GASTROESOPHAGEAL REFLUX AND METABOLIC SYNDROME

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GASTROESOPHAGEAL REFLUX AND METABOLIC SYNDROME (Abstract) The aim of our study was to evaluate gastric, duodenal and gallbladder motility disorders in patients with gastroesophageal reflux disease (GERD) and metabolic syndrome. Material and methods: We studied 128 patients with GERD divided into two groups: first group with metabolic syndrome and the second without metabolic syndrome. By abdominal ultrasound we monitored our patients for the gastric emptying rate, the duodenal motility and the nonlithiasic pathology of gallbladder (cholesterosis). Results: We found that patients with metabolic syndrome had three kind of abnormal motility disorders including stomach, duodenum, and gallbladder. The patients without metabolic syndrome we found only two abnormal motility disorders: of the duodenum and gallbladder. Hyperglycemia and high serum cholesterol level in the first group were correlated with stomach, duodenum and gallbladder abnormal motilities. In our opinion metabolic syndrome can aggravate gastroesophageal reflux disease due to these metabolic abnormalities. Conclusions: We consider that treatment of reflux disease in these particular cases must also involve measures to correct metabolic disorders. Keywords: METABOLIC SYNDROME; CHOLESTEROSIS GALLBLADDER GASTROESOPHAGEAL REFLUX.

Metabolic syndrome is a cluster of metabolic disorders defined as the presence of an increased waist circumference and two of the following components: high blood pressure, hypertriglyceridemia, low levels of high density lipoprotein (HDL)-cholesterol, or diabetes mellitus (DM)/hyperglycemia (1). This syndrome is associated with high risk for cardiovascular diseases and has become one of the major health problems worldwide (1).

Gastroesophageal reflux disease is characterized by the presence of esophageal mucosal injury or reflux symptoms caused by the abnormal reflux of gastric content into the esophagus (2). Several studies have shown the relationship between obesity, erosive esophagitis and GERD symptoms (3). Also other studies demonstrated that metabolic syndrome was associated with GERD (4) through the precise mechanisms have not been fully determined. However, literature on whether metabolic syndrome influences the gastric, duodenal and gallbladder motility in patients with GERD is scant.

The aim of this study was to determine whether metabolic syndrome influences the gastric, duodenal and gallbladder motility and aggravates the symptoms in patients with GERD.
MATERIAL AND METHODS

Patients
We conducted a prospective case-control study, on patients admitted in a tertiary hospital, from January 2010-December 2012, diagnosed with GERD.

We excluded patients with prior gastric surgery, gastric cancer and peptic ulcer.

After a medical history was taken, all patients had physical examination, hematological and biochemical blood tests, an abdominal ultrasound and completed a questionnaire.

Patients were diagnosed with metabolic syndrome if they had an increased waist circumference and two of the following component: high blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic), hypertriglyceridemia (≥150 mg/dl), low levels of HDL-c (≤40 mg/dl in males or ≤50 mg/dl in females), or DM/hyperglycemia (1).

All participants completed a validated questionnaire that identified reflux symptoms, such as irritating heartburn and/or regurgitation experience during the preceding year (5). Values between 0-7 points were associated with less probable GERD, a score between 8-10 points revealed GERD with discomfort and unpleasant symptoms and a score of 11-18 points characterized GERD with discomfort and severe symptoms.

Measurements
The sonographic examination was performed using a Philips XD11XE ultrasound machine, using a C5-2 transducer.

The gastric motility was assessed by the method proposed by Darei Che and Osman (6). The method considers that gastric volume is directly proportional with antral area (Aa). Gastric emptying rate (GER) represents the percentage of Aa reduction measured 15 minutes and 90 minutes after a standard meal. Normal values for Aa are 489 mm$^2$ (377-745 mm$^2$) for 15 minutes and 166 mm$^2$ (124-279 mm$^2$) for 90 minutes. The average GER value is 63% (58-69%) (6). The longitudinal diameter (D1) and anteroposterior diameter (D2) of the antral section were obtained placing the traducer in a longitudinal position at the level of the abdominal aorta and the left hepatic lobe. The formula for Aa is: Aa=3,14 x D1xD2/4 and it was applied for Aa measured at 15 minutes and at 90 minutes. GER =(Aa90'/Aa15'-1) x 100 (7). We used a standard meal which contained 50g carbohydrates, 15g proteins and 12g lipids.

The duodenal motility was assessed by sonographic observing of peristaltic and antiperistaltic waves. This type of movements could be observed during the physiological phase of duodenal digestion and if they are enhanced it could have pathological consequences.

Gallbladder colesterolosis was defined using ultrasound criteria described by Sporea (7). We calculated the gallbladder volume before and after Boyden meal and then we calculated the ejection ratio (ER) of gallbladder by the formula: E.R= V1-V2/V1x100, where V1 is gallbladder volume before Boyden meal, V2 is gallbladder volume after Boyden meal. The formula for gallbladder volume is V=0,5x LxL x g, L is the length of gallbladder, L is the width of gallbladder, g is the thickness of gallbladder wall. Normal values are 50-60%.

Statistical analysis
Statistical analysis was performed using the $\chi^2$ test for comparison of discrete variables and the $t$-test for comparison of continuous variables. The continuous variables measured in this study were expressed as the mean±SD. Correlations were performed.
Gastroesophageal reflux and metabolic syndrome

using Spearman correlation test. Linear and logistic regression were used to calculate odds ratio (OR) and 95% confidence interval (CI). A two-tailed p value of <0.05 was considered statistically significant.

This study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

RESULTS
In this study we included 128 patients diagnosed with GERD. Fifty-nine patients had metabolic syndrome and 69 patients represented the control group, without metabolic syndrome (tab. I).

### TABLE I
Baseline characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>GERD with metabolic syndrome (n=59)</th>
<th>GERD without metabolic syndrome (n=69)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41±2.3</td>
<td>40±2.9</td>
<td>0.553</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>35/24</td>
<td>40/29</td>
<td>0.486</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.77±5.2</td>
<td>29±4.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>58</td>
<td>55</td>
<td>0.125</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>255±45.2</td>
<td>159±32.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-col (mg/dl)</td>
<td>176±21.4</td>
<td>112±20.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>290±43.6</td>
<td>236±35.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HTA(%)</td>
<td>78</td>
<td>51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>39</td>
<td>16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hiatal hernia (%)</td>
<td>75</td>
<td>68</td>
<td>0.058</td>
</tr>
<tr>
<td>Esofagitis (%)</td>
<td>24</td>
<td>19</td>
<td>0.244</td>
</tr>
<tr>
<td>GERDQ questionnaire (points)</td>
<td>14±2.4</td>
<td>9±1.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI: body mass index, LDL: low density lipoproteins, HTA: arterial hypertension, DM: diabetes mellitus, GERDQ: gastroesophageal reflux questionnaire.

The mean age was 40.5 years and 58.5% of the subjects were men.

We found a significant increased in the mean BMI, systolic blood pressure, glucose, cholesterol in patients with metabolic syndrome compared to the controls.

Patients with GERD and metabolic syndrome had a higher GERD questionnaire score than controls (p=0.033), corresponding with more severe reflux disease.

The presence of metabolic syndrome determined a high rate of cholesterolosis, an increased duodenal motility and ER of gallbladder, and decreased gastric emptying in cases than controls (tab. II). None of the controls had low values of GER.

In group with metabolic syndrome we found three kind of abnormal motility disorders: low GER values (100%); enhanced duodenal motility (40%) and high values of gallbladder ER (42%). In the control group we found only two kinds of motility disorders: enhanced duodenal motility 16% and high values of gallbladder ER. We diag-
nosed gallbladder cholesterolosis in cases 45% than controls in 10%.

TABEL II
Odds ratio for metabolic syndrome and GERD by multiple logistic regression

<table>
<thead>
<tr>
<th>Metabolic syndrome and GERD</th>
<th>OR</th>
<th>CI 95%</th>
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</thead>
<tbody>
<tr>
<td>Decreased GER</td>
<td>2.32</td>
<td>1.36-5.48</td>
</tr>
<tr>
<td>Increased duodenal motility</td>
<td>1.58</td>
<td>0.97-5.63</td>
</tr>
<tr>
<td>Colesterolosis</td>
<td>1.21</td>
<td>0.83-7.45</td>
</tr>
<tr>
<td>Gallbladder Er&gt;50-60%</td>
<td>0.98</td>
<td>0.53-2.77</td>
</tr>
</tbody>
</table>

Abbreviations: GERD: gastroesophageal reflux disease, GER: gastric emptying rate, ER: emptying rate.

In patients with GERD and metabolic syndrome we found an inverse correlation between serum glucose and GER value, and a direct correlation between cholesterol values and duodenal motility.

DISCUSSION
GERD is caused by the abnormal reflux of gastric contents into the esophagus (4). Its occurrence is related to multiple factors, such as gastric acid secretion, hiatal hernia, lower esophageal sphincter (LES) function, esophageal motility, and esophageal perception (2). In addition, dietary habits, such as alcohol intake and eating foods with high components of fat or in large portions, may cause not only visceral fat accumulation, but also frequent gastroesophageal reflux due to a reduction in LES pressure and an increase in the number of transient LES relaxations (TLESR) (2).

In the present study we investigated the relation between metabolic syndrome and gastric, duodenal and gallbladder motility disorders, and our results clearly demonstrated that the presence of metabolic syndrome was associated with decreased gastric emptying, and increased duodenal motility. In addition, the presence of metabolic syndrome was suggested to worsen reflux symptoms (3) fact confirmed by our study.

All cases with cholesterolosis had high values of gallbladder ER and associated enhanced duodenal motility. This fact means that the bile which is rich in cholesterolosis reaches the duodenal lumen quickly and can induce the enhanced duodenal movements which sometimes opens the pylorus and allows the reflux of duodenal juice containing bile and pancreatic juice in the stomach. If the gastric motility is low (low GER values) the gastroesophageal reflux is getting worse.

In the first group patients with three motility disorders had high values of GERDQ (11-18 points) meaning that the reflux was severe. Controls, with only two abnormal motilities disorders, had lower values of GERDQ (8-10 points) which means that the gastroesophageal reflux was not severe as in the first group.

Previously, Chung et al. (8) demonstrated that the presence of metabolic syndrome and visceral obesity in a Korean population were significant risk factors for the occurrence of reflux esophagitis. The results of our study appear to fit well with those findings. An augmented effect of dyslipidemia on the prevalence of reflux esophagitis was also demonstrated in the study of Chung et al. (8), though the precise mechanism of the dyslipidemia-induced high prevalence of GERD and reflux esophagitis remains unclear. We demonstrated that high cholesterol levels imply high excretion into biliary tract followed by development of gallbladder cholesterolosis. The bile rich in cholesterol reaches the duodenum and induces enhanced
motility. Therefore, the intake of meals with a high level of fat might induce not only dyslipidemia, but might also lead to aggravate GERD symptoms.

In the present study, low values of GER were statistically related with high values of blood glucose. It is known that GERD prevalence in patients with DM, is higher in comparison with that in healthy individuals, and is reported to be caused by a decline in salivary secretion, delayed gastric emptying-induced increases in TLESR, and an increase in gastroesophageal reflux (3, 4). In our study, we observed that low values of GER in the first group were similar to those from diabetic patients (7) in which the vegetative vagal neuropathy induced delayed gastric emptying.

**CONCLUSIONS**

Our results indicate that metabolic syndrome enhanced GERD symptoms by gastroduodenal and gallbladders motility disorders. These results allow us to assert that in all cases with gastroesophageal reflux which associates metabolic syndrome the treatment must be addressed also to this complex entity.

**REFERENCES**