metabolic syndrome. However the effects of eradication of HP infection on dyslipidemia and MetS parameters have shown conflicting results. Unfortunately, most of these studies were done on patients who did not suffer from morbid obesity.
Based on this fact, we conducted a prospective open label trial aimed at evaluating the changes in the components of MetS and inflammatory parameters after HP eradication in patients with morbid obesity.

**Subjects and Methods**

This was a prospective, open-label, longitudinal, single-center study. The study involved 136 consecutive patients affected by morbid obesity fulfilling the criteria of MetS between January 2010, and 30 December 2012. Patients were referred to the Gastroenterology Unit of Farwaniya Hospital (a 1000-bed regional hospital in Kuwait) for endoscopic evaluation of the possibility of sleeve gastrectomy surgery. All patients included in this study was diagnosed to have HP infection using a rapid urease test (RUT) and histological examination with Giemsa stain and received a triple therapy for eradication of HP.

We excluded subjects who showed evidence of taking current medications with lipid lowering agents or anti-inflammatory properties, proton pump inhibitors, H2 receptor blockers, bismuth preparations, prokinetics or antibiotics in the preceding two months, an underlying chronic disease (hepatic, renal, pulmonary, endocrine or oncological diseases), an acute infection or pregnancy. The occurrence of MetS was defined using the International Diabetes Federation definition [24]. People were classified as having MetS if they had central (abdominal) obesity with a waist circumference 94 cm (men) or 80 cm (women) (Arab populations), and were matching two or more of the following criteria: Fasting serum glucose of 110 mg/dL or more, triglycerides of 150 mg/dL or higher, HDL-cholesterol level less than 40 mg/dL in men or less than 50 mg/dL in women, or blood pressure of 130/85 mmHg or higher.

**Anthropometrical and laboratory methods:**

Body weight was measured to the nearest half-kilogram with the patient in light clothing and without shoes. Height was measured to the nearest half centimeter. Waist circumference was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Body mass index (BMI) was calculated as weight (kilograms) divided by height squared (meters). Blood pressure was measured sitting, after a minimum resting period of 5 min, using a mercury sphygmomanometer. Phase-I and Phase-V Korotkoff sounds were used to identify systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively; SBP and DBP values were an average of three different measurements separated by 2 min from one another.

Blood samples were obtained following an overnight (12 hour) fast. Samples were taken from a cubital vein into blood tubes, measuring complete blood count using (Sysmex K-1000, Bohemia, NY, USA) and the rest of the samples stored at 4°C. The serum was then separated by centrifugation at 3,000 rpm for 10 min and assays for glucose, total cholesterol (TC), high density lipoprotein (HDL-C), and triglyceride (TG), Serum low-density lipoprotein (LDL-C) C-reactive protein (CRP) were measured using an autoanalyzer (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland). Serum insulin levels were measured using the MEIA (microparticle enzyme immunosobent assay) method by an autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). Insulin resistance was evaluated using a homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR=Fasting plasma glucose (mg/dL) x fasting serum insulin (pU/mL)/405 [25]. All samples were analyzed in the same laboratory.

**Diagnosis and eradication therapy of HP:**

Upper gastrointestinal endoscopy was done for all patients of the study as an assessment for sleeve gastrectomy using a video-endoscope system (GIF-160 Diagnostic Gastro-videoscopes, Olympus, Tokyo, Japan). Four gastric biopsies were taken from the antrum and corpus, the two from the antrum were used for RUT (CLO test; Kimberly-Clark Ltd., Draper, Utah, USA) and the two from the corpus were fixed in 10% buffered formalin and embedded in paraffin for histological examination with Giemsa stain. When the CLO test showed red-violet color within 24h at room temperature, or HP bacteria irrespective of their density were found in one or more of the biopsy specimens, the diagnosis of HP infection was made. If both tests were negative the patient was considered HP-negative.

All patients received a triple therapy for eradication of HP which comprised of a fourteen-day course using a proton pump inhibitor and two antibiotics (standard OAC regimen; 20 mg omeprazol-1000 mg amoxicillin-500 mg clarithromycin). Compliance with therapy and adverse events was assessed by twice weekly clinical visits during treatment. Eradication was assessed six weeks after the end of triple therapy by C-urea breath test [26].

Ethical Considerations Written informed consent was obtained from all the participants before starting the protocol, and the study was approved
by the Hospital Ethical Committee on Human Research.

**Statistical analysis:**

Data were analyzed using SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, IL, USA). Results were expressed as means±standard deviation. Paired t-test was used for comparing the pre-treatment and post-treatment values of patients. p-values below 0.05 were considered statistically significant in all analyses.

**Results**

We included in the study 136 patients fulfilling the criteria of the MetS and proved to have HP infection by histology and RUT. A 50 patients were male (36.7%) and 86 patients were female (63.2%). The mean age was 34±11.9 while the mean BMI was 47.3±5.7 kg/m². The demographic and clinical data of the patients are presented in Table (1).

<table>
<thead>
<tr>
<th>Item</th>
<th>Clinical variables (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34±11.9</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>50/86</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>138.5±26.2</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>133.3±15.7</td>
</tr>
<tr>
<td>Body mass index (BMI; kg/m²)</td>
<td>47.3±5.7</td>
</tr>
<tr>
<td>White blood cell count (x1000/u1)</td>
<td>7.2±2.1</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.44±0.59</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>193.92±35.03</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>161.10±95.39</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>45.53±12.74</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>124.94±29.83</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>131.22±6.12</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>75.01±7.20</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>106.45±12.92</td>
</tr>
<tr>
<td>Insulin (µU/dl)</td>
<td>11.12±8.95</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.50±3.68</td>
</tr>
</tbody>
</table>

Data are presented as Mean±SD.

M: Male Gender.
F: Female.
CRP: C-reactive Protein.
HDL: High-density Lipoprotein-cholesterol.
LDL: Low-density Lipoprotein-cholesterol.
HOMA-IR: Homeostasis Model Assessment Of Insulin Resistance.

A 23 patients developed adverse events of eradication therapy (bloating 8, diarrhea 8, nausea 7) which were mild and self limiting, 8 patients did not complete the follow-up 6 weeks after the end of therapy as they did the sleeve gastrectomy and were excluded from the study. 88 patients became negative for C-urea breath test with HP eradication rates 68.75% by per protocol analysis (PP) and 64.7% by intention-to-treat analysis (ITT).

Among the 88 patients with successful eradication, there were no significant differences in all variables before and after eradication of HP. There is minor increase in the mean of weight before and after eradication of HP but with no significant difference as shown in Table (2).

<table>
<thead>
<tr>
<th>Item</th>
<th>Before HP eradication</th>
<th>After HP eradication</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>137.1±24.2</td>
<td>139.6±18.2</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>132.2±13.7</td>
<td>135.5±14.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (BMI; kg/m²)</td>
<td>46.9±5.2</td>
<td>47.4±6.9</td>
<td>NS</td>
</tr>
<tr>
<td>White blood cell count (x1000/u1)</td>
<td>7.01±1.99</td>
<td>6.91±1.75</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.40±0.55</td>
<td>0.38±0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>192.82±34.03</td>
<td>191.66±43.62</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>161.10±95.39</td>
<td>158.77±84.21</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>45.53±12.74</td>
<td>46.05±13.87</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>124.94±29.83</td>
<td>123.82±43.38</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>131.22±6.12</td>
<td>130.88±7.32</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>75.01±7.20</td>
<td>74.49±8.10</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>106.33±6.3</td>
<td>105.9±7.1</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (µU/dl)</td>
<td>11.11±7.95</td>
<td>11.22±10.83</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.32±2.11</td>
<td>3.08±2.59</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: Non significant.
p<0.05 was considered significant after performing the Student t-test.

**Discussion**

In the present study, the effectiveness of the current standard triple therapy for HP eradication became more poor, 68.75% in PP analysis and 64.7% in ITT analysis.

In a previous study that was conducted in Kuwait, Alazmi et al., found the eradication rates in ITT and PP were 72.3% and 76.1% respectively [27]. The decrease in the eradication rate in spite
of the age of the patients were younger and the duration of the treatment was extended to two weeks which are important factors in improving eradication success [28,29] may be due to clarithromycin resistance which growing rapidly in Kuwait and must give attention to use other clarithromycin free regimens.

In this study, a longitudinal comparison within the group of patients who were cleared from HP infection showed no significant change in all studied parameters including the metabolic and inflammatory data.

Many studies were done in the past few years to assess any relation between HP infection and MetS- related morbidity including cardiovascular disease but all these studies had reported conflicting results [30-33].

Recently, Ramazan et al., found that HP eradication had a beneficial effects on insulin resistance, atherogenic lipid abnormalities and low grade inflammation [34]. The dilemma of these reported studies may be due to the following factors:
- The worldwide increasing incidence of both HP infection and MetS may make this casual relationship.
- Different criteria of MetS and different methods for diagnosis of HP infection in these studies.
- Most of the studies which assessed the effect of eradication therapy on the metabolic and inflammatory parameters had a study population of healthy individuals or dyspeptic adults and they did not suffer from any criteria of MetS.

In the present study, the mean weight of the patients increase after eradication of HP but with no significant differences, there are many studies explain the relation of obesity and HP eradication. Blaser and Atherton assumed that HP-induced persistent and uncontrolled gastric inflammation would lead to dysregulation of appetite and caloric homeostasis through its effect on the expression of gut hormones such as ghrelin [34]. Tatsuguchi et al found that After successful eradication of HP the number of ghrelin positive cells increases significantly irrespective of the presence of gastric atrophy [35]. This could lead to increased appetite and weight gain. Also, in an experimental study in which HP infection was induced, significant decrease in ghrelin mRNA levels and plasma ghrelin levels occurred [36]. Also, HP infection significantly increases gastric leptin expression and eradication of HP decreases gastric leptin expression. The plasma leptin levels do not change, but there is a significant decrease in immunoreactivity of leptin in mucus of the fundus [37]. Increased leptin signalling leads to decreased food intake and, in addition, to increased energy expenditure and increased thermogenesis [38]. The effects of HP on ghrelin and leptin strongly suggest that the bacterium 'protects' against obesity. The decreasing incidence of this infection may be contributing to an increase in appetite and food intake [39].

In the current study, the lack of control group and the absence of long term follow-up for the metabolic and inflammatory parameters after HP eradication make the generalization of our results should be considered cautiously. However, our study has an important advantage that the patients' population had metabolic syndrome that making the results more reliable.

Conclusion:
HP eradication has no effect on metabolic and inflammatory parameters including lipid profile, blood sugar, insulin resistance and C-reactive protein in patients with morbid obesity. Further large scale prospective study with long term follow-up is needed to confirm our results.

References

10- PASCERI V., CAMMAROTA G., PATTI G., et al.: Association of virulent helicobacter pylori strains with


