Pathophysiology of gastro-oesophageal reflux disease

Fisiopatologia della malattia da reflusso gastroesofageo

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Key words

Gastro-oesophageal reflux • Aetiology • Physiopatology

Parole chiave

Reflusso gastroesofageo • Eziologia • Fisiopatologia

Summary

Gastro-oesophageal reflux disease is a condition in which the reflux of gastric contents into the oesophagus provokes symptoms or complications and impairs quality of life. Typical symptoms of gastro-oesophageal reflux disease are heartburn and regurgitation but gastro-oesophageal reflux disease has also been related to extra-oesophageal manifestations, such as asthma, chronic cough and laryngitis. The pathogenesis of gastro-oesophageal reflux disease is multifactorial, involving transient lower oesophageal sphincter relaxations and other lower oesophageal sphincter pressure abnormalities. As a result, reflux of acid, bile, pepsin and pancreatic enzymes occurs, leading to oesophageal mucosal injury. Other factors contributing to the pathophysiology of gastro-oesophageal reflux disease include hiatal hernia, impaired oesophageal clearance, delayed gastric emptying and impaired mucosal defensive factors. Hiatal hernia contributes to gastro-oesophageal reflux disease by promoting lower oesophageal sphincter dysfunction. Impaired oesophageal clearance is responsible for prolonged acid exposure of the mucosa. Delayed gastric emptying, resulting in gastric distension, can significantly increase the rate of transient lower oesophageal sphincter relaxations, contributing to postprandial gastro-oesophageal reflux disease. The mucosal defensive factors play an important role against development of gastro-oesophageal reflux disease, by neutralizing the backdiffusion of hydrogen ion into the oesophageal tissue. While the pathogenesis of oesophageal symptoms is now well known, the mechanisms underlying extra-oesophageal airway manifestations are still poorly understood. Two hypotheses have been proposed: direct contact of gastric acid with the upper airway and a vago-vagal reflex elicited by acidification of the distal oesophagus, leading to bronchospasm. In conclusion, gastro-oesophageal reflux disease can be considered as the result of a complex interplay of factors, all promoting the contact of gastric acidic contents with the oesophageal mucosa, leading to different degrees of oesophageal damage.

Riassunto

La malattia da reflusso gastroesofageo (MRGE) è una condizione in cui il reflusso di contenuto gastrico in esofago provoca sintomi o complicanze e riduce la qualità di vita. Sintomi tipici della MRGE sono la pirosi retrosternale ed il rigurgito, ma tale patologia sembra essere coinvolta anche nella patogenesi di manifestazioni extraesofagee, come l'asma, la tosse e la laringite cronica. La patogenesi della MRGE è multifattoriale e include i rilasciamenti transitori dello sfintere esofageo inferiore (SEI) ed altre anomalie del tono basale dello SEI. Ciò conduce al reflusso in esofago di acido, bile, pepsina ed enzimi pancreatici, fattori responsabili di danno mucosale esofageo. Altri fattori che contribuiscono alla fisiopatologia della MRGE sono l'ernia iatale, un'alterata clearance esofagea, il ritardato svuotamento gastrico e l'alterazione dei fattori difensivi mucosali. L'ernia iatale contribuisce alla patogenesi della MRGE causando alterazioni funzionali dello SEI. L'alterata clearance esofagea è responsabile di una prolungata esposizione acida della mucosa esofagea. Il ritardato svuotamento gastrico, causando distensione dello stomaco, è in grado di aumentare significativamente il numero di rilasciamenti transitori dello SEI, contribuendo al reflusso post-prandiale. I fattori difensivi mucosali rivestono un ruolo importante nel prevenire la MRGE, neutralizzando la retrodiffusione degli idrogenioni nel tessuto esofageo. Mentre la patogenesi dei sintomi esofagei è ben conosciuta, i meccanismi alla base dei sintomi extraesofagei a carico delle vie aeree sono ancora poco chiari. Sono state proposte due ipotesi: il diretto contatto dell'acido con la mucosa respiratoria e un riflesso vagovagale elicitato dall'acidificazione dell'esofago distale, che sono entrambi causa di broncospasmo. In conclusione, la MRGE può essere considerata come il risultato di un concatenarsi di fattori, ciascuno favorente il contatto dell'acido gastrico con la mucosa esofagea, risultando in ultima analisi in differenti gradi di danno esofageo.

Introduction

Gastro-oesophageal reflux disease (GERD) is generally defined as a chronic relapsing condition in which the reflux of stomach content into the oesophagus and beyond provokes symptoms and/or complications. Symptoms considered to be related to gastro-oesophageal reflux, principally heartburn and regurgitation, are widespread, in the general population. Community-based surveys of randomly-selected in-

dividuals, not necessarily seeking health care, indicate that reflux-like symptoms are encountered by 20-40% of the population during a 6-12 month period with variable intensity and frequency [1]. Gastro-oesophageal reflux becomes pathological when related symptoms impair quality of life (QoL) and/or complications occur. A pragmatic definition of GERD, taking into account symptoms, QoL and endoscopic lesions, has been proposed by the Genval workshop, that suggested inclusion in the term GERD of: "*all individuals who are exposed to the risk of physical complications from gastro-oesophageal reflux, or who experience clinically significant impairment of health-related well-being due to the reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms*" [2].

GERD comprises a wide spectrum of disorders, ranging from the presence of typical symptoms alone, through to the more severe complications, including erosive oesophagitis, Barrett's oesophagus and oesophageal carcinoma. Atypical symptoms, like dysphagia and chest pain, and extra-oesophageal manifestations, such as asthma, chronic cough and laryngitis may also be related to gastro-oesophageal reflux and, in some cases, they represent the only clinical presentation of the disease. Since the majority of symptomatic patients do not have mucosal breaks or other oesophageal injuries at endoscopy, expressions such as "non-erosive reflux disease" (NERD) or even "functional heartburn" have been introduced, reflecting the attempt made, in the last decade, to redefine more precisely the GERD concept and in order to characterize GERD as divided in separate entities rather than a continuous spectrum [3].

As in other acid-related diseases, such as duodenal and gastric ulcer disease, GERD is thought to develop when aggressive factors, potentially harmful to the oesophagus, overcome protective mechanisms such as the oesophago-gastric junction barrier, oesophageal acid clearance and mucosal resistance, which normally contribute to maintain a physiologically balanced state. Therefore, a crucial role, in the pathogenesis of GERD, is played by contact with the oesophageal mucosa of refluxate, which can be composed of acid, pepsin, bile and duodenal contents. Acid plays the major role in most patients affected by GERD and the severity of reflux oesophagitis as well as the prevalence of complications such as Barrett's oesophagus increase with the duration of acid exposure. The role of other components of the refluxed material, such as biliary acids or pancreatic enzymes, may contribute to the pathogenesis, especially in severe or complicated disease; usually, however, there is some synergy between acid and non-acid factors to create symptoms and lesions. The mechanisms involved in the pathogenesis of GERD are multiple and include: a) motor abnormalities, such as impaired lower oesophageal sphincter (LES) resting tone, transient LES relaxations (TLESR), impaired oesophageal acid clearance and delayed gastric emptying; b) anatomical factors, such as hiatal hernia; c) visceral hypersensitivity; d) impaired mucosal resistance. Herewith, each of these mechanisms, as well as the pathophysiology of extra-oesophageal manifestations of GERD are discussed.

LES pressure abnormalities

The LES is an anatomically complex zone located at the gastro-oesophageal junction, comprising two components: the true LES, a segment of tonically contracted smooth muscle located in the distal oesophagus and the crural portion of the diaphragm. Both the LES and the diaphragm contribute to gastro-oesophageal sphincter competence. Physiologically, relaxations of the LES, prior to contractions of the oesophagus, allows food to pass through into the stomach. In resting conditions, LES maintains a high-pressure zone that is 15-30 mmHg above intragastric pressures, depending on individual variability.

A minority of patients with GERD have a constantly weak, low-pressure LES, which permits reflux every time the pressure in the stomach exceeds the LES pressure. This occurs when LES pressure is < 6 mmHg [4]. A chronically decreased LES resting tone is usually associated with severe oesophagitis. Similarly, LES defects have been found in many patients with other GERD complications, such as oesophageal stricture and Barrett's oesophagus.

Factors that decrease LES tone include endogenous hormones (cholecystokinin, progesterone in pregnancy) [5], medications (nitrates, calcium channel blockers, etc.), specific foods like high-fat meals and chocolate [6], and voluptuary habits like smoking, caffeine and alcohol.

Transient lower oesophageal sphincter relaxations (TLESRs)

Many GERD patients have a normal LES resting tone and do not have hiatal hernia, therefore the abnormal gastro-oesophageal reflux in these subjects is explained by an alternative theory. In fact, studies in healthy volunteers have identified reflux episodes during sleep and the postprandial period that are due to an increased number of inappropriate LES relaxations [7]. TLESRs are brief episodes of LES relaxation unrelated to swallowing or peristalsis [8]. Neurophysiology studies indicate that TLESRs are visceral reflexes with vagal afferent and efferent pathways that transmit information to and from the dorsal nucleus of the vagus [9]. Gastric distension, by stimulation of proximal gas-

tric tension and stretch receptors, has been recognized as a major factor inducing TLESRs [10].
In normal subjects, gastro-oesophageal reflux occurs only during TLESRs and swallow-induced LES relaxations [11], whereas in patients with GERD, TLESRs account for 48-73% of reflux episodes [12]: thus TLESRs account for the majority of gastro-oesophageal reflux episodes. Patients with GERD have an equal frequency of TLESRs compared with normal individuals, although they have a higher percentage of TLESRs associated with reflux [12].
Like LES resting pressure, the frequency of TLESRs is influenced by foods (fat, chocolate, etc.), alcohol and smoking.

Impaired oesophageal acid clearance

The degree of oesophageal mucosal injury and frequency and severity of symptoms are determined by the degree and duration of oesophageal acid exposure. Indeed, the process of oesophageal acid clearance is an important protective mechanism against GERD developing. This process involves peristalsis as well as the swallowing of salivary bicarbonate. Both primary and secondary peristalsis are essential mechanisms of oesophageal clearance. Swallowing-related primary peristalsis occurs about 60 times per hour, while secondary peristalsis occurs in the absence of swallowing and can be elicited by oesophageal distension or acidification [13]. The swallowing of saliva (pH 7.8-8.0) is crucial in completion of oesophageal acid clearance and restoration of oesophageal pH.
In experimentally induced or spontaneous reflux, patients with GERD have been found to present acid clearance times that are two to three times longer than those of subjects without GERD [14]. Impaired oesophageal clearance can be caused by an increase in volume of the refluxate and may very occasionally be due to an underlying disease such as scleroderma. Two mechanisms of impaired volume clearance have been identified: peristaltic dysfunction and re-reflux. Peristaltic dysfunction is characterized by failed peristalsis and low-amplitude contractions (< 30 mmHg), leading to incomplete oesophageal emptying. Peristaltic dysfunction often increases with increasing severity of oesophagitis. Re-reflux is associated with certain hiatal hernias, when the cleared fluid trapped in the hernia returns into the oesophagus after LES relaxation.
Moreover, acid clearance is prolonged by a reduced salivary rate or by decreased salivary capacity to neutralize acid. Reduced salivation during, or immediately before, sleep accounts for markedly prolonged acid clearance times, which appears to be a major causative factor in serious forms of GERD [15].
Reduced frequency of swallowing-induced peristalsis during sleep also prolongs oesophageal acid exposure. Salivation is also reduced in cigarette smokers and in patients using anticholinergic drugs, thereby prolonging the process of mucosal neutralization in these individuals [16].

Delayed gastric emptying

Delay in gastric emptying results in the extended retention of acidified gastric contents in the stomach during the post-prandial period, which may increase the likelihood of GERD. There is no agreement in the literature concerning the real contribution of gastric emptying in the predisposition to reflux and the different research methodologies used would appear to account for the controversial findings [17]. Using recently established control values for scintigraphic gastric emptying assessment, it has been revealed that 26% of GERD patients had abnormal results at 240 min post-prandially.
In conclusion, it is currently believed that delayed gastric emptying contributes to the pathogenesis of GERD in a small proportion of patients, primarily by increasing available amounts of refluxate and causing gastric distension. The effects of gastric distension were investigated in a study by inflating an intra-gastric balloon in patients with GERD and controls [10]. In both groups, gastric distension significantly increased the rate of TLESRs, suggesting that gastric distension may be a triggering factor in post-prandial GERD.

Hiatal hernia

A hiatal hernia is frequently found in patients with GERD [18]. The proximal stomach is dislocated through the hiatus of the diaphragm into the chest, and the crural diaphragm becomes separated from the LES [4], This represents an important factor disrupting the integrity of the gastro-oesophageal sphincter, resulting in increased oesophageal acid exposure. Hiatal hernia is present in ≥ 90% of patients with severe erosive oesophagitis, especially if complications are present, such as oesophageal stricture or Barrett's oesophagus. A study assessing the role of hiatal hernia in patients with Barrett's oesophagus found a hernia > 2 cm in length in 96% of the patients studied [19].
Whether or not the hernia is an initiating factor in GERD, it clearly plays a role in sustaining GERD, accounting for the chronicity of the disease. One of the ways in which hiatal hernia is believed to affect the chronicity of GERD is by hindering LES function [20]. Susceptibility to reflux associated with abrupt increases in intra-abdominal pressure, such as inspira-

tion or coughing, is related both to diminished LES pressure and hiatal hernia. Another potential mechanism by which hiatal hernia can lead to reflux is by acting as a reservoir for acid-containing material, whereby acid becomes trapped in the hernia sac during oesophageal acid clearance and subsequently refluxes into the oesophagus during LES relaxation when the patient swallows. This mechanism is responsible for impaired acid clearance associated with GERD [21].

Visceral hypersensitivity

A subset of subjects with GERD symptoms has been shown to experience hypersensitivity to pain in the absence of excessive oesophageal acid exposure. One study evaluated 20 patients with GERD symptoms who had normal oesophageal acid exposure on 24-h pH monitoring [22]. These patients and a matched control group were tested for tolerance to oesophageal balloon distension. The study group showed enhanced sensitivity to oesophageal discomfort and distension compared to controls. This finding suggests that a group of patients with normal oesophageal acid exposure might experience symptoms of GERD as a result of visceral hypersensitivity. The mechanisms underlying this impaired visceral perception are still unclear, but are believed to involve altered cerebral processing of sensory input through cortical neural activity [23].

Impaired mucosal resistance

The ability of the oesophageal mucosa to withstand injury is a determining factor in the development of GERD. The oesophageal mucosa contains several structural and functional components that serve as a protective defence against noxious luminal substances. These include a relatively weak pre-epithelial defence and a strong epithelial defence that is supported by the blood supply [24]. The pre-epithelial defence consists of a small water layer with limited buffering capacity, presumably due to the presence of bicarbonate derived from swallowed salivary secretions and from secretions of the oesophageal submucosal glands [24]. Its buffering capacity is limited, but seems sufficient to maintain the surface pH values in a range that avoids pepsin activation. When this mechanism fails, the major defence of the epithelium relies soley upon the epithelium itself. The epithelial defence consists of three main components: 1) the cell membranes and the intercellular junctional complex, which limit the rate of hydrogen ion penetration into the intercellular space or cell cytosol; 2) the presence of cellular and intercellular buffers (bicarbonate, proteins, phosphate) that neutralize back-diffusing luminal acid; and 3) the presence of cell membrane ion transporters which serve to extrude acid from the cell cytosol when intra-cellular pH falls to acidic levels [24].

However, these defence mechanisms have their limits, which can be reached either by refluxates containing high levels of luminal acidity or by ingestion of substances high in alcohol, heat, osmolality or smoke-derived chemicals. When aggressive factors overwhelm the oesophageal defence, mucosal injury occurs. Acid and acid-pepsin initially attack and damage the intercellular junctions, thus resulting in an increase in para-cellular permeability, reflected morphologically by the presence of dilated intercellular spaces. This feature is present in the esophageal epithelium of both erosive and non erosive ERD patients and can help to explain the symptoms (heartburn) and signs of reflux disease. The symptoms are explained by the presence of sensory neurones within the intercellular spaces that can generate impulses for central transmission. The signs (erosions) are explained by luminal acid back-diffusing in sufficient quantities to acidify the intercellular space. This, in turn, results in intra-cellular acidification and, ultimately, cell oedema and necrosis [24]. Furthermore, epithelial repair is another defence that prevents necrosis from producing erosions; this process is dependent upon the presence of the salivary epidermal growth factor, which appears to be reduced in patients with reflux oesophagitis, thus resulting in defective repair [25].

Extra-oesophageal manifestations

GERD can be the primary cause or an aggravating factor in a wide variety of conditions affecting extra-esophageal structures, including: 1) pulmonary symptoms and diseases, such as asthma, bronchitis and pulmonary fibrosis; 2) otolaryngologic findings, such as hoarseness, cough, laryngitis, sub-glottic stenosis and laryngeal cancer; 3) other supra-oesophageal manifestations, such as sinusitis, pharyngitis and dental erosions. The cause is often difficult to establish, since many patients with suspected extra-oesophageal problems do not have typical GERD symptoms, pH testing does not accurately classify these patients, and placebo-controlled studies with high-dose proton-pump inhibitors (PPIs) show very inconsistent results in this group of patients.

The exact aetiology of extra-oesophageal manifestations of GERD remains unknown. However, two main hypotheses, not necessarily mutually exclusive, have been proposed: direct contact of aspirated gastric refluxate with the upper airway and a vago-vagal reflex [26].

The larynx and pharynx are in close proximity to the oesophagus, increasing the likelihood that these organs may be exposed when gastric refluxate is aspirated. Laryngeal mucosa is believed to be more sensitive than oesophageal mucosa to exposure to gastric refluxate, because of a lower expression of carbonic anhydrase, an enzyme which contributes to provide mucosal protection against acid exposure via acid neutralization. This fact suggests that laryngeal tissue may be more susceptible to acid-induced injury [27].

A vago-vagal reflex is another potential mechanism responsible for extra-oesophageal manifestations. The reflex is triggered by acidification of the distal portion of the oesophagus and by micro-aspiration: stimulation of vagal afferents triggers a vago-vagal reflex that induces bronchospasm [28]. Acidification of the distal oesophagus also increases bronchial hyperresponsiveness to methacholine [29]. In addition, a dysfunction of the upper oesophageal sphincter (UES), which normally increases its pressure when minute amounts of gastric fluid are in contact with the pharynx to protect upper airway from further exposure, may have an important role in the aetiology of extra-oesophageal manifestations [30].

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