# Study of insulin resistance in patients with variable grades of gastroesophageal reflux diseases

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**Abstract:** Back ground: Gastroesophageal reflux disease (GERD) is becoming increasingly prevalent worldwide; its community-based prevalence is 19.8%. GERD not only affect the quality of patient's live but also increase risk of esophageal adenocarcinom***a***. Recent studies have linked insulin resistance (IR), a principle component of metabolic syndrome to carcinogenesis, moreover increased insulin resistance was identified in association with increased prevalence of **GERD. Aim of the work:** The aim of this study was to investigate the influence of insulin resistance on the severity of Gastroesophageal reflux disease. **Subject and Methods:** this study was conducted on 90 patients with GERD symptoms. The patients were divided into 4 groups. 30 patients with non-erosive GERD included in Group I. 30 patients with mild GERD (grade A and B) included in group II. Group III (n=20) included patients with severe GERD (grade C and D). In addition 10 patients with Barrette esophagitis were tested (group IV). The diagnosis and grading of GERD and barrett's esophagitis based on endoscopic findings. Insulin resistance was measured for all subjects using the equation (Homeostasis model assessment of insulin resistance HOMA-IR). *H pylori* IgG was tested for all subjects. **Results:** The mean age of included subjects was 36.5±16.8 years, 36 were females (40%) and 54 were males (60%). The mean HOMA-IR was 2.86±2.2 Iu/l. While 32 patients were reacting for *H. pylori*-IgG antibodies, 58 were *H. pylori* -IgG negative. There were no significant differences among patients with different GERD grades regarding the level of fasting insulin or HOMA-IR. In addition there were no significant differences between the grades of GERD and *H. pylori* serostatus. **Conclusion:** there is no significant relation between insulin resistance and severity of GERD in our study. The relation between GERD and IR seems to be multifactorial.

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## 1. Introduction:

Gastroesophageal reflux disease (GERD) is becoming increasingly prevalent worldwide. When GERD is defined as presence of at least one of heartburn or regurgitation, once a week or more often, its community-based prevalence is 19.8%. GERD not only affect the quality of patient's live but also increase risk of esophageal adenocarcinoma **(Locke *et al.*, 1997).**

Complications of GERD include erosion/ulceration, hemorrhage, stricture, and Barrett's esophagus **(Spechler, 2003).** It has been known for more than a century that chronic inflammation can contribute to cancer formation. Chronic inflammatory conditions of the gastrointestinal tract, such as ulcerative colitis and chronic pancreatitis, are well known to predispose patients to carcinogenesis. **Lassen *et al.*, 2006** have reported that the risk of esophageal adenocarcinoma was fivefold greater among patients with esophagitis, but most of these cancers seemed to be related to Barrett's esophagus. Several studies have indicated that a dose-response relationship exists between the severity of erosive esophagitis and the incidence of esophageal adenocarcinoma **(Lagergren *et al.*, 1999).**

Identification of risk factors for increasing GERD severity may serve as the basis for prevention of esophageal adenocarcinoma. Metabolic syndrome is a common syndrome that threatens public health in many countries. Recent studies have linked insulin resistance (IR), a principle component of metabolic syndrome to carcinogenesis **(Chen *et al.*, 2008),** moreover increased insulin resistance was identified in association with increased prevalence of GERD **(Hsu *et al.*, 2011).**

**Aim of the work**

In this study we were aiming to investigate the influence of insulin resistance on the severity of Gastroesophageal reflux disease.

**Subject and Methods**

This prospective study has been approved by the Internal Medicine Department and the research board

of Al-Azhar University. It included 90 patients with GERD symptoms. All patients divide into 4 groups:

30 patients with non-erosive esophagitis included in **Group I**. 30 patients with mild erosive esophagitis (grade A and B) included in **group II**. **Group III** (n=20) included patients with severe erosive esophagitis (grade C and D). In addition 10 patients with Barrette esophagitis were tested **group IV**.

**Inclusion criteria:**

All patients complaining from heart burn and reflux symptoms

**Exclusion criteria:**

Patients, who receive proton pump inhibitor, histamine-2 receptor antagonist, aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) in the 6 months preceding endoscopy, Those who underwent gastrectomy, patients with liver cirrhosis or malignancy,

**All patients were subjected to the following:**

**1. Complete clinical evaluation thorough**

**A- Full history taking with special emphasis on :**

Age, sex

Educational status,

Smoking and alcohol consumption.

**B -Clinical examination including :**

Body mass index calculated as weight in kilograms divided by height in meters squared ($kg/m^2$).

Metabolic syndrome assessed according to international diabetes federation consensus worldwide definition 2006 ***(*Alberti *et al*., 2005).***

2**. Laboratory investigations including :**

Serum fasting (12h fast) glucose

Serum fasting (12h fast) insulin

triglycerides, total cholesterol, low density lipoprotein, and high density lipoprotein.

aspartate aminotransferase, alanine aminotransferase measured for all patients.

Helicobacter pylori (*H. Pylori*) IgG antibodies were tested for all patients.

***Determination of IR:***

It determined using the homoeostasis model assessment (HOMA-IR), according to the following formula HOMA-IR = fasting insulin (mU/L) X fasting glucose (mg /dl)/ 405.

**Fasting insulin measurement:**

Fasting serum insulin was measured for all patients by ELISA ***(Chung et al., 2008)***

**GERD questionnaire:**

Presence, frequency and severity of heartburn, regurgitation, non-cardiac chest pain and dysphagia; presence of odynophagia, dyspepsia, chronic pharyngitis, laryngitis and asthma; frequency of visits to the physician; as well as any treatment received with respect to acid-inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) and eradication therapy for *H. pylori* searched for. This questionnaire validated previously ***(Klauser et al., 1990).*** Reflux score, used for evaluation of GERD symptoms. The relation between GERD questionnaire and different patients' groups as well as patients parameters assessed.

**Diagnosis of liver cirrhosis:**

Liver cirrhosis assessed according to the presence of two or more of the following sonographic findings, coarse or heterogeneous echo pattern increased parenchymal echogenecity, nodularity of liver surface, or signs of portal hypertension (splenomegaly, ascites or porto-systemic collaterals).

**3. Upper Gastrointestinal Endoscopy:**

Diagnostic criterion for endoscopic erosive GERD based on the presence of one or more mucosal injury at the distal esophagus on endoscopy. Los Angeles classification was used in evaluation and grading of the patients with erosive distal esophagitis ***(Chiba et al., 2012)***. The presence and extent of Barrett's epithelium based on the Prague C & M Criteria. According to these criteria, Barrett's epithelium is defined as the macroscopic identification, using a standard endoscopy examination, of abnormal columnar esophageal epithelium suggestive of columnar-lined distal esophagus. Presence of specialized intestinal epithelium on the anatomical gastroesophageal junction on a segment of more than 3 cm called long-segment Barrett's and a segment of less than 3 cm called short-segment Barrett's. The diagnosis of hiatus hernia was confirmed by the presence of gastric folds ≥3 cm above the diaphragmatic hiatus. Based on the endoscopic findings, patients were divided into those with non-erosive, erosive esophagitis and BE.

## 3. Results

Among 90 patients included; 36(40%) were females and 54(60%) were males. Their mean age was 39.57±16.8 years (ranged from 15 to 84 years) and means MBI 28.8±6.5 $kg/m^2$. Although thirty one (34.4%) were smokers, only 4 (4.44%) had history of alcohol intake. Thirty two (35.3%) patients proved *H. Pylori* positive by *H. Pylori*-IgG antibodies. The mean fasting glucose and fasting insulin were 109.1±43.4 and 12.83±17.03 respectively. The mean HOMA-IR was 2.86±2.2 IU/l. While the mean reflux score was 6.64 ± 2.36 the mean heart burn score was 6.72±1.6 (Table 1).

Group I included 30 patients, 14 (46.7%) females and 16 (53.3%) males. Their mean age was 39.13±18.2 y and mean BMI was 27.1±6.26 $kg/m^2$. Group II included 30 patients, 14 (46.7%) females and 16 (53.3%) males. their mean age was 39.03±15.67y and mean BMI was 30.66±6.95$kg/m^2$. Group III

included 20 patients, 14 (46.7%) females and 16 (53.3%) males. Their mean age was 39.25±12.9y and mean BMI was 28.43±6.13 kg/m$^2$. Group IV included 10 patients, 1 (10%) females and 9 (90%) males. Their mean age was 43.1±23.8y and mean BMI was 29.1±6.3kg/m$^2$ (Table 5). There were no statistically significant difference between groups regarding age, sex, BMI, smoking, or alcohol consumption ($P$ >0.05). As well reflux symptoms and heart burn was not significantly different between different groups.

Two scores were assessed in GERD questionnaire, reflux and heart burn scores. The mean reflux scores were 5.77±2.4, 7.13±2.7, 6.6±1.6 and 6.3±2.05, in groups I, II, III, and IV respectively. In addition the heart burn and regurgitation scores were 6.7±1.9, 6.7±1.46, 7.6±1.4 and 6.1±1.4 in groups I, II, III, and IV respectively (table 5). Indeed there was no significant difference of reflux or heart burn score between different groups. The heart burn and regurgitation score was significantly elevated in female patients, ($P$<0.05). There were significant correlation between elevated reflux score on one hand and heart burn score (r= 0.219), older age(r=-0.228), AST levels (r=0.214) as well as triglyceride levels (r=-0.225) on the other hand ($P$< 0.05) (Table 2).

Although the fasting blood sugar steadily increased with progression of GERD in deferent groups, this difference was not statistically significant ($P$ >0.05), (Table 5). As well there was no significant difference between groups regarding total cholesterol and triglyceride levels (Table 5). In addition there was no significant difference between groups regarding ALT and AST levels (Table 5).

While fasting insulin ranged from 2.7 – 121 IU/L, the HOMA-IR ranged from 0.61 – 9.2 IU/L, among included patients. The mean fasting insulin was 13.3 ± 19.29, 11.35 ± 6.35, 14.84 ± 26.69 and 12.07 ± 8.6 among groups I, II, III, and IV respectively. As well the HOMA- IR was 2.76 ± 2.4, 2.99 ± 1.84, 2.26 ± 1.98 and 3.76 ± 2.79 among groups I, II, III, and IV respectively (Table 5). Yet there were no significant difference between different groups regarding fasting insulin or HOMA- IR ($P$ >0.05), (Table 5). There was significant positive correlation between HOMA- IR on one hand and waist circumference (r=0.377), BMI (0.413), and fasting glucose levels (r=0.319), on the other hand. In contrast there was significant negative correlation between HOMA-IR and *H. Pylori*- IgG antibody serostatus (r = -0.388) ($P$ < 0.05) (Table 3).

While 32 patients were reactive for *H. Pylori*- IgG antibodies, 58 were *H. Pylori*- IgG negative. Patients with GERD had no significant relation with *H. Pylori* serostatus, in addition there were no significant relation between the grade of GERD and *H. Pylori* serostatus ($P$ >0.05), (Table 5). There were no significant difference between *H. Pylori* sero-positive and sero-negative patients regarding age, sex, alcohol, smoking, waist circumference and BMI ($P$ >0.05), (Table 4). As well the *H. Pylori* serostatus was not related to FBS, ALT, AST, total cholesterol and triglycerides ($P$ >0.05), (table 4). Surprisingly *H. Pylori* sero-positive patients had significantly lower fasting insulin levels as well as lower HOMA-IR ($P$ ≤0.05), (Table 3).

**Table (1):** Basic characteristics of studied patients

| | N (%) | Range | Mean ± SD |
|---|---|---|---|
| **Sex** | | | |
| **Female** | 36(40) | | |
| **Male** | 54 (60) | | |
| **Smoking** | | | |
| **Non smoker** | 59 (65.56) | | |
| **Smoker** | 31 (34.44) | | |
| **Alcohol** | | | |
| **No** | 86 (95.56) | | |
| **Yes** | 4 (4.44) | | |
| **Age(years)** | | 15-84 | 39.567±16.809 |
| **Waist(cm)** | | 40-125 | 83.77±20.097 |
| **BMI(kg/m²)** | | 15.4-43.65 | 28.823±6.548 |
| **Fasting glucose(mg/dl)** | | 59-399 | 109.067±43.39 |
| **Fasting insulin(uIU/l)** | | 2.7-121 | 12.833±17.033 |
| **HOMA-IR** | | 0.61-9.2 | 2.86±2.189 |
| **ALT(IU/l)** | | 1-29 | 6.101±4.824 |
| **AST (IU/l)** | | 1-68 | 9.101±8.45 |
| **Total cholesterol(mg/dl)** | | 78-345 | 194.046±43.961 |
| **Triglycerides(mg/dl)** | | 81-440 | 154.545±57.579 |
| ***H. Pylori*- IGg** | | 0.1-2.2 | 0.808±0.536 |
| **Reflux scoring** | | 3-14 | 6.46±2.366 |
| **Heartburn scoring** | | 3-11 | 6.724±1.597 |

N=number; SD=standard deviation; HOMA-IR= Homeostasis model assessment of insulin resistance; ALT=Alanine Aminotransaminase; AST=Aspartate Aminotransferase; BMI=Body Mass Index; *H. Pylori=Helicobacter Pylori*; IgG=Immunoglobulin G

**Table (2): The correlation between reflux and heartburn with clinical and laboratory variables**

| Correlations | | | | |
|---|---|---|---|---|
| | Reflux | | Hertburn | |
| | r | *P*-value | R | *P*-value |
| Heartburn scoring | 0.219 | 0.042* | | |
| Age (years) | 0.228 | 0.033* | -0.038 | 0.726 |
| Waist (cm) | 0.072 | 0.509 | 0.014 | 0.901 |
| BMI (kg/m²) | 0.160 | 0.138 | 0.110 | 0.312 |
| Fasting Glucose (mg/dl) | 0.148 | 0.174 | -0.074 | 0.496 |
| Fasting Insulin(uIU/ml) | -0.149 | 0.175 | -0.064 | 0.558 |
| HOMA-IR | -0.030 | 0.784 | -0.031 | 0.782 |
| ALT(IU/l) | 0.052 | 0.635 | -0.029 | 0.789 |
| AST(IU/l) | 0.214 | 0.048* | -0.032 | 0.770 |
| Total cholesterol(mg/dl) | 0.145 | 0.188 | 0.036 | 0.746 |
| Triglycerides(mg/dl) | 0.225 | 0.039* | -0.104 | 0.346 |
| *H. Pylori*- IGg | 0.015 | 0.888 | -0.055 | 0.615 |

**Table (3): Correlation between IR and clinical and laboratory variables**

| Correlations | IR | |
|---|---|---|
| | R | *P*-value |
| Age(years) | -0.079 | 0.473 |
| Waist circumference (cm) | 0.377 | <0.001* |
| BMI(kg/m²) | 0.413 | <0.001* |
| fasting Glucose(mg/dl) | 0.319 | 0.003* |
| fasting Insulin(uIU/ml) | 0.867 | <0.001* |
| ALT(IU/l) | -0.037 | 0.741 |
| AST(IU/l) | 0.140 | 0.206 |
| Total cholesterol(mg/dl) | 0.144 | 0.196 |
| Triglycerides (mg/dl) | 0.189 | 0.087 |
| *H. Pylori* –IGg | -0.388 | <0.001* |
| Reflux scoring | -0.030 | 0.784 |
| Heartburn scoring | -0.031 | 0.782 |

**Table (4):** Correlation between H pylori antibodies with clinical and laboratory variables

| Correlations | *H. Pylori* IGg | |
|---|---|---|
| | R | *P*-value |
| Age (years) | 0.243 | 0.030* |
| Waist (cm) | -0.091 | 0.434 |
| BMI (kg/m²) | 0.036 | 0.752 |
| Fasting Glucose (mg/dl) | -0.255 | 0.023* |
| Fasting Insulin (uIU/ml) | -0.202 | 0.076 |
| ALT (IU/l) | -0.094 | 0.408 |
| AST (IU/l) | -0.167 | 0.142 |
| Total cholesterol (mg/dl) | -0.038 | 0.738 |
| Triglycerides (mg/dl) | 0.060 | 0.597 |

**Table (5):** Comparison between studied groups

| | | Group I | | | Group II | | | Group III | | | Group IV | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N (%) | Range | M + SD | N(%) | Range | M + SD | N (%) | Range | M + SD | N (%) | Range | M + SD | $X^2$ | f | *P*-value |
| **Sex** | **Female** | 14(46.7) | | | 14(46.7) | | | 8(40) | | | 1(10) | | | 5.574 | | 0.134 |
| | **Male** | 16(53.3) | | | 16(53.3) | | | 12(60) | | | 9(90) | | | | | |
| **Smoking** | **Non smoker** | 19(63.3) | | | 23(76.7) | | | 12(60) | | | 5(50) | | | 3.1 | | 0.376 |
| | **Smoker** | 11(36.7) | | | 7(23.3) | | | 8(40) | | | 5(50) | | | | | |
| **Alcohol** | **No** | 29(96.7) | | | 30(100) | | | 19(95) | | | 8(80) | | | 6.01 | | 0.111 |
| | **Yes** | 1(3.33) | | | 0(0) | | | 1(5) | | | 2(20) | | | | | |
| ***H.Pylori* -IgG** | **Negative** | 19(63.3) | | | 20(66.6) | | | 14(70) | | | 5(50) | | | 1.229 | | 0.746 |
| | **Positive** | 11(36.6) | | | 10(33.3) | | | 6(30) | | | 5(50) | | | | | |
| **Age** | | | 17-77 | 39±18.2 | | 17±81 | 39±15.7 | | 18±63 | 39±12.9 | | 15±84 | 43±23.8 | | 0.162 | 0.922 |
| **Waist** | | | 40-125 | 79±19.2 | | 40±123 | 87±24.6 | | 61±115 | 87±14.1 | | 62±115 | 83±15.1 | | 1.083 | 0.361 |
| **BMI** | | | 17.7-43.7 | 27±6.26 | | 15.4±42.9 | 31±6.95 | | 19±40.6 | 28±6.13 | | 22±39 | 29±6.32 | | 1.525 | 0.214 |
| **Fasting glucose** | | | 79-174 | 102±22.4 | | 59±399 | 109±57.7 | | 75±244 | 111±39.2 | | 80±254 | 124±50.7 | | 0.654 | 0.583 |
| **Fasting insulin** | | | 2.7-102 | 13±19.3 | | 3.8±29.3 | 11±6.36 | | 3.4±121 | 15±26.7 | | 3.3±28.1 | 12±8.6 | | 0.172 | 0.915 |
| **IHOMA-IR** | | | 0.71-9.2 | 2.8±2.41 | | 0.61±8 | 3±1.84 | | 0.7±8.2 | 2.3±1.98 | | 0.76±8 | 3.7±2.79 | | 0.909 | 0.44 |
| **ALT** | | | 1-29 | 6±5.23 | | 1±25 | 5.9±4.73 | | 2±16 | 7±3.45 | | 1±22 | 5.2±6.41 | | 0.345 | 0.793 |
| **AST** | | | 2-16 | 7.2±2.85 | | 1±68 | 10±11.8 | | 2±18 | 8.5±4.14 | | 2±46 | 13±12.8 | | 1.253 | 0.296 |
| **Cholesterol** | | | 118-345 | 198±50.8 | | 78±311 | 193±45.9 | | 115±267 | 189±37.8 | | 148±225 | 194±24.3 | | 0.19 | 0.903 |
| **Triglycerides** | | | 82-440 | 150±68.5 | | 81±313 | 170±51.6 | | 96±312 | 143±49.2 | | 91±246 | 143±50.5 | | 1.12 | 0.346 |
| **H.Pylori -IgG** | | | 0.1-2 | 0.8±0.48 | | 0.1±2.1 | 0.8±0.59 | | 0.1±1.7 | 0.8±0.48 | | 0.3±2.2 | 1±0.67 | | 0.424 | 0.736 |
| **Reflux Score** | | | 3-14 | 5.8±2.39 | | 3±14 | 7.1±2.68 | | 4±10 | 6.6±1.62 | | 3±9 | 6.3±2.06 | | 1.744 | 0.164 |
| **Heartburn Score** | | | 3-11 | 6.7±1.89 | | 4±10 | 6.7±1.46 | | 4±10 | 7.1±1.39 | | 4±8 | 6.1±1.37 | | 0.752 | 0.524 |

## 4. Discussion

Gastroesophageal reflux disease is a spectrum of diseases with three distinct entities, non-erosive GERD, erosive GERD and Barrett's esophagitis. GERD prevalence is increasing parallel to similar rises in the frequency of metabolic disorders. The transition from one to other entity may handle different therapeutic responsiveness among patients with GERD ***(Lee et al., 2009).*** Knowledge of GERD various entities and its relationship with metabolic risk factors is very informative not only to identify which individual should undergo endoscopic screening but also to develop individually tailored preventive and therapeutic strategies. Obesity is an established risk factor for esophageal adenocarcinoma, although the mechanism is unclear. A pathway from reflux to inflammation through metaplasia is the dominant hypothesis, and an added role relating to visceral adiposity and the metabolic syndrome has mooted in Barrett's esophagus patients. In Japanese population obesity and hyperglycemia were independent risk factors for erosive esophagitis ***(Moki et al., 2007).*** Moreover, the presence of metabolic syndrome and a higher visceral adipose tissue area were risk factors for erosive GERD among Koreans ***(Chung et al., 2008).*** **Hsu *et al.,*** also demonstrated that IR associated with increased prevalence of both erosive GERD and GERD severity ***(Hsu et al., 2011).*** In the current study, the prevalence of IR in various GERD entities including Barrette esophagitis investigated to clarify the possible role of IR in GERD progression.

A strong relationship between the natural course of GERD and metabolic disorders has been accurately described in an original study that reported the transition rates between each state of esophagitis as a natural history in patients with metabolic syndrome ***(Lee et al., 2009).*** The population studied included 3669 subjects undergoing four upper endoscopies (endoscopy 1 at baseline, endoscopy 2 after 528 d, endoscopy 3 after 392 d, and endoscopy after 352 d). During the study periods, only 84 patients progressed from non-erosive to erosive disease, whereas 256 regressed to the non-erosive stage. Multivariate analysis showed that the clinical course of an individual is affected by gender, smoking, metabolic syndrome and short-term proton pump inhibitors or histamine 2 receptor antagonists' therapy. The authors conclude that the value of identifying risk factors and protecting the esophageal mucosa from irreversible damage may be a key point since spontaneous regression is possible in patients with the mild erosive disease without pharmacological treatment.

In the current study there was no significant difference of basic parameters including age, sex, alcohol, or smoking between different groups. Also, the anthropometric parameters in all patients groups including BMI and waist circumference, were matched. As well the metabolic laboratory parameters, fasting blood sugar, fasting insulin, insulin resistance, total cholesterol, and triglycerides were not significantly different between patients with none erosive GERD, erosive GERD, and Barrette esophagitis. Notably the mean IR was greater than 2, and the mean BMI was higher than 25 $kg/m^2$, in all studied groups. Patients with proven BE or GERD were randomly selected for metabolic syndrome screening, anthropometry studies, and laboratory tests ***(Healy et al., 2010).*** One hundred and eighteen BE patients and 113 age- and sex-matched GERD controls were studied. The authors concluded that central obesity, IR and the metabolic syndrome are common in both Barrett's and GERD cohorts, but not significantly different, suggesting that central obesity IR, and the metabolic syndrome does not per se impact on the development of BE in a GERD population. Several studies had demonstrated gender, age, smoking, and short-term proton pump inhibitors therapy related differences in insulin senstivity ***(Moki et al., 2007 and Lee et al., 2009).*** Therefore, it is reasonable to hypothesis that association of IR and different GERD entities may be age, gender, smoking and alcohol dependent. In fact the sample of our study was matched for both age and sex; moreover there were no significant difference between groups regarding smoking and alcohol habits that may

explain the absence of significant IR difference between different GERD entities.

Another important point of the current study is the relation between H. pylori prevalence and severity of GERD. H. pylori infection and GERD are highly prevalent conditions globally. The prevalence of *H. pylori* varies geographically and among ethnicities. To date, cohort studies and randomized controlled trials of the effects of H. pylori eradication on GERD are inconclusive. Recent epidemiological reports indicated an inverse relationship between *H. pylori* infection and GERD or Barrett's esophagus in the western countries and East Asian countries ***(Chung et al., 2011, Gunji et al., 2011, Chiba et al., 2012).*** This negative association was also evident in patients with severe GERD and *H. pylori* infection with virulent CagA-positive strains in Western countries. The prevalence of *H. pylori* infection is inversely correlated with the risk and severity of reflux esophagitis; ***(Weston et al., 2000, Chung et al., 2011)*** and the prevalence of *H. pylori* infection suggests a protective role in both GERD and Barrett's esophagus ***(Corley et al., 2008, Thrift et al., 2012).***

Going with the above results the prevalence of *H. pylori* negatively correlated with the presence of GERD and Barrette esophagitis. Yet this negativity not correlated with GERD severity, in our cohorts, where 30%, 36%, 30% of non erosive GERD, erosive GERD and Barrette esophagitis were sero-positive for *H. Pylori*. This discrepancy may be related to the small number of our cohorts, genetic background of studied populations and genotype of infecting organism.

The association between *H. Pylori* and diabetes was first explored in Simon et al.'s study ***(Simon et al., 1989).*** Recently, a meta-analysis ***(Zhou et al., 2013)*** showed *H. Pylori* infection was increased to 1.33 among patients with diabetes. In addition, some studies have shown an increased incidence of diabetes among people with *H. Pylori* infection so that the first report that *H. Pylori* infection increased incidence of diabetes was in a study by Jeon et al. ***(Jeon et al., 2012)*** using a prospective cohort of 782 Latino individuals >60 years of age. Etiopathogenesis of *H. Pylori* infection in diabetic patients has not been defined clearly. One of the hypotheses about *H. Pylori* infection as a risk factor for diabetes is increased insulin resistance in these patients. As insulin resistance can develop in the presence of inflammation or as a result of alterations in counter regulatory hormones that affect insulin, *H. Pylori* may thus promote insulin resistance by inducing chronic inflammation and affecting insulin-regulating gastrointestinal hormones ***(Shinohara et al., 2002).***

The first direct evidence for an association between chronic *H. Pylori* infection and insulin resistance rose from Aydemir et al.'s study ***(Aydemir et al., 2005)*** showing higher HOMA-IR scores in *H. Pylori* positive individuals. This study addressed the association between *H. Pylori* and insulin resistance, although the sample size was small ***(Aydemir et al., 2005).*** In 2009 Gunji and colleagues ***(Gunji et al., 2009)*** have studied 1107 non-diabetic Japanese patients and found that among those with higher insulin resistance score (HOMA-IR $\geq$ 2.5), the prevalence of the *H. Pylori* was higher (39.4 versus 28.7%, $P$ = 0.027). Although people with higher insulin resistance were fewer (99cases versus 1008), a recent systematic review for the association between *H. Pylori* infection and quantitative indexes of insulin resistance showed a positive association between *H. Pylori* infection and insulin resistance, independent of several confounders ***(Polyzos et al., 2011).***

On the contrary, opposite studies exist too. For example, Gillum stated that there is no consistent association between *H. Pylori* infection and diabetic prevalence or variables of the insulin resistance syndrome in American men 40–74 years of age ***(Gillum et al., 2004).*** Also, Malamug and colleagues' study in 2014 was in accordance with that study **[Malamug *et al.*, 2014].** According to single study Insulin resistance was significantly higher in diabetic patients with *H. Pylori* infection. In contrast, although in *H. Pylori* positive nondiabetic patients insulin resistance was higher than seronegative individuals. ***(Vafaeimanesh et al., 2014).***

## Conclusion

- No significant relation between IR and severity of GERD in our study.
- There were no correlation between *H. pylori* prevalence and presence of GERD in our study.
- There were negative correlation between *H. pylori* distribution and IR as well as fasting insulin levels.
- Heartburn and regurgitation score was significantly elevated in females.
- Reflux score correlated positively with heartburn and regurgitation score, old age and triglycerides levels
- The risk factors of GERD seems to be multifactorial and may not be explained by one risk factor study.
- The presence of H. pylori infection is not related to the occurrence of GERD in our study.

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