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EDITORIAL

Metabolic syndrome and gastro-esophageal reflux: A link towards a growing interest in developed countries

Enzo Ierardi, Rosa Rosania, Mariangela Zotti, Simonetta Principe, Giulio Laonigro, Floriana Giorgio, Vincenzo de Francesco, Carmine Panella

Enzo Ierardi, Rosa Rosania, Mariangela Zotti, Simonetta Principe, Giulio Laonigro, Floriana Giorgio, Vincenzo de Francesco, Carmine Panella, Gastroenterology Section, Department of Medical Sciences, University of Foggia, Foggia 71100, Italy

Author contributions: Ierardi E and Panella C designed the study, revised the manuscript and approved the final version; Rosania R, Zotti M, Prencipe S and Laonigro G collected the data; De Francesco V, Giorgio F and Ierardi E analyzed the data; and Rosania R, Zotti M, Prencipe S and Giorgio F drafted the manuscript.

Correspondence to: Enzo Ierardi, MD, Profesor, Section of Gastroenterology, Department of Medical Sciences, University of Foggia, Ospedali Riuniti, Viale L. Pinto, Foggia 71100, Italy. enzo.ierardi@fastwebnet.it

Telephone: +39-0881-733848 Fax: +39-0881-733849
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Abstract

The aim of this Editorial is to describe the growing possibility of a link between gastro-esophageal reflux disease (GERD) and metabolic syndrome on the light of recent epidemiological and pathophysiological evidence. The state of the art of GERD is described, based on recent definitions, pathophysiological evidence, epidemiology in developed countries, clinical subtypes together with a diagnostic approach specifically focussed on the appropriateness of endoscopy. Metabolic syndrome is accurately defined and the pivotal role of insulin resistance is emphasized. The strong relationship between GERD and metabolic syndrome has been pathophysiologically analyzed, taking into account the role of obesity, mechanical factors and metabolic changes. Data collected by our group regarding eating habits and GERD are briefly summarized at the end of a pathophysiological analysis. The literature on the subject strongly supports the possibility that lifestyle and eating habits may be involved in both GERD and metabolic syndrome in developed countries.

Key words: Gastroesophageal reflux disease; Metabolic syndrome; Obesity; Insulin resistance

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INTRODUCTION

Gastroesophageal reflux disease (GERD) was compared by Castell in 1985[1] as an "iceberg", in which only a small part is visible and requiring a medical intervention.Since then, the visible part of the "iceberg" has been growing steadily, until it has affected, at least sporadically, about half of people living in developed countries.

Metabolic syndrome is another relevant disorder which has been shown to be strongly linked to environmental conditions and the normal habits of people in developed countries, and is invoked to explain some disorders involving different apparatus with a particular regard to the digestive tract.

In this Editorial, the growing link between the abovementioned two conditions is analyzed in the light of recent epidemiological and pathophysiological evidence.

GASTROESOPHAGEAL REFUX DISEASE

Definition, epidemiology, pathogenesis

Gastroesophageal refux disease (GERD) is defined as an

abnormal reflux of gastric contents into the esophagus at least once a week, leading to symptoms such as heartburn and/or acid regurgitation, and/or esophageal mucosal damage, which may also provoke long-term complications, such as Barrett's esophagus[2-3]. According to the Montreal definition and classification of the disease[4], GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.

GERD is the most common upper gastrointestinal disease in the Western countries, with 10%-20% of the population experiencing weekly symptoms[5-8]. Its prevalence is also increasing in the Far East (Japan) and other areas in Asia[9].

GERD is a multifactorial disease in which anatomical and functional factors both play a pathogenetic role. Generally it is grouped into two types: the primitive type and the secondary type.

In the primitive type the main pathogenetic mechanism is considered to be a transient lower esophageal sphincter relaxation[10] that is a visceral reflex occurring mainly in response to gastric distension.

The secondary type has been correlated with a heterogeneous group of disorders, such as metabolic or endocrine diseases, collagenopathies, systemic neuropathies, asthma, abdominal surgery, drugs and pregnancy.

The esophageal expression could include the typical reflux syndrome, the reflux chest pain syndrome and the syndrome with esophageal injury.

GERD is often associated with a hiatal hernia, especially a sliding hernia (Type I hernia). In this type, the cardia of the stomach is allowed to migrate back and forth between the posterior mediastinum and the peritoneal cavity. The gastro-esophageal junction is thus incompetent and large volumes of gastric contents pass unimpeded into the hiatal sac[11-12].

GERD encompasses a large spectrum of clinical features, generally characterized as esophageal and extra-esophageal expressions.

Gastroesophageal refux disease subtypes

The esophageal expression includes the typical reflux syndrome, the reflux chest pain syndrome and the syndrome with esophageal injury, further divided into non-erosive reflux disease, reflux esophagitis, reflux stricture, Barrett's esophagus and esophageal adenocarcinoma. In summary, GERD is a categorical disease which manifests itself in three distinct ways: non-erosive or erosive esophagitis, and Barrett's esophagus. These three phenotypes represent different disorders. A cange from one condition to another condition is limited, thus suggesting that these, once established, remain distinct entities[13-14]. Moreover, when after discontinuing treatment, reflux symptoms tend to recur, the patient presenting one of the 3 entities at the onset will very often relapse in the same manner. According to this information, GERD is a chronic disease, probably without progression, and reflux symptoms do not tend to recur in relation to endoscopic findings[15]. However, some studies state that the progression of NERD to erosive esophagitis is possible in only 10% of GERD patients, thus indirectly confirming the hypothesis of a respective phenotypic presentation.

Gastroesophageal refux disease diagnostic approach: The appropriateness of endoscopy

Although many tools are available for the diagnosis of GERD, such as endoscopy, manometry, ambulatory pH monitoring and esophagograms, none of them is considered to be the gold standard.

The main use of upper gastrointestinal endoscopy in patients with GERD should be limited to the evaluation of treatment failures and esophageal injury. However endoscopic esophageal mucosal breaks, erosion or ulcerationare absent in more than 50% of individuals who have had heartburn two or more times 1 wk for 6 mo. Even the recognition of minor endoscopic mucosal changes, such as erythema, edema or mucosal friability attributed to GERD is so unreliable that these findings are of not useful for the diagnosis of reflux esophagitis[15-16]. Endoscopy plays a key role in the presence of alarm symptoms, including vomiting, weight loss, dysphagia, anemia, blood loss, chest pain or epigastric mass[17]. The American Society for Gastrointestinal Endoscopic guidelines consider endoscopy appropriate for evaluating esophageal reflux symptoms which are persistent or recurrent, despite appropriate therapy, which needs to be given to a patient with typical symptoms without further investigation[18]. Indeed, a response is a diagnostic investigation "per se" (proton pump inhibitor test). Sequential or periodic endoscopy may be indicated, moreover, for the surveillance of patients with Barrett's esophagus[19].

The above reported diagnostic approach is summarized in the flow-chart in Figure 1[20].

A very promising diagnostic tool is offered by pH impedance testing, which allows the recognition of every intraesophageal regurgitation independently by its source (acid, bile, air, food *etc.*), even if its real use in clinical practice remains to be recorded only in the next few years.

METABOLIC SYNDROME

Definition

Metabolic syndrome is a cluster of metabolic abnormalities that has been highlighted as a risk factor for cardiovascular and other chronic diseases. It affects one fifth of the population in the developed world and its preva lence increases with the age. Some studies estimate the prevalence in the USA to be up to 25% of the population[21].

The International Diabetes Federation (IDF) consensus in 2006 defined the metabolic syndrome as the association of central obesity. Central obesity is, in turn, defined as waist circumference with ethnicity specific values as reported in Table 1 with two of the following altered parameters: triglycerides > 150 mg/dL (1.7 mmol/L) or a specific treatment for this lipid abnormality, reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females or a specific treatment for this lipid abnormality, raised blood systolic (> 130) or diastolic pressure (> 85 mm Hg) or treatment of previously diagnosed hypertension and raised fasting

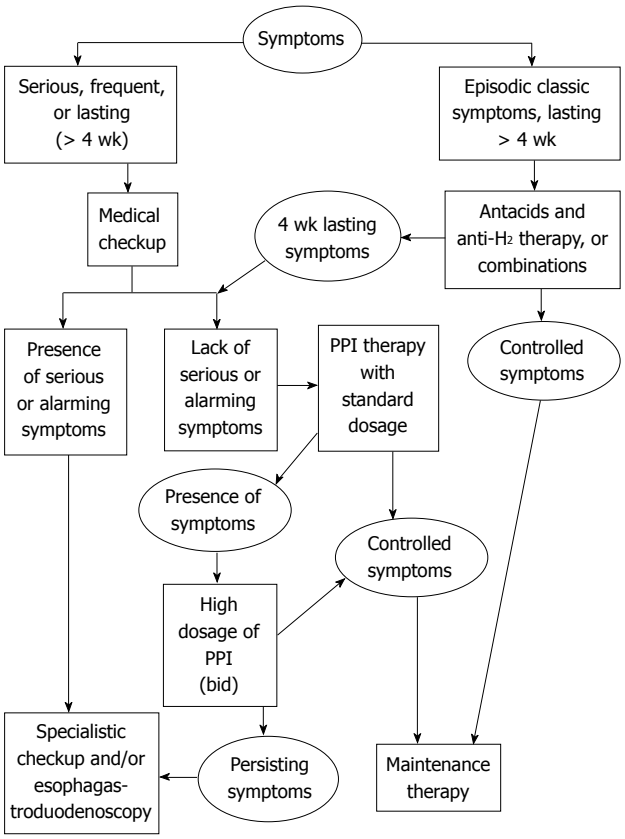

Figure 1 American Gastroenterology Association guidelines for gastro-esophageal reflux disease diagnostic approach with a particular regard to esophagastroduodenoscopy appropriateness[20].

plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes[22].

Role of insulin resistance

The pathophysiology of metabolic syndrome is extremely complex, and has been only partially elucidated. Most patients are old and obese with a sedentary lifestyle and a variable degree of insulin resistance. Stress can also be a contributing factor[23].

A relevant pathogenetic factor is represented by insulin resistance (IR), a condition in which body cells become less sensitive to the hormone[24]. This phenomenon is frequent in people with visceral adiposity, hypertension, hyperglycemia and dyslipidemia. IR in fat cells results in elevated hydrolysis of stored triglycerides which increases the mobilization of free fatty acids into the plasma. IR reduces glucose uptake in skeletal muscle, and in hepatocytes it impairs glycogen synthesis and storage, suppressing glucose production and release into the blood. The main effects of IR are reported in Figure 2[25].

Various diseases make body tissues more resistant to the actions of insulin,for example, infections mediated by the tumour necrosis factor-alpha (TNF-α) and acidosis. In the presence of IR, the visceral adipose cells in particular produce significant amounts of proinflammatory cytokines, such as TNF-α, IL1 and IL6. In experimental models, these proinflammatory cytokines disrupt normal insulin action in fat and muscle cells, and this may be the major factor in causing the whole-body insulin resistance observed in patients with visceral adiposity[26]. Further, visceral adiposity is related to an accumulation of fat in the liver, a condition known as nonalcoholic fatty liver disease (NAFLD)[27]. The result of NAFLD is an excessive release of free fatty acids into the bloodstream, and an increase in hepatic glucose production, both of which have the effect of exacerbating peripheral insulin resistance and increasing the likelihood of Type 2 diabetes.

Table 1 Waist circumference with ethnicity specific values

	WHO (1998)	EGIR (1999)	NCEP (2001)	IDF (2005)
Waist circumference	BMI > 30 and/or waist/hip comparison	Abdominal weight	Abdominal weight	Abdominal weight
	> 0.90 (men)	> 0.94 cm (men)	> 102 cm (men)	> 94 cm men
	> 0.85 (women)	> 0.80 cm (women)	> 88 cm (women)	> 80 cm (women)

BMI: body mass index; WHO: World Health Organization;EGIR: The European Group for Study of Insulin Resistance; NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation.

GASTROESOPHAGEAL REFUX DISEASE AND METABOLIC SYNDROME

Relationship between gastroesophageal refux disease and metabolic syndrome

A strong relationship between the two 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[28]. The study was a voluntary health promotion program that used a standard protocol, including physical examination, blood chemistry, plain radiography, abdominal ultrasonography and endoscopy. 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). Data were analysed using a three-state Markov model to estimate transition rates (according to the Los Angeles classification) regarding the natural course of the disease. During these three consecutive 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 weight of an individual is affected by gender, smoking, metabolic syndrome and short-term PPI or H_2RA therapy. This finding has had important implications for the design of effective strategies of prevention and screening, since this study demonstrates that intra-oesophageal damage is a dynamic process, in which the metabolic syndrome is associated with accelerated progression to, or attenuated regression from, erosive states.

The authors conclude that the value of identifying risk factors and protecting the oesophageal mucosa from

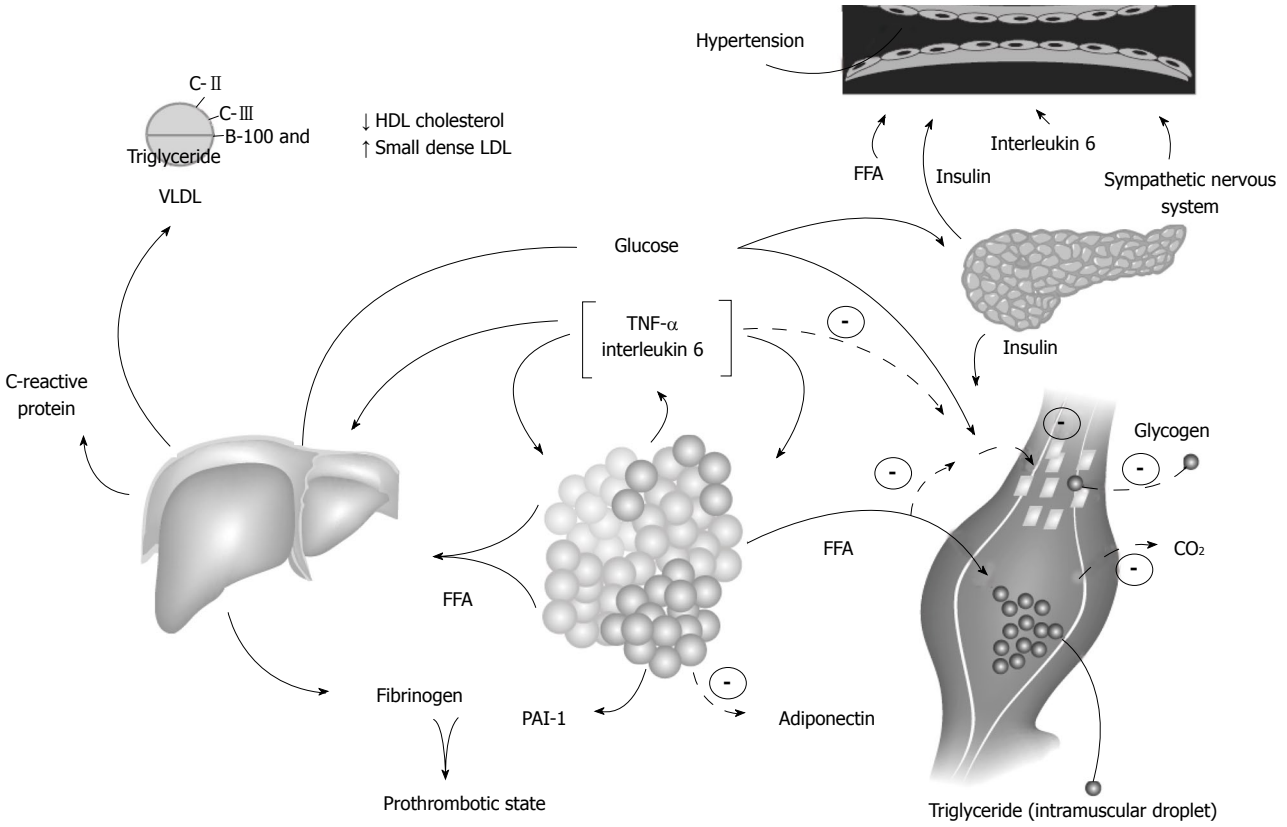

Figure 2 Role of insulin resistance in metabolic syndrome (from Eckel *et al*[25], Lancet 2005).

irreversible damage may be a key point, since spontaneous regression is possible in patients with mild erosive disease without pharmacological treatment. The evaluation of individual risk at this stage would therefore give patients the opportunity to modify their behaviour (weight reduction, giving up smoking) and enable clinicians only to select patients most likely to develop irreversible changes for endoscopic screening, and to offer them early pharmacological treatment. A similar conclusion may be drawn from the experience of our group, which is described later.

Mechanical factors: The role of obesity

In the recent past, the occurrence of GERD has paralleled the increasing prevalence of obesity, with the incidence of GERD in the Western world found in more than 20% of the population[29]. The consensual increase in the frequency of obesity and GERD in Western countries[30] has suggested a possible pathogenetic link between these two diseases, and has generated great interest in explaining the mechanisms demonstrating this association.

Since there are probably multiple pathogenetic mechanisms of GERD, it is possible that not all of them are related to, or influenced by, the presence of obesity[31]. Obesity may be considered as an independent risk factor for GERD, and it seems that the risk of developing GERD increases with increasing weight. However, the exact pathophysiological mechanisms underlying the association have not been fully identified, even if some hypotheses have been suggested. It has long been hypothesized that visceral adiposity, expressed by an increased abdominal waist circumference, could be associated with increased intra-abdominal pressure, which in turn promotes GERD by increasing intragastric pressure[32-35]. Furthermore, obesity might cause increased intra-abdominal pressure that results in extrinsic gastric compression by visceral fat, with a subsequent increase in intragastric pressure and the gastroesophageal pressure gradient[36], as well as an increased risk for developing a hiatal hernia[37-40]. In obese patients, other factors that play a role in the pathophysiology of GERD are esophageal peristaltic abnormalities, such as malfunction of the lower esophageal sphincter, nutcracker esophagus and non-specific motility disorders[41].

Role of metabolic changes

However, the most important reflux mechanism in obese subjects seems to be a transient lower esophageal sphincter relaxation[10], generated by gastric distension, which leads to intense stimulation of both stretch and tension mechanoreceptors in the proximal stomach[42-43].

Recently, a European study investigated the prevalence of central adiposity, metabolic syndrome, and a proinflammatory state in patients with Barrett's esophagus, and found that the proinflammatory impact of adipocytokines associated with the metabolic syndrome of central adiposity may play an important role in the pathogenesis of esophageal cancer[44-45]. In particular, it has been demonstrated that visceral fat is metabolically active[46] as well as being associated with low serum levels of protective cytokines, such as adiponectin. Therefore, high levels of

Table 2 Body mass index and macronutrient intake in gastro-esophageal reflux disease patients[1]

Parameters	Controls	Symptoms	*P*
BMI	26.4 ± 4.5	26.1 ± 2.7	< 0.88
Kcal/die	2015 ± 384	1782 ± 420	< 0.05
Lipids (%)	31.4 ± 3.2	33.9 ± 3.9	< 0.02
Proteins (%)	16.8 ± 1.6	17.1 ± 2.5	< 0.70
Glucids (%)	48.8 ± 5.1	52.1 ± 3.2	< 0.01
Fibers (g/die)	43.8 ± 12.7	26.2 ± 7.6	< 0.04

BMI: body mass index; [1]The experience of Gastroenterology Unit of the University of Foggia: The peculiarity of the study was that gastro-esophageal reflux disease diagnosis was supported by 24 h pH metry.

inflammatory cytokines, such as TNF-α, IL-1β and IL-6 all contribute to GERD development and symptoms.

DIETARY HABITS IN PATIENTS WITH GASTROESOPHAGEAL REFUX DISEASE: OUR EXPERIENCE

Lifestyle factors (overweight/obesity, incorrect dietary habits, lack of regular physical activity and smoking) have frequently been suggested to be possible GERD risk factors. However, their exact pathogenetic role is still unclear, and the beneficial effect of specific recommended changes in lifestyle habits is controversial[10].

It is a common belief that some foods may induce or worsen GERD symptoms; in fact, in daily clinical practice, this leads to medical staff advising patients to avoid the suspected foods[47]. Furthermore, since GERD symptoms are most commonly reported postprandially, the role of diet components in inducing symptoms through a lower esophageal sphincter release or a delayed gastric emptying has been suggested. Nevertheless, different and conflicting results exist in the literature for identifying the most "refluxogenic" foods. Old experimental and clinical studies have shown a decrease in LES pressure and an increase in esophageal acid exposure in response to the ingestion of food rich in fats, chocolate and carminatives[48-49].

Our study examined the effects of dietary intake on GERD and, although performed on a small sample, represents the only study in which the diagnosis was based not only on the clinical symptoms, but also on the measurement of esophageal pH over a 24 h period.

The aim of this study was to evaluate the correlation between pH-metry results in GERD patients and their daily food intake, including the assessment of fibre consumption. We enrolled 60 patients, stratified for age and sex, divided into three groups of 20 patients each. The first group included subjects with pH-metry results showing a pathological acid reflux and with typical GERD symptoms; in the second group typical symptoms were present even if pH-metry was not irrefutably pathological (pH < 4 for a period < the 10% of record); the third group was composed by healthy volunteers[50]. For each patient, Body Mass Index was calculated, and a weekly dietary intake questionnaire, which allowed calculating daily caloric and macronutrient intake with the use of a dedicated software (Winfood) had to be completed.

Our results are summarized in Table 2. Lipidic and glucidic intake was directly correlated to symptom presence independently by pH-metry results by statistical univariated analysis. Nevertheless with statistical multivariated analysis, only lipid intake correlated with typical GERD symptom presence and pH-metry results. Finally, fibre intake seemed to play a protective role in the relief of GERD symptoms.

Whilst lipids are known for their ability to reduce lower esophageal sphincter pressure and delay gastric empting, a possible explanation for glucidic intake may be only speculative (i.e. their fermentation by intestinal bacterial flora may cause the production of gas enabling sphincter release and, consequently, GERD symptoms).

CONCLUSION

Epidemiologic evidence has consistently shown a growing association between metabolic syndrome and GERD in developed countries. Changes in gastroesophageal physiology may explain the link between these two conditions. Recent data suggest that central adiposity may be the most important factor for the development of reflux and complications such as Barrett's esophagus and esophageal adenocarcinoma. Weight loss through caloric restriction (especially of lipids and glucids) appears to be beneficial in reducing GERD symptoms. These remarks as well as the recent experience of our group seem to support the relevance of eating habits and suggest a correction of lifestyle and diet as a primary therapeutic approach for GERD.

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