H. pylori Eradication and Strict Diet Regimen’s Synergetic Effect on Glycemic State in Type Two Diabetics on Insulin Therapy

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H. pylori (H. pylori) infection affects nearly 50% of the human population reaching an incidence rate of about 70% in developing countries. Egypt is one of the highest endemic areas for this infection. H. pylori infection is associated with gastro-intestinal and extra gastric diseases. Type two diabetes mellitus (T2DM) is the prevalent type of DM reaching about 90%, WHO predicting the number of patients to be 438 million by year 2030. Inflammation is the playing factor in the etiology of DM and insulin resistance. H. pylori could be the source of infection. This research aimed to detect the effect of H. pylori eradication on glycemic control in T2DM on insulin therapy with and without diet planning. This is a randomized controlled clinical trial involving 68 well known T2DM patients on insulin therapy proved H. pylori positive by detection of antigens using ELISA kit (Epitope diagnostics. USA). In the stool. those patients were recruited from the outpatient clinics of the National Research Centre. The patients were randomized into 4 equal groups; Group 1 (M) received their routine medical treatment only, group 2 (MD) received medical treatment and individualized planned dietary regimen, group 3 (MH) received medical and anti-H. pylori treatment while group 4 (MHD) received medical, anti-H. pylori treatment and dietary regimen. Initial baseline evaluation included: diabetes panel, lipid profile, liver enzymes, renal functions and BMI which is repeated at the end of 6 months follow up. The results showed a significant decrease of mean FBG, PPG and HbA1c levels at the end of 6 months intervention from baseline levels in the 4 groups, however the mean difference increased from group 1 to group 4. Mean BMI and Uric acid significantly decreased in all groups except group-M. Cholesterol and triglycerides significantly decreased in all groups. Non-statistically significant changes regarding ALT, AST and serum creatinine were observed in all groups. Based on these results it is recommended to use the combined regimen of medical treatment together with anti H. pylori and diet control for better glycemic and lipid profile control in patients with type II diabetes who depends on insulin therapy.

Keywords: H. pylori, diabetes, insulin, diet

Introduction

H. pylori infection is caused by a Gram-negative bacterium that mainly causes gastric disorders ranging from gastritis up to peptic ulcer disease (10-15%) and MALT lymphoma (less than 1%) of the total infected population with a high prevalence rate reaching about 50% of the world population affecting the developing countries more frequent than the developed countries (Horiki et al., 2009). H. pylori infection is commonly transmitted either by the oral or the feco- oral route (Fallone, 2000).
H. pylori infection causes chronic active gastritis infiltrating the lamina propria by inflammatory cells; neutrophils, macrophages, T and B lymphocytes and mast cells. Mast cells are responsible for the host immune reaction with great evidence that H. pylori is not invading the gastric mucosa but taking a niche within the mucosa to be protected from the gastric secretions. After mucosal contact with the H. pylori the release of chemotactic factors could recall the inflammatory cells within the infected area. Interferon-gamma inducible protein–10 (IP-10) and the monokine-induced by interferon-gamma (MIG) are released by the endothelial cells and the mononuclear cells of the host infected by chronic H. pylori gastritis. Another hypothesis that H. pylori itself may recall immune cells from afar by its own membrane molecules such as urea or lipopolysaccharide (LPS) (HSU et al., 2014).

The sequela of this infection is variable from mild to severe gastritis about 10-15% will develop gastric ulcers while less than 1% will develop malignancy in the form of gastric adenocarcinoma (Paziak-Domańska et al., 2000). The difference in the outcome of the infection is mostly contributed to variations in the lifestyles, socioeconomic levels and diet of the host population in addition to the presence of CagA strains (Bruewer et al., 2003).

The relation of H. pylori infection and extragastric diseases is recently detected. The relation of H. pylori infection and iron deficiency anemia either by erosive gastritis (Papagiannakis et al., 2013) or decrease the acid production due to gastric atrophy (El-Eshmawy et al., 2011) or due to the presence of CagA protein of H. pylori which share in iron acquisition from interstitial holotransferrin (Xu et al., 2017).

Molecular mimicry may be responsible for the correlation between H. pylori infection and Immune thrombocytopenic purpura (ITP) it is claimed that the monoclonal antibodies generated against H. pylori react with GP IIb/IIIa identified on the platelet surface (Azuma et al., 2002).

There was an association between H. pylori infection and Diabetes mellitus (DM), insulin resistance and poor glycemic control (Choi et al., 2016). The association of H. pylori infection and the coronary artery disease is also documented where several studies related the infection with acute coronary syndrome and risk of myocardial infarction (Zojaji et al., 2013).

The relationship between H. pylori infection and obesity was controversial where some studies documented this relation (Dai et al., 2015) while other studies deny the relation (Horikawa et al., 2014).

Patients and Methods

Study design

Enrolment of 68 diabetic patients who have been proven to be H. pylori positive by stool antigen test by ELISA kit (Epitope diagnostics. USA). Study setting were at the outpatient clinics of the National Research Centre, Egypt. Study subjects were randomly divided into 4 groups; group 1: received their standard medical treatment for diabetes (M), group 2: received standard medical treatment for diabetes and individualized diet regimen (MD), group 3: received standard medical treatment for diabetes and drug treatment of H. pylori (MH) and group 4: received standard treatment for diabetes and drug treatment of H. pylori and individualized diet regimen (SHD).

Inclusion criteria

1- Adults, both sexes have been involved.
2- Type II diabetics on insulin therapy.
3- H. pylori positive cases with stool antigen test or urea breath test.
4- Regularly attend the NRC outpatient clinic.

Exclusion criteria

1- Type I diabetic patients.
2- History of recent anti H. pylori treatment within the last 6 months with the same prescribed regimen.

Study details

For all involved patients, 1) detailed medical and dietary history was taken, 2) revised appropriate dosage of their standard medical treatment for diabetes was done.

For the first group: after termination of the study (6 months intervention), they were offered treatment for H. pylori and detailed individualized diet regimen.

For the second group: they received in addition a detailed individualized diet regimen. After termination of the study, treatment for H. pylori was provided.

For the third group: anti-H. pylori treatment was prescribed. After termination of the study, they were offered detailed individualized diet regimen.
For the fourth group: anti-H. pylori treatment was prescribed and detailed individualized diet regimen.

History taking was documented including both medical history and dietary history anthropometric measures was undertaken in addition to clinical examination (Westat Inc., 1988).

A detailed individualized diet regimen was applied according to his requirements and the available resources. Dietary calories were evaluated and each patient was asked to follow his/her dietary plan as follows:

Calories intake plan was discussed individually for each patient according to Eating patterns and meal planning. American Diabetes Association, 2019.

The treatment regimen for the H. pylori as follows:

- Non bismuth quadruple sequential therapy as a treatment of H. pylori in the form of:
  - PPI plus amoxicillin for 7 days followed by
  - PPI plus clarithromycin and metronidazole for another 7 days

The following laboratory investigations were done as an initial evaluation of each patient:

- FBG, PPG, HBA1C, Lipid profile (cholesterol, triglyceride), liver enzymes, creatinine level, serum uric acid using Olympus Au-800 Automated Chemistry Analyzer (Olympus, Japan).

Randomization and concealment

Following enrollment, we randomly assigned 64 patients to one of the 4 study groups according to the time of enrollment. Randomization was by using a computer-generated random numbers table. The assigned treatment was written on a card and sealed in opaque envelopes consecutively numbered. These envelopes opened just immediately before the procedure.

Study patients were planned to have every 2 weeks visit for follow up the medical treatment and the strict follow up of the dietary plan.

Of the received patients whom were about 85 patients, 81 patients accepted to be enrolled, 68 patients have been proven to be H. pylori positive by ELISA (Epitope diagnostics. USA) reaching a percentage of 83.9% of the total patients received.

After explanation of the study and the plan of treatment to every patient and signing the consent by the patient the study was initiated individually.

Results

Group-M: Cases received medical treatment only.

Group-MD: Cases received medical treatment and dietary regimen.


Baseline characteristics and measures between study groups showed none significant difference regarding age, sex, BMI, diabetes panel, liver enzymes, creatinine, uric acid or lipid profile (table 1).

A significant reduction of mean value of BMI (6 month- baseline levels) was observed in all groups except group-M. Highest difference was found in group-MHD, followed by group-MH& then group-MD.

Diabetes panel (FBG, PPBG and HbA1c), showed significant reduction of mean values, however the highest difference was in group-MHD.

No significant difference between the studied groups regarding ALT and AST month-6 after intervention and baseline values.

Mean cholesterol and triglycerides month-6 after intervention from baseline showed significance difference in each of the studied groups.

Regarding uric acid, a significant reduction of mean value (6 month- baseline levels) was observed in all groups except group-M. Highest difference was found in group-MHD, followed by group-MH& then group-MD.

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 18.0, IBM Corp., Chicago, USA, 2009.

Descriptive statistics were done for quantitative data as minimum& maximum of the range as well as mean±SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses were done for quantitative variables using Shapiro-Wilk test for normality testing, paired t-test in cases of two dependent groups and ANOVA test with post hoc Tukey test for more than two independent groups. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.
### TABLE 1. Baseline characteristics and measures of studied Type2DM on insulin therapy.

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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean±SD (range)</td>
<td>50.3±7.5 (37.0–62.0)</td>
<td>50.4±6.8 (34.0–64.0)</td>
<td>51.6±5.4 (44.0–60.0)</td>
<td>47.7±8.6 (35.0–61.0)</td>
<td>0.445</td>
</tr>
<tr>
<td>Sex</td>
<td>Male Female (No %)</td>
<td>5 (29.4%)</td>
<td>12 (70.6%)</td>
<td>3 (17.6%)</td>
<td>14 (82.4%)</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean±SD (range)</td>
<td>27.6±2.7 (24.0–32.0)</td>
<td>27.9±2.4 (25.0–32.0)</td>
<td>27.1±2.4 (23.0–33.0)</td>
<td>28.2±2.5 (22.0–32.0)</td>
<td>0.611</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>Mean±SD (range)</td>
<td>180.1±41.1 (110–240.0)</td>
<td>174.4±48.8 (100.0–270.0)</td>
<td>187.1±65.5 (105–370)</td>
<td>195.0±46.4 (130–275)</td>
<td>0.222</td>
</tr>
<tr>
<td>PPBG (mg/dL)</td>
<td>Mean±SD (range)</td>
<td>242.2±103.2 (120–425)</td>
<td>240.2±97.4 (110–472)</td>
<td>261.6±99.1 (125–470)</td>
<td>274.7±104.2 (140–450)</td>
<td>0.717</td>
</tr>
<tr>
<td>HbA1c (range)</td>
<td>Mean±SD (range)</td>
<td>7.9±1.8 (5.0–11.0)</td>
<td>7.9±1.8 (5.5–13.0)</td>
<td>8.5±2.1 (5.8–12.5)</td>
<td>9.2±2.3 (6.0–13.0)</td>
<td>0.199</td>
</tr>
<tr>
<td>ALT (IU/mL)</td>
<td>Mean±SD (range)</td>
<td>33.2±11.0 (20–60)</td>
<td>34.4±12.3 (18–55)</td>
<td>35.3±11.2 (22–55)</td>
<td>37.2±10.8 (20–58.0)</td>
<td>0.771</td>
</tr>
<tr>
<td>AST (IU/mL)</td>
<td>Mean±SD (range)</td>
<td>29.5±9.5 (18.0–50.0)</td>
<td>30.4±12.4 (17.0–62.0)</td>
<td>29.1±7.8 (17.0–60.0)</td>
<td>35.2±11.6 (20.0–60.0)</td>
<td>0.303</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>Mean±SD (range)</td>
<td>0.97±0.34 (0.40–1.8)</td>
<td>0.98±0.35 (0.5–1.8)</td>
<td>1.04±0.21 (0.7–1.4)</td>
<td>1.12±0.36 (0.5–2.0)</td>
<td>0.530</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>Mean±SD (range)</td>
<td>5.6±1.9 (2.9–9.0)</td>
<td>5.5±1.7 (3.5–9.0)</td>
<td>6.1±1.6 (3.5–8.5)</td>
<td>5.2±0.8 (4.0–7.0)</td>
<td>0.392</td>
</tr>
<tr>
<td>t.Cholesterol (mg/dL)</td>
<td>Mean±SD (range)</td>
<td>212.6±64.4 (140–350)</td>
<td>231.8±58.1 (150–350)</td>
<td>208.5±74.5 (140–400)</td>
<td>242.9±53.5 (150–350)</td>
<td>0.348</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>Mean±SD (range)</td>
<td>172.6±51.2 (100–300)</td>
<td>178.5±41.5 (110–255)</td>
<td>159.7±65.6 (100–350)</td>
<td>182.4±53.9 (90–300)</td>
<td>0.632</td>
</tr>
</tbody>
</table>

**Assessed for eligibility**  
(N=85)  
**Excluded (N=17)**  
#Exclusion criteria (N=13)  
#Refuse to participate (N=4)  

**Randomized**  
(N=68)  

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<tr>
<td>Loss of follow up (N=0)</td>
<td>Loss of follow up (N=0)</td>
<td>Loss of follow up (N=0)</td>
<td>Loss of follow up (N=0)</td>
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<tr>
<td>Analyzed (N=17)</td>
<td>Analyzed (N=17)</td>
<td>Analyzed (N=17)</td>
<td>Analyzed (N=17)</td>
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</table>

Fig. 1. Flow chart shows study subjects enrollment.
TABLE 2. Mean difference 6 months after intervention from baseline of body mass index, blood glucose levels, liver, renal functions and lipid profile of studied Type2DM on insulin therapy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group-M</th>
<th>Group-MH</th>
<th>Group-MD</th>
<th>Group-MHD</th>
<th>Sig. ^ P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m^2) Mean±SD</td>
<td>-0.2±0.8</td>
<td>4.0±0.5</td>
<td>-0.4±0.7</td>
<td>-0.4±0.4</td>
<td>0.516</td>
</tr>
<tr>
<td>P value</td>
<td>0.390</td>
<td>0.010*</td>
<td>0.022*</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>FBG (mg/dL) Mean±SD</td>
<td>-14.5±75.0</td>
<td>0.029*</td>
<td>-18.2±32.5</td>
<td>-26.2±33.0</td>
<td>0.174</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.034*</td>
<td>0.005*</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>PPG (mg/dL) Mean±SD</td>
<td>-28.6±31.3</td>
<td>0.002*</td>
<td>-28.5±40.7</td>
<td>-38.9±39.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.011*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>HbA1c Mean±SD</td>
<td>-0.4±0.4a</td>
<td>0.002*</td>
<td>0.002*</td>
<td>-0.7±0.8ab</td>
<td>0.066*</td>
</tr>
<tr>
<td>P value</td>
<td>0.002*</td>
<td>0.028*</td>
<td>0.002*</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>ALT (IU/mL) Mean±SD</td>
<td>0.2±5.4</td>
<td>0.1±6.2</td>
<td>0.2±5.1</td>
<td>-2.2±4.5</td>
<td>0.466</td>
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<tr>
<td>P value</td>
<td>0.894</td>
<td>0.939</td>
<td>0.887</td>
<td>0.056</td>
<td></td>
</tr>
<tr>
<td>AST (IU/mL) Mean±SD</td>
<td>0.3±4.5</td>
<td>0.2±5.4</td>
<td>0.4±3.9</td>
<td>0.4±5.1</td>
<td>0.963</td>
</tr>
<tr>
<td>P value</td>
<td>0.791</td>
<td>0.860</td>
<td>0.711</td>
<td>0.746</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl) Mean±SD</td>
<td>-0.3±0.7</td>
<td>0.005*</td>
<td>0.007</td>
<td>-0.5±0.4</td>
<td>0.720</td>
</tr>
<tr>
<td>P value</td>
<td>0.002*</td>
<td>0.409</td>
<td>0.400</td>
<td>0.346</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dl) Mean±SD</td>
<td>-0.3±0.7</td>
<td>0.005*</td>
<td>0.003*</td>
<td>-0.5±0.4</td>
<td>0.720</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.139</td>
<td>0.032*</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dL) Mean±SD</td>
<td>-14.1±17.8a</td>
<td>0.005*</td>
<td>-29.4±23.0ab</td>
<td>-35.6±41.3ab</td>
<td>0.018*</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.005*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL) Mean±SD</td>
<td>-20.9±22.9</td>
<td>0.002*</td>
<td>-24.6±23.1</td>
<td>-25.9±42.5</td>
<td>0.431</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>&lt;0.001*</td>
<td>0.020*</td>
<td>0.003*</td>
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</tbody>
</table>

Mean difference = 6th month – baseline (negative values indicate reduction, Paired t-test compare mean difference in each group ^ANOVA test, pylori treatments.)

Group-MHD: Cases received medical and anti-H. pylori treatments and dietary regimen.

with post hoc Tukey’s test  *Significant

Fig.2. Comparison between the studied groups regarding HbA1c reduction.

Fig.3. Comparison between the studied groups regarding cholesterol change.
Discussion

Chronic infection with H. pylori can cause serious complications on stomach. Recent studies have linked between H. pylori infection and incidence of various illnesses. H. pylori is believed to have a bad effect on glycemic state in diabetic patients. Our study aimed to assess the efficacy of diet control and H. pylori eradication therapy on the glycemic control of the patients.

Eighty five diabetic patients divided into equal four groups. The four groups were homogeneous and showed no statistical difference in baseline characteristics. Our study showed that both diet control and anti H. pylori therapy causes a decrease in the body mass index of all study participants which could be referred to the proper lifestyle measures that was followed during the study. On the other hand Xu et al, Azuma et al. and Choi et al. have all concluded that BMI increases after H. pylori eradication on both children and adults. They referred that to termination of annoying symptoms of epigastric pain and reflux which encourage the patients to eat larger quantities. But all these studies rely on eradication therapy only without making a proper supplementary nutrition plan for study participants.

Eradication of H. pylori as well as diet therapy have aided in proper glycemic control of patients of all groups except group M which showed poor reduction in Fasting, post prandial and glycosylated hemoglobin values. Group MHD showed the best results denoting the beneficial synergetic effect of diet control and H. pylori eradication on glycemic state. Zojaji et al also stated that H. pylori eradication aids in improvement of glycemic state of patients. Dai et al revealed the association of H. pylori infection and poor glycemic control however they didn’t confirm any beneficial role of H. pylori eradication. On the other hand Horikawa et al and Candelli et al have concluded the H. pylori eradication has no role in improving the glycemic state of diabetic patients.

There was no statistical changes in liver transaminases in all groups. While Salehi et al results revealed the beneficial role of H. pylori eradication on lowering the unexplained high liver transaminases Non significant changes in the current study because all patients had normal baseline liver transaminases.

Many studies discussed the relation of H. pylori and dyslipidemia (Kim, et al., 2011). Also high cholesterol level can aid in H. pylori resistant (McGee et al., 2011), however – up to our knowledge – No study has discussed the role of eradication on cholesterol levels. Our study results showed statistical reduction in total cholesterol and triglycerides in each study at 6th month than baseline.

H. pylori eradication has no effect on creatinine levels and this comes in agreement with results of Bahar Caliskan et al study which deny any role of H. pylori eradication on creatinine levels (Caliskan et al., 2014). Moreover our study was – up to our knowledge – the first one to discuss H. pylori eradication effect on uric acid levels which was significantly improved after eradication in each of intervention study groups.

Conclusion

After enrolment of 68 patients meeting the inclusion criteria and their random equal distribution among 4 groups it was noticed that FBG, PPBG and HbA1c significantly decreased in all groups, however the best reduction was intervention group received both anti H. pylori and strict diet regimen. BMI significantly decreased in all groups except group-M., ALT, AST and serum creatinine non-significantly changed in all groups, Cholesterol and triglycerides significantly decreased in all groups while Uric acid significantly decreased in all groups except group-M.

According the above results, the combined regimen that include (medical treatment + Anti H. pylori + Diet control) shows a promising effect on the glycemic control and lipid profile of type II Diabetic patients under insulin therapy.

References


