Duodeno-Gastric Reflux and Duodeno-Gastro-Oesophageal Reflux

128

Rok Orel

Introduction

Reflux of duodenal juice, containing bile and pancreatic secretions into the stomach, is called duodeno-gastric reflux (DGR). When contents of duodenal juice are mixed with contents of the stomach and reflux in the oesophagus, we are speaking of duodeno-gastro-oesophageal reflux (DGER). As bile is most commonly used for the detection of both DGR and DGER for research and clinical practice, the term "bile reflux", although being to some extent erroneous since it neglects other refluxate components, is often used synonymously for DGR and DGER.

Only a few studies have been published about DGR and DGER in children, and to the best of my knowledge, no such studies were done in infants. Therefore, a majority of data about physiology, pathology and clinical importance of DGR and DGER in this chapter derive from the results of studies made in experimental animal models and in adult patients. Moreover, a lot of knowledge about the importance of these refluxes came from studies performed in patients with partial or total gastrectomy who represent an in vivo model with excessive reflux of duodenal juice because of disrupted pyloric anti-reflux barrier. With total gastrectomy, no acid and pepsin secretions interfere with harmful effects of duodenal juice components and represent an ideal possibility for studying duodeno-oesophageal reflux.

Duodeno-gastric reflux is a physiological phenomenon. In healthy people, it occurs sporadically during phase II and III of the interdigestive migrating motor complexes (MMC) of the antrum and is regularly present postprandially [1] and during the night [2]. Beside the motility of stomach, pylorus and duodenum, the amount and concentration of bile, pancreatic and duodenal secretions as well as food intake and its composition are likely to determine the duration and quantity of DGR. Postprandial DGR is provoked by a great amount of bile and pancreatic secretions in the duodenum after a meal and enhanced duodenal motor activity. Lipid-rich meals are probably associated with higher reflux rates and a higher concentration and total amount of duodenal juice in the stomach when compared to protein-rich meals [3]. At the end of the antral phase III, reflux of bicarbonate and immunoglobulins IgA, but not bile, from the duodenum aided by duodenal retro-peristalsis may play an important physiological role in the chemical and immunological restitution of the gastric mucosal barrier function after the exposure to high acid and pepsin concentrations [4]. In this physiologic

R. Orel, MD, PhD
Department of Gastroenterology, Hepatology and Nutrition, University Medical Centre Ljubljana, Children's Hospital, Bohoričeva 20, 1000 Ljubljana, Slovenia
e-mail: rok.orel@kclj.si

H. Till et al. (eds.), *Esophageal and Gastric Disorders in Infancy and Childhood*,
DOI 10.1007/978-3-642-11202-7_128

DGR, bile reflux is prevented by deviation to the gallbladder, probably by a phase III-associated occlusion of the sphincter of Oddi [5]. In view of the presumed role of MMC phase III as a gastrointestinal housekeeper, a role of gastric phase III in clearing of duodenal contents from the stomach seems likely [1].

The extent and duration of physiologic DGR in healthy persons show great interpersonal and intrapersonal day-to-day variability. The results of DGR detection are mostly dependent on the methods that were used. Even measurements with bilirubin monitoring system Bilitec 2000, probably the most accurate method for the DGR detection, which is explained in details in the section about the methods for DGR and DGER measurement, show very wide normal ranges. The median duration of bile presence in the stomach, the most frequently used marker for DGR, varied from 1.4 to 24.0 % of the day in healthy adults with an upper normal quartile cut-off levels from 7.8 to 72.0 % [6–12]. A comparison of gastric bilirubin exposure between proximal and distal sites within the stomach shows very big similarity that indicates that the duodenal refluxate is well mixed and evenly distributed within the stomach rather than concentrated more in the antrum and prepyloric area [9]. Since duodenal refluxate is relatively frequently present in the stomach, it is obvious that during gastro-oesophageal reflux episodes, it can reflux into the oesophagus.

Therefore, DGER can also be regarded as a part of normal physiology, although it does not appear regularly in all healthy people. Reflux episodes in healthy people are most common postprandially, and in healthy volunteers, more DGER was found during daytime than during the night. The median percentage of time with bile in the oesophagus in studies in healthy adults varied from practically none to up to 19.6 % [6, 13–16]. The amount of DGER may increase with ageing as more DGER was found in older volunteers [6]. For that reason, the adult normal values should not be directly extrapolated to children. Although the amount of DGER in healthy children has not been evaluated because of ethical reasons, the percentages of total time, upright time and supine time with bile in the oesophagus measured in children with gastro-oesophageal reflux symptoms but without reflux oesophagitis are comparable to those measured in healthy young adults (Table 128.1) [17]. After a reflux episode, refluxed material is cleared from the oesophagus by peristalsis and by washing with saliva end oesophageal gland secretions. Using simultaneous measurement of volume reflux by intraluminal impedance technique, acid reflux by pH monitoring and bile reflux by bilirubin absorptiometry with Bilitec 2000, we found out that volume bolus is cleared fast, followed by slower normalisation of oesophageal pH, whilst bile clears from the oesophagus as the last (unpublished observation). That can be explained by the fact that bolus clearance depends mostly on peristalsis, but the clearance of small amounts of refluxed material is the result of washing by saliva. Whilst acid can be chemically neutralised by relatively alkaline salivary and oesophageal glands' secretions faster than the washing process are finished, acid reflux episodes seem to finish faster than bile reflux episodes.

Table 128.1 Results of DGER measurement by Bilitec 2000 in children without oesophagitis

Bilirubin absorbance ≥0.14	Mean (SD)	95th percentile
% total time	0.3 (0.93)	1.17
% upright time	0.45 (1.44)	1.77
% supine time	0.13 (0.8)	0.5

Methods for Detection and Measurement of DGR and DGER

Several methods have been used in the past for the detection of DGR and DGER; however, each of them has its own strengths and shortcomings.

The observation of bile in the stomach or oesophagus during endoscopy is a poor indicator because of the intermittent nature of DGR and DGER and its clinical significance has never been demonstrated. Therefore, the endoscopy has a low accuracy and a low predictive value, and even histological picture of the mucosa, although suggestive of bile reflux, is not pathognomonic [18].

Aspiration studies with chemical analysis of aspirate contents produced a lot of scientifically important information but are inappropriate for everyday medical practice. Whilst using single aspiration yields a high rate of false-positive and false-negative results, frequent or even continuous sampling overcomes this drawback but may induce refluxes by creating pressure gradient [19].

Detection of bile acids, bilirubin or other constituents of duodenal juice in mouth saliva has been applied as a marker for DGER [20], but this method has not been validated enough and its accuracy is very questionable.

Scintigraphy is another possible method to detect DGR and DGER. A radioactive marker, for example, iminodiacetic acid (HIDA), which is rapidly eliminated through the liver and the bile ducts into the duodenum, is given to patients. Intermittent imaging of abdomen with gamma camera reveals refluxes as the appearance of the marker in the gastric or oesophageal area. Although non-invasive, it is relatively insensitive, because of the overlap of other organs and patient movement and especially due to the intermittent nature of refluxes, particularly the oesophageal one [21].

Detection of DGR and DGER by pH monitoring is based on the assumption that these refluxes cause an increase of pH over 7 because of alkaline nature of the duodenal juice. A term "alkaline reflux" was used as a synonym for DGR and DGER [22]. Simultaneous pH monitoring in oesophagus and stomach was frequently used in an effort to relate alkaline shifts in the stomach to those in the oesophagus [21]. However, detection of DGR and DGER with more objective methods revealed that these refluxes infrequently cause an increase in pH over 7. Moreover, the majority of bile reflux episodes take place at acidic or neutral pH [23–25]. Therefore, a pH of less than 7 does not exclude DGR and DGER. A pH above 7 may be caused by other factors, such as saliva, food, bicarbonate secreted by oesophageal submucosal glands, etc. [21]. DGR and DGER can therefore not be detected by pH monitoring alone, and the term "alkaline reflux" is a misnomer for describing refluxes of duodenal juice into the stomach and the oesophagus.

A fiberoptic spectrophotometer, Bilitec 2000, detects DGR and DGER independently of pH and can be used in an ambulatory setting [26]. This system utilises the optical property of bilirubin, the main biliary pigment, that has a characteristic spectrophotometric absorption band with a peak between 390 and 460 nm. The basic working principle of the instrument is that absorption of light near these wavelengths implies the presence of bilirubin and, therefore, represents bile reflux. In vitro validation experiments using Bilitec in differing dilutions of a bilirubin solution revealed a linear correlation between absorbance and bilirubin concentration, but in acidic environment ($pH < 3.5$), the bilirubin concentration can be underestimated by at least 30 % [27, 28]. It has been shown that bilirubin absorbance also correlates with the concentration of bile acids; however, this relationship was weaker in vivo [29]. In clinical practice, the method is not used for measuring bilirubin concentrations but to detect the presence or absence of bile in the stomach or in the oesophagus. For that purpose, threshold values of absorbance have been set on experimental basis to be sensitive and specific enough for bile detection. Absorbance ≥ 0.14 is usually applied for DGER detection, but different threshold values, ranging from ≥ 0.14 to ≥ 0.30, are used for DGR [6, 30]. By increasing the threshold value, the specificity of the method increases, but its sensibility decreases. The results are expressed as percentage of time of the recording with the presence of DGR or DGER. Ingested substances, in particular heavily coloured foods, may absorb light at the same wavelengths as bilirubin, thus interfering with the accuracy of the method and generating false-positive measurements. For that reason, a special "white diet" is recommended during monitoring [14, 31, 32]. Another drawback of the method is a possibility that a particle of food or other substance obstructs the tiny gap between fiberoptic probe and reflecting cap at its end (Fig. 128.1) and causes the disappearance of the signal [26]. Despite its limitations, bilirubin spectrophotometry represents the most practical and accurate method for DGR and DGER detection for both experimental and clinical purposes.

Fig. 128.1 The tip of a fiberoptic spectrophotometer Bilitec 2000

Multichannel intraluminal impedance is a method that enables detection of volume reflux independently of its pH. Usually, it is used simultaneously with pH monitoring so reflux episodes can be recognised as acid, weakly acid and alkaline [33]. However, impedance cannot detect a chemical composition of the refluxed material and is therefore inappropriate for the detection DGR and DGER.

In the future, new technologies using biosensors specific for bile acids or other reflux constituents seem a promising practical tool for DGR and DGER measurement. Such a biosensor could be devised using molecular imprinting technology (MIP) based on recognition characteristics of polymers that have complimentary size, shape and binding site to specific substrates and have already been applied to recognise steroids such as cholesterol and bile acids which share the same four-ring structure as other steroids [34].

Mechanisms of Inflammation and Oncogenesis Produced by the Duodenal Refluxate Constituents

Numerous studies using animal models or tissue culture experimental models revealed that duodenal juice constituents play an important role in the development of inflammation and oncogenesis in the stomach and the oesophagus.

Trypsin and perhaps other pancreatic proteases cause tissue damage and release of intracellular inflammation mediators [35]. Trypsin is thought to digest intercellular substances and surface structures that contribute to the maintenance of cohesion between cells, causing the dilution of intercellular spaces and the shedding of epithelial cells [36–38]. It has been shown that trypsin induces the expression of pro-inflammatory cytokines on epithelial cells through the activation of specific receptors, protease-activated receptors (PARs). Human oesophageal cells stimulated with trypsin produce interleukin-8 and prostaglandin E_2 [39]. Trypsin's activity depends on pH and is optimal in the pH range from 5 to 8.

Another important component of duodenal juice is lysolecithin that is formed when pancreatic phospholipase A hydrolyses the lecithin in bile. Studies have demonstrated that in the presence of acid, lysolecithin is able to injure oesophageal mucosa, causing almost complete tissue breakdown [36, 40].

Bile salts are normal duodenal juice components. Human liver converts an average of 0.78–1.29 mmol (300–500 mg) of cholesterol into bile acids daily. These primary bile acids, cholate and chenodeoxycholate, are synthesised by hepatocytes in a ratio of 2–1. Secondary bile acids, deoxycholic acid and lithocholic acid, are formed from primary bile acids as metabolic by-products of intestinal bacteria, most importantly *bacteroides* and *bifidobacteria*, by deconjugation and 7α-dehydroxylation. Prior to secretion into bile, 98% of bile acids are conjugated with taurine or glycine in a ratio of about 3–1. Bile acid synthesis is regulated by feedback inhibition from reabsorbed bile acids from the gut reaching the liver via the portal vein. Bile acids have to be deconjugated by intestinal bacteria before absorption and are reconjugated in the liver before re-entering the bile. This enterohepatic circulation maintains a composition of human bile consisting of 54% cholic, 31% chenodeoxycholic, and 15% deoxycholic acid, of which about 80% is conjugated with taurine and 20% with glycine [41]. Damaging effect of bile salts on the mucosa is dependent on their conjugation state. The conjugation state depends mostly on the pH. When the pH is equal to the pKa, the bile acid is half ionised and half protonated, the ionised half being soluble [40].

Although the mechanism by which bile acids damage the mucosa is not fully understood, available studies suggest more hypotheses. The first is that bile acids damage mucosal cells by their detergent property and solubilisation of their lipid membranes [38]. This theory is supported by studies in gastric mucosa in which bile acid mucosal injury was correlated with the release of phospholipids and cholesterol into the lumen [42]. The second hypothesis suggests that bile acids gain entrance across the mucosa because of their lipophilic state, causing intramucosal damage by disorganising membrane structure and interfering with cellular metabolism [38]. Once bile acids have penetrated the mucosal barrier, they are trapped inside the cells by intracellular ionisation that results in severalfold increase in their intracellular concentration [43, 44]. The unionised lipophilic forms predominate at more acidic pH for conjugated bile acids (i.e. pKa 1.9) and at more neutral pH for unconjugated bile acids (i.e. pKa 5.1) [38]. As the damage caused by bile salts depends on their solubility, conjugated bile salts cause mucosal damage under acidic and unconjugated under neutral and alkaline conditions [36, 37]. Moreover, by dissolution of cell membranes and tight junctions, bile acids open the doors to other harmful substances such as acid, pepsin and pancreatic enzymes [45].

It is known that bile acids can also stimulate cell proliferation and promote tumorigenesis and are therefore implicated in the development of Barrett's oesophagus, gastric and oesophageal squamous cell carcinoma and adenocarcinoma [35, 46–50]. Damaged mucosal cells produce inflammatory mediators such as cytokines, which recruit inflammatory cells to the site of inflammation. These cells produce free radicals whose primary role is to remove the damaged cells, but they may also induce genetic mutations. Bile acids are known to induce oxidative stress and DNA damage [51, 52]. They can induce up-regulation of superoxide-generating NADPH oxidase NOX5-S expression and increase in cell proliferation depend on activation of TGR5 receptor (a bile acid receptor) and Cαq protein which is involved in hydrogen peroxide production [53]. Whilst most of these changes will lead to cell death, others may confer a survival advantage and lead to a clonal expansion of the premalignant, Barrett's or malignant cell type [54].

One of the characteristics of premalignant and especially malignant cells is also their loss of differentiation. The vitamin A derivate retinoic acid is an inducer of differentiation, and there is evidence that bile acids compete for one of its nuclear receptors [55]. Cyclooxygenase (COX) is the enzyme responsible for the rate-limiting step in the production of prostaglandins. Whilst COX-1 is constitutively expressed in the normal gastric and oesophageal mucosa and has a protective function, the role of COX-2 includes inflammation, cell adhesion, blocking apoptosis, invasion, angiogenesis and metastasis and is induced by inflammatory and cancerous processes [54]. Bile acids have been shown to stimulate production of COX-2 and prostaglandins such as prostaglandin E_2 which may play an important role in cell metaplasia, dysplasia and tumorigenesis [56, 57]. They can also activate mitogen-activated protein (MAP) kinase and NF-κB pathways, thereby increasing cell proliferation and decreasing cell apoptosis [53].

Experimental studies suggest that bile acids can directly induce DNA changes which may lead to mutations and may be thus implicated in the initiation of carcinogenesis [58]. Many chromosomal losses and gains were detected by a high-resolution oligonucleotide comparative genomic hybridisation in the neoplastic cells developed by experimental reflux of duodenal juice [59]. Moreover, by entering cellular nucleus and binding to nuclear receptors, bile acids may induce the expression of oncogenes. For example, the proto-oncogene C-myc is up-regulated and expression is increased by exposure to bile acids [60].

In conclusion, duodenal juice contents as pancreatic enzymes, lysolecithin and conjugated and unconjugated bile acids are implicated in mucosal damage, inflammation, metaplasia and malignant alteration through different mechanisms; however, their detrimental effect depends on pH. In acidic conditions, conjugated bile acids and lysolecithin can damage mucosa in synergism with hydrochloric acid and pepsin from the

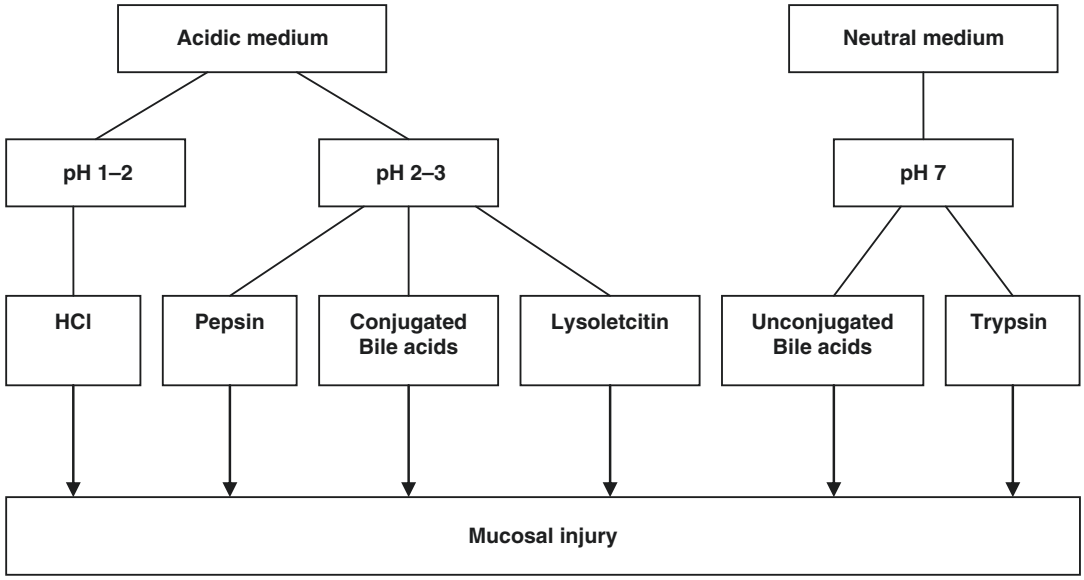

Fig. 128.2 A schematic representation of pH dependence of different agents responsible for mucosal injury

gastric juice. At neutral or alkaline pH, unconjugated bile acids and pancreatic trypsin can damage gastric and oesophageal mucosa (Fig. 128.2).

Clinical Presentation

Excessive DGR and DGER have been suggested to be involved in the pathogenesis of several foregut diseases such as chemical gastritis, functional dyspepsia, reflux oesophagitis, Barrett's oesophagus and gastric and oesophageal carcinoma. Symptoms are non-specific such as upper abdominal pain or discomfort, postprandial fullness, regurgitation and, occasionally, bile vomiting. Therefore, the objective diagnostic methods are necessary to prove pathologic amount of reflux as well as its connection with the disease.

A lot of knowledge about the importance of DGR and DGER has arrived from observations in surgical patients. In patients after partial or total gastrectomy with gastroduodenostomy (Billroth I), gastrojejunostomy (Billroth II) or reconstruction with biliary diversion (Roux-en-Y), excessive DGR had been documented by objective measurements with intragastric bilirubin spectrophotometry, caused by the loss of pyloric sphincter functioning as a physiologic barrier to retrograde flow of duodenal contents into the stomach [10, 61, 62]. Not only dyspeptic symptoms but also remnant gastritis, gastric ulcerations, gastric stump carcinoma, gastro-oesophageal reflux disease and oesophageal adenocarcinoma have been attributed to excessive DGR in these patients [10].

Moreover, excessive DGR with its consequences has also been discovered in patients who underwent cholecystectomy, endoscopic sphincterotomy or other hepatobiliary operative procedures [63–65]. In contrast with healthy subjects in whom DGR was present most often postprandially, in cholecystomised patients, bile is present in stomach also during fasting [65]. This profile may be explained by the surgical loss of the normal gallbladder reservoir for bile, which is then excreted into the duodenum at the same rate it is secreted by the liver. Thus, after cholecystectomy, more bile enters the duodenum when fasting and less after eating compared with subjects with a normal gallbladder. The more constant presence of bile in the duodenum creates conditions predisposing to increased duodeno-gastric bile reflux. Moreover, a number of motility abnormalities were noted after cholecystectomy [66]. Phase II in the antrum, the "clearance" wave, was found to occur at a significantly slower

rate. Also, there was less build-up to phase III of the interdigestive migrating motor complex, with a lengthened phase I and reciprocally shortened phase II. Furthermore, the phase III front migrates down the duodenum at half the speed that it does in healthy subjects. This may slow clearance of the increased proximal duodenal pool of biliary secretions, which is then available to reflux into the stomach where it is ineffectively cleared [66]. In children operated for choledochal cyst, excessive DGR was found following hepaticoduodenostomy but not following Roux-en-Y hepaticojejunostomy [67].

In contrast to this, serious gastric pathology caused by primary excessive DGR without previous gastrointestinal surgery is relatively rare. It has been postulated that DGR produces consistent histological changes in the gastric mucosa, so-called chemical or reactive gastropathy or bile reflux gastritis. The histological feature most strongly associated with DGR was intestinal metaplasia at the gastric antrum. DGR was also positively associated with the severity of glandular atrophy, chronic inflammation, lamina propria oedema and foveolar hyperplasia. As a result, a histological index, the bile reflux index (BRI), was derived. Evaluation studies showed that its values above a threshold 14 have a sensitivity of 70 % and a specificity of 85 % for a bile acid concentrations >1.00 mmol/l, which is the upper limit of physiological reflux [68]. Increased DGR has been incriminated in the genesis of symptoms in patients with functional dyspepsia. Although in some studies significantly increased DGR has been found in these patients compared to controls [10], other groups found the role of DGR to be minor since its amount during fasting was normal and only slightly increased after eating [65]. In patients with dyspeptic symptoms with pathologic amount of DGR, the mucosal lesions such as active inflammation, chronic inflammation, intestinal metaplasia, atrophy and *Helicobacter pylori* infection in the whole stomach were more severe than those in dyspepsia patients without DGR, and the bile reflux time was well correlated with the severity of pathological changes [69]. However, the relationship between *H. pylori* infection and DGR remains controversial. Some data suggest that *H. pylori* may induce DGR, and therefore both may act synergistically on the gastric mucosa, causing chronic gastritis, which may lead to the carcinoma sequence [68, 70, 71]. On the other hand, there are reports proposing that DGR decreases *H. pylori* colonisation and even suggesting to use bile acids for the treatment of *H. pylori*-related gastritis [72, 73]. However, by comparing the amount of DGR before and after *H. pylori* eradication [74], and the presence of *H. pylori* infection in patients with and without DGR [75], no causative relationship could be proved between DGR and *H. pylori* infection. Primary DGR has been rarely reported as a proposed mechanism of gastric pathology in children unresponsive to classical antacid therapy [76].

The principal role of acid reflux of gastric juice in the development of reflux oesophagitis, Barrett's oesophagus and oesophageal cancer has been well established. First ideas about the importance of DGER came from the observations in patients with atrophic gastritis, pernicious anaemia and following gastrectomy who developed oesophagitis despite practically absent gastric acid secretion [77–79]. Although DGER can be a consequence of excessive DGR, it can appear from either increased or normal gastric exposure to duodenal contents [80]. Therefore, pathologic DGR can be an important mechanism but is not a prerequisite for increased DGER. In contrast with paucity of convincing clinical evidence that DGR can produce serious pathology in intact (non-operated) stomach, numerous quality clinical studies elucidated the importance of DGER in oesophageal pathology, both in adults and children.

Some but not all of the studies using gastric or oesophageal aspiration and chemical analysis of the aspirate showed an increase in the presence of bile acids in gastro-oesophageal reflux (GERD) patients in comparison with healthy controls [45]. The differences in the results can be partially explained by different techniques of sampling and particularly by different methods of chemical analysis. In addition, particularly increased bile acid concentration was found amongst patients with Barrett's oesophagus, with

the highest concentrations amongst those with complicated Barrett's oesophagus (stricture, ulcer, dysplasia) [81, 82]. However, even in studies which found increased amounts of bile acids in GERD patients, their concentration seldom exceeded 1.0 mmol/l, the concentration regarded high enough to produce oesophageal mucosal lesions [83].

Although it is clear today that increase of pH above 7 cannot be regarded as a marker of DGER, oesophageal pH monitoring was used in the past to trace for "alkaline reflux". Several groups published their findings of significantly higher amounts of both acid and alkaline reflux in patients with complicated oesophagitis, Barrett's oesophagus and complicated Barrett's oesophagus [84]. These investigators went on to suggest that prolonged exposure of oesophageal mucosa to duodenal contents alone may promote the development of complicated Barrett's oesophagus and even adenocarcinoma.

Most of the knowledge about the clinical importance of DGER in oesophageal pathology arrives from studies using simultaneous oesophageal pH monitoring and bilirubin spectrophotometry with Bilitec 2000. These studies again pointed out the importance of DGER in the development of Barrett's oesophagus as in the majority of them patients with Barrett's oesophagus had a significantly greater exposure to both acid and duodenal contents than patients with reflux oesophagitis or healthy controls [14, 85, 86]. Moreover, it seems that patients with long segment and complicated Barrett's oesophagus have particularly increased exposure to DGER [82, 87]. In comparison with patients with short segment Barrett's oesophagus, they have similar acid reflux but significantly greater reflux of duodenal contents. With some exceptions that did not find significant differences in GERD between controls and patients with reflux oesophagitis [14], a gradual increase of both acid reflux and DGER has been proven across the GERD spectrum, being the lowest in healthy persons and in patients without oesophagitis, higher in patients with reflux oesophagitis and the highest in patients with Barrett's oesophagus [15, 86, 88]. Barrett's oesophagus is a rare disorder in children; therefore, paediatric studies did not include patients with Barrett's oesophagus. However, both acid reflux and DGER exposure were found to increase stepwise with the severity of oesophagitis. They were lower in children with GERD symptoms but without reflux oesophagitis compared with children with reflux oesophagitis, and children with severe oesophagitis (Los Angeles grades C and D) had more refluxes than those with mild oesophagitis (Los Angeles grades A and B) (Fig. 128.3) [17].

Duodeno-gastro-oesophageal reflux may cause symptoms, although symptom episodes in patients with GERD seem to be more often related to acid reflux episodes [89, 90]. There is a growing evidence that pathologic amounts of DGER without pathologic acid reflux can result in erosive reflux oesophagitis both in adults [91–94] and children [17, 95]. In my experience, a majority of children without oesophagitis has no pathologic refluxes. Isolated pathologic acid reflux or isolated DGER cause mild oesophagitis, and a combination of both cause severe oesophagitis (Fig. 128.4) [17]. However, in some patients with reflux oesophagitis or even Barrett's oesophagus, the results of both pH monitoring and bilirubin spectrophotometry can be normal [96].

Duodeno-gastro-oesophageal reflux may play an important role in the pathophysiology of proton pump inhibitor-refractory GERD [97, 98]. Although pathologic acid reflux, pathologic DGER or a combination of both were found in adults and children not responsive to the therapy with proton pump inhibitors (PPIs), acid exposure did not differ according to the presence of oesophagitis, but patients with substantial oesophagitis had significantly higher DGER exposure than those without oesophagitis [98, 99]. DGER may also participate in the development of more severe forms of GERD in children with additional risk factors like neurological and developmental disorders, cystic fibrosis and operated anomalies of upper gastrointestinal tract. Significantly higher gastric bilirubin levels were found in children with cystic fibrosis when compared with healthy subjects that may result in exaggerated DGER [100].

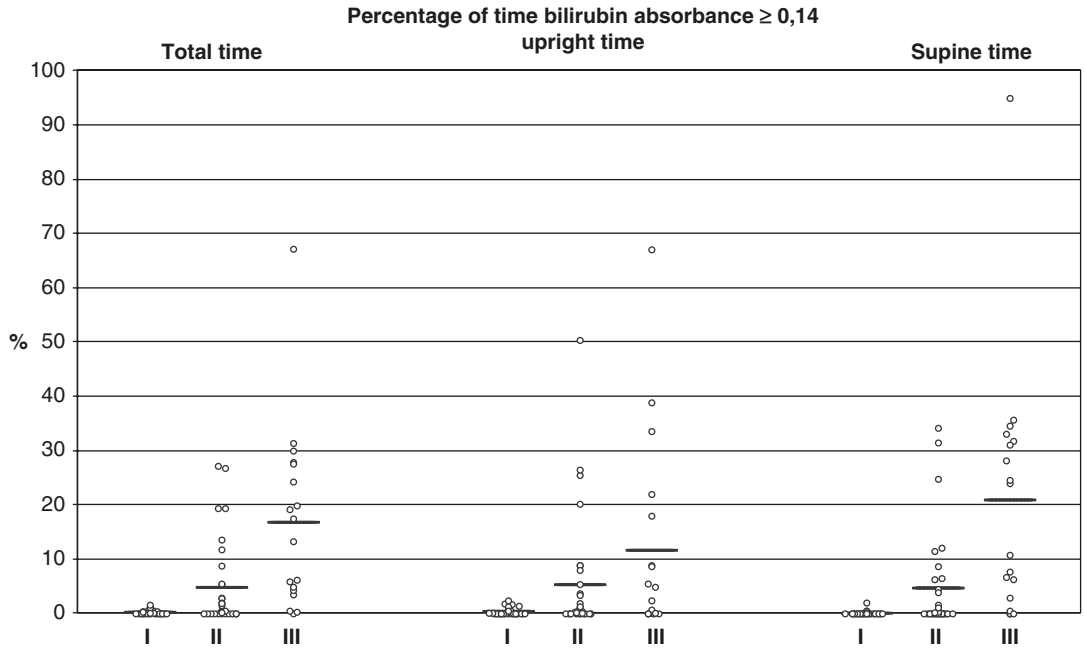

Fig. 128.3 Results of 24 h DGER monitoring with fiber-optic spectrophotometer expressed as mean and individual values in children without oesophagitis (I), with mild to moderate oesophagitis (II) and with severe oesophagitis (III) for percentages of total time, upright time and supine time with bilirubin absorbance ≥0.14 [17]

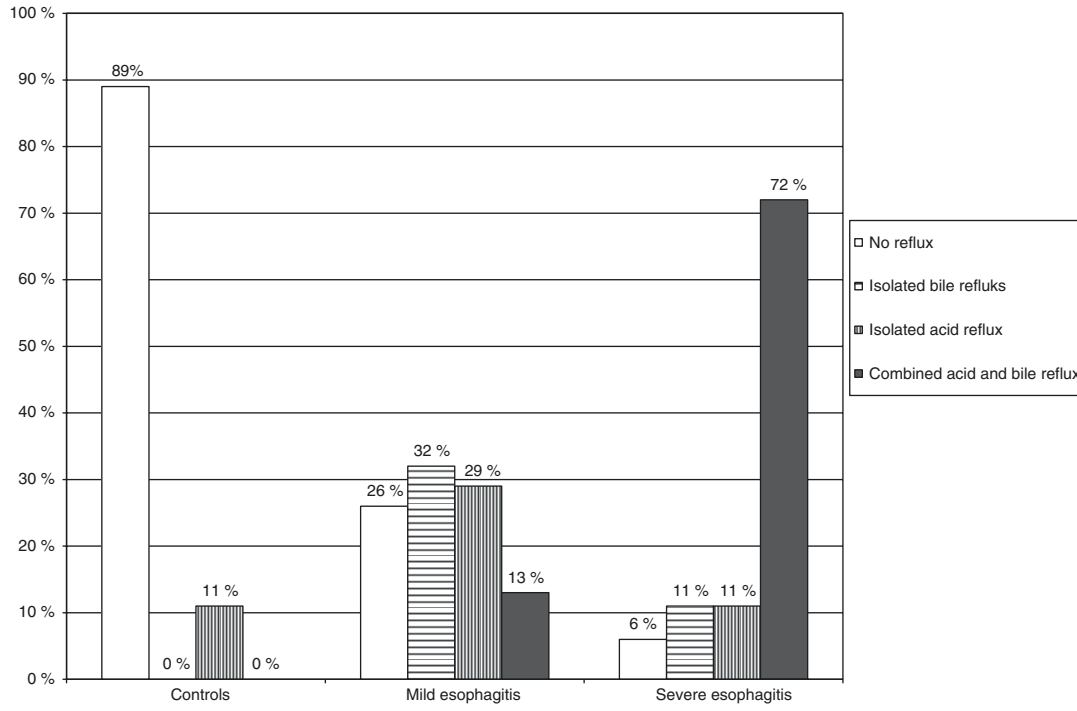

Fig. 128.4 Percentage of patients with no pathologic reflux and with three different patterns of pathologic reflux (isolated bile reflux, isolated acid reflux and combined acid and bile reflux) in the groups of children without oesophagitis, with mild to moderate oesophagitis and with severe oesophagitis [17]

As DGER or its effects may extend beyond the oesophagus, it may cause or contribute to a variety of supra-oesophageal manifestations. Pathological DGER was found in patients with unexplained excessive throat phlegm [101]. Significant higher prevalence of symptoms and findings of laryngeal damage including laryngeal neoplastic lesions was reported in patients after gastric surgery with presence of bilirubin and bile acids, indirect markers of DGER, in saliva [20]. Moreover, pathological acid reflux and especially excessive "alkaline" reflux were found to be elevated and could be implicated into the pathogenesis of neoplastic lesions of the pharynx and larynx [102].

Simultaneous oesophageal pH monitoring and bilirubin spectrophotometry explained the exact relationship between DGER and oesophageal pH. Firstly, these studies revealed that DGER rarely coincide with so-called alkaline shift (a rise of pH over 7), suggesting that the term "alkaline reflux", previously often used synonymously with DGER, is a misnomer [24, 88]. Secondly, DGER appears across the whole oesophageal pH spectrum. Whilst some studies found DGER episodes most frequently between oesophageal pH 4 and 7 [14, 24], the others discovered the majority in an acidic environment (pH < 4) [15]. It was shown that in children, DGER episodes most frequently begin at pH between 6 and 7, the pH of an empty oesophagus. However, after the beginning of an episode, oesophageal pH may change. The pH of the refluxate depends on the proportions of acid gastric juice, food and duodenal juice in it. It is interesting that in children without oesophagitis, relative duration of DGER was longest between pH 5 and 6, in children with mild oesophagitis between pH 4 and 5, whilst in those with severe esophagitis, it was between pH 2 and 4 [25]. From these observations, one can hypothesise that the lower the pH at which DGER occurs, the more severe the oesophageal damage, resulting from simultaneous effects of gastric and duodenal juice components.

Therapy

Both pharmacological and surgical therapies of excessive DGR and DGER have been profoundly studied.

Specific aims of treating DGR and DGER with medications can be directed at three components: decreasing gastric acid secretion, promoting motility and gastric emptying and neutralising or binding bile acids and making them less injurious to the gastric and oesophageal mucosa [103].

Acid suppression, particularly with PPIs, is the mainstay of treatment of gastric and oesophageal diseases. Several clinical studies revealed that treatment with PPIs and even H_2-blockers dramatically decreases not only acid reflux but also reflux of duodenal juice into the oesophagus, both in adults [88, 104–107] and children [108] (Fig. 128.5). The proposed mechanism is reduction of the volume of gastric secretions, with less fluid available in the stomach for any DGR to mix with and thence to reflux into the oesophagus. This mechanism may also explain the reduction in DGR to the upper part of the stomach, a prerequisite for DGER [104]. Moreover, some studies showed that acid suppression therapy can influence gastric and duodenal motility by increasing antral phase III MMC, which have the role of "street sweeper" and clean the duodenal reflux contents from stomach. MMC III is evoked by a presence of bile and pancreatic juice and neutralisation of acid in the duodenum but can be inhibited by acidic pH. Therefore, PPIs may also decrease DGR and DGER through increasing MMC III due to increased duodenal pH [107]. The second proposed mechanism seems more likely since studies using combined oesophageal pH monitoring and intraluminal impedance revealed that therapy with PPIs does not affect volume reflux into the oesophagus [109]. It should not be forgotten that several DGER components such as conjugated bile acids and lysolecithin are most dangerous to the oesophageal mucosa at acidic pH when their harmful effect is synergistic with gastric acid and pepsin. Their activity can be neutralised by rising oesophageal refluxate pH with acid suppression therapy.

Cisapride promotes the release of acetylcholine from the myenteric plexus and thereby improves gastric emptying and increases lower oesophageal sphincter pressure. Several studies showed that cisapride relieves symptoms in both adult [110] and paediatric [98, 111] patients with excessive duodenal reflux. However, the results of studies using objective

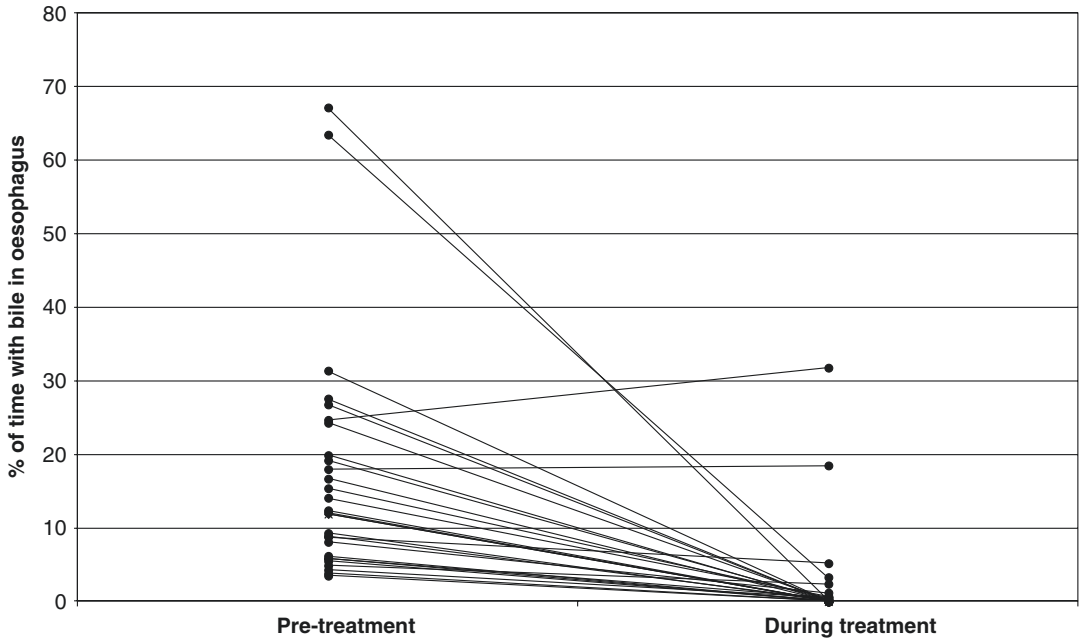

Fig. 128.5 The effect of therapy with omeprazole on duodeno-gastro-oesophageal reflux in children [108]

measurements of DGR or DGER for assessment of the efficacy of cisapride are conflicting. Significant decrease of DGER was observed during therapy with cisapride in a placebo-controlled trial in postgastrectomy patients [110], but not in patients with gallstones and intact stomach [112]. Cisapride is not available any more, as it has been withdrawn from the market because of its interactions with many other drugs and serious side effects.

Domperidone, a peripheral dopamine (D_2) receptor antagonist, acts as an antiemetic and prokinetic agent through its effects on the chemoreceptor trigger zone and motor function of the stomach and small intestine, thus promoting gastric emptying by augmenting gastric peristalsis and improving antroduodenal coordination. Domperidone was effective both in amelioration of symptoms and in decreasing nocturnal bile reflux into the stomach in patients with functional dyspepsia [113].

Erythromycin, an antibiotic with prokinetic properties, almost completely normalised DGR in all patients with pathological DGR after biliary surgery [114].

Baclofen, the gamma-aminobutyric $acid_B$ ($GABA_B$) agonist, inhibits the occurrence of transient lower oesophageal sphincter relaxations that are the main pathophysiological mechanism underlying the gastro-oesophageal reflux. In a study in patients with DGER refractory to PPIs, baclofen reduced both the number and the duration of DGER episodes significantly [115].

Cholestyramine is a basic anionic exchange resin that binds bile salts. In an uncontrolled study, cholestyramine helped some patients with mild bile reflux gastritis [116], but this finding was not confirmed in a later randomised, double-blind study [117].

Aluminium hydroxide but not magnesium hydroxide antacids absorb conjugated bile acids and lysolecithin with an affinity and capacity comparable with cholestyramine. Their efficacy in symptom relief of bile reflux gastritis was equivalent to cholestyramine but not better than placebo [117].

Ursodeoxycholic acid (UDCA) is potentially effective by changing the composition of the refluxed bile, which may be less noxious to the gastric and oesophageal mucosa. In a placebo-controlled study in patients with bile reflux gastritis, a therapy with UDCA resulted in significant amelioration of symptoms but had no effect on the macroscopic and microscopic appearance of the gastric mucosa [118].

Sucralfate is the basic aluminium salt of sulphated sucrose that adheres to exposed proteins

in damaged mucosa, protecting them from acid, pepsin and bile acids. In a placebo-controlled study in patients with bile reflux gastritis, sucralfate lowered the gastric inflammatory cell scores but was not associated with improvement of symptoms [119].

Remnant chemical gastritis as a consequence of excessive DGR after subtotal gastrectomy can probably be prevented by choosing reconstructive procedures which decrease retrograde flow of duodenal juice and particularly bile into the stomach. Studies revealed that Roux-en-Y reconstruction is better than Billroth I or II [120, 121]. With Roux-en-Y operation, a 45–60 cm-long isoperistaltic limb of jejunum is created between partially resected stomach and jejunal limb draining the pancreatic biliary system [103]. The Roux-en-Y operation was shown to preserve the cardia and the position of the remnant stomach better than other procedures. In patients after resection of the extrahepatic bile duct, Roux-en-Y hepaticojejunostomy was more effective in prevention of excessive DGR than hepaticoduodenostomy [67]. The Roux-en-Y anastomosis is also a successful therapy for patients with intractable symptoms of remnant gastritis and documented increased DGR after other gastric operations [122, 123]. However, side effects include ulceration, delayed gastric emptying and dumping [103]. Duodenal switch is an operation in which the stomach and proximal 5–7 cm of the duodenum are left intact. The jejunum is divided about 25 cm distal to the ligament of Treitz. The distal limb is anastomosed end to end to the proximal portion of the duodenum, and the proximal limb of the jejunum is anastomosed end to side to the distal jejunum. This may be the preferred operation in patients with excessive DGR and intact stomach as complications are markedly reduced compared to Roux-en-Y operation [103, 124]. However, such aggressive surgery is nowadays not a realistic therapeutic option in patients and especially in children with pathology due to excessive DGR and DGER without previous gastric or biliary operation. Exceptions to this rule are patients with severe gastro-oesophageal reflux disease refractory to pharmacological therapy who may benefit from anti-reflux surgery. Several studies showed that DGER adequately decreases after Nissen fundoplication [125, 126].

References

1. Koek GH, Vos R, Sifrim D, Cuomo R, Janssens J, Tack J. Mechanisms underlying duodeno-gastric reflux in man. Neurogastroenterol Motil. 2005;17:191–9.
2. Fiorucci S, Distrutti E, Di Matteo F, Brunori P, Santucci L, Mallozzi E, Bigazzi U, Morelli A. Circadian variations in gastric acid and pepsin secretion and intragastric bile acid in patients with reflux esophagitis and in healthy controls. Am J Gastroenterol. 1995;90:270–6.
3. Sonnenberg AM-LS, Weiser HF, Müller-Duysing W, Heinzel F, Blum AL. Effect of liquid meals on duodenogastric reflux in humans. Am J Physiol. 1982;243:G42–7.
4. Dalenback J, Abrahamson H, Bjornson E, Fandriks L, Mattsson A, Olbe L, Svennerholm A, Sjovall H. Human duodenogastric reflux, retroperistalsis, and MMC. Am J Physiol. 1998;275:R762–9.
5. Castedal M, Bjornsson E, Gretarsdottir J, Fjalling M, Abrahamsson H. Scintigraphic assessment of interdigestive duodenogastric reflux in humans: distinguishing between duodenal and biliary reflux material. Scand J Gastroenterol. 2000; 35:590–8.
6. Bollschweiler E, Wolfgarten E, Putz B, Gutschow C, Holscher AH. Bile reflux into the stomach and the esophagus for volunteers older than 40 years. Digestion. 2005;71:65–71.
7. Bechi P, Cianchi F. Technical aspects and clinical indications of 24-hour intragastric bile monitoring. Hepatogastroenterology. 1999;46:54–9.
8. Byrne JP, Romagnoli R, Bechi P, Attwood SE, Fuchs KH, Collard JM. Duodenogastric reflux of bile in health: the normal range. Physiol Meas. 1999;20:149–58.
9. Manifold DK, Anggiansah A, Marshall RE, Owen WJ. Reproducibility and intragastric variation of duodenogastric reflux using ambulatory gastric bilirubin monitoring. Dig Dis Sci. 2001;46:78–85.
10. Fein M, Freys SM, Sailer M, Maroske J, Tigges H, Fuchs KH. Gastric bilirubin monitoring to assess duodenogastric reflux. Dig Dis Sci. 2002;47:2769–74.
11. Bowrey DJ, Williams GT, Carey PD, Clark GW. Inflammation at the cardio-esophageal junction: relationship to acid and bile exposure. Eur J Gastroenterol Hepatol. 2003;15:49–54.
12. Marshall RE, Anggiansah A, Owen WA, Manifold DK, Owen WJ. The extent of duodenogastric reflux in gastro-esophageal reflux disease. Eur J Gastroenterol Hepatol. 2001;13:5–10.

13. Tack J, Bisschops R, Koek G, Sifrim D, Lerut T, Janssens J. Dietary restrictions during ambulatory monitoring of duodenogastroesophageal reflux. Dig Dis Sci. 2003;48:1213–20.
14. Kauer WK, Peters JH, DeMeester TR, Ireland AP, Bremner CG, Hagen JA. Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone. The need for surgical therapy re-emphasized. Ann Surg. 1995;222:525–31; discussion 531–533.
15. Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. Gastroenterology. 1996;111:1192–9.
16. Okholm M, Sorensen H, Wallin L, Boesby S. Bile reflux into the esophagus. Bilitec 2000 measurements in normal subjects and in patients after Nissen fundoplication. Scand J Gastroenterol. 1999;34:653–7.
17. Orel R, Markovic S. Bile in the esophagus: a factor in the pathogenesis of reflux esophagitis in children. J Pediatr Gastroenterol Nutr. 2003;36:266–73.
18. Stein HJ, Smyrk TC, DeMeester TR, Rouse J, Hinder RA. Clinical value of endoscopy and histology in the diagnosis of duodenogastric reflux disease. Surgery. 1992;112:796–803; discussion 803–804.
19. Girelli CM, Cuvello P, Limido E, Rocca F. Duodenogastric reflux: an update. Am J Gastroenterol. 1996;91:648–53.
20. De Corso E, Baroni S, Agostino S, Cammarota G, Mascagna G, Mannocci A, Rigante M, Galli J. Bile acids and total bilirubin detection in saliva of patients submitted to gastric surgery and in particular to subtotal Billroth II resection. Ann Surg. 2007;245: 880–5.
21. Marshall REAA, Owen WJ. Bile in the esophagus: clinical relevance and ambulatory detection. Br J Surg. 1997;84:21–8.
22. Pellegrini CADT, Wernly JA, Johnson LF, Skinner DB. Alkaline gastroesophageal reflux. Am J Surg. 1978;135:177–84.
23. Just RJ, Leite LP, Castell DO. Changes in overnight fasting intragastric pH show poor correlation with duodenogastric bile reflux in normal subjects. Am J Gastroenterol. 1996;91:1567–70.
24. Marshall REKAA, Owen WA, Owen WJ. The temporal relationship between esophageal bile reflux and pH in gastro-esophageal reflux disease. Eur J Gastroenterol Hepatol. 1998;10:385–92.
25. Orel R, Vidmar G. Do acid and bile reflux into the esophagus simultaneously? Temporal relationship between duodenogastro-esophageal reflux and esophageal pH. Pediatr Int. 2007;49:226–31.
26. Baldini F. In vivo monitoring of the gastroesophageal system using optical fibre sensors. Anal Bioanal Chem. 2003;375:732–43.
27. Caldwell MT, Byrne PJ, Brazil N, Crowley V, Attwood SE, Walsh TN, Hennessy TP. An ambulatory bile reflux monitoring system: an in vitro appraisal. Physiol Meas. 1994;15:57–65.
28. Vaezi MF, Lacamera RG, Richter JE. Validation studies of Bilitec 2000: an ambulatory duodenogastric reflux monitoring system. Am J Physiol. 1994;267:G1050–7.
29. Barrett MW, Myers JC, Watson DI, Jamieson GG. Detection of bile reflux: in vivo validation of the bilitec fibreoptic system. Dis Esophagus. 2000;13:44–50.
30. Bechi P, Pucciani F, Baldini F, Cosi F, Falciai R, Mazzanti R, Castagnoli A, Passeri A, Boscherini S. Long-term ambulatory enterogastric reflux monitoring. Validation of a new fiberoptic technique. Dig Dis Sci. 1993;38:1297–306.
31. Barrett MW, Myers J, Watson DI, Jamieson GG. Dietary interference with the use of Bilitec to assess bile reflux. Dis Esophagus. 1999;12:60–4.
32. Zacharioudakis G, Chrysos E, Athanasakis E, Tsiaoussis J, Karmoiris K, Xynos E. Is there any mediterranean diet not affecting bilitec assessment of bile reflux? Digestion. 2004;70:84–92.
33. Tutuian R, Castell D. Review article: complete gastro-esophageal reflux monitoring – combined pH and impedance. Aliment Pharmacol Ther. 2006;24:27–37.
34. Nehra D. Bile in the esophagus-model for a bile acid biosensor. J Gastrointest Surg. 2010;14 Suppl 1:S6–8.
35. Tack J. Review article: the role of bile and pepsin in the pathophysiology and treatment of gastro-esophageal reflux disease. Aliment Pharmacol Ther. 2006;24 Suppl 2:10–6.
36. Kivilaakso E, Fromm D, Silen W. Effects of bile salts and related compounds on isolated esophageal mucosa. Surgery. 1980;87:280–5.
37. Lillemoe KD, Johnson L, Harmon JW. Alkaline esophagitis: a comparison of the ability of components of gastroduodenal contents to injure the rabbit esophagus. Gastroenterology. 1983;85:621–8.
38. Vaezi MF, Richter JE. Duodenogastresophageal reflux and methods to monitor nonacidic reflux. Am J Med. 2001;111(Suppl 8A):160S–8.
39. Naito Y, Uchiyama K, Kuroda M, Takagi T, Kokura S, Yoshida N, Ichikawa H, Yoshikawa T. Role of pancreatic trypsin in chronic esophagitis induced by gastroduodenal reflux in rats. J Gastroenterol. 2006;41:198–208.
40. Guillem PG. How to make a Barrett esophagus: pathophysiology of columnar metaplasia of the esophagus. Dig Dis Sci. 2005;50:415–24.
41. Kauer WK, Stein HJ. Emerging concepts of bile reflux in the constellation of gastresophageal reflux disease. J Gastrointest Surg. 2010;14 Suppl 1:S9–16.
42. Tanaka K, Fromm D. Effects of bile acid and salicylate on isolated surface and glandular cells of rabbit stomach. Surgery. 1983;93:660–3.
43. Schweitzer EJ, Bass B, Batzri S, Harmon JW. Bile acid accumulation by rabbit esophageal mucosa. Dig Dis Sci. 1986;31:1105–13.
44. Batzri S, Harmon J, Schweitzer EJ, Toles R. Bile acid accumulation in gastric mucosal cells. Proc Soc Exp Biol Med. 1991;197:393–9.

45. Katz P. Review article: the role of non-acid reflux in gastro-esophageal reflux disease. Aliment Pharmacol Ther. 2000;14:1539–51.
46. Chen KH, Mukaisho K, Ling ZQ, Shimomura A, Sugihara H, Hattori T. Association between duodenal contents reflux and squamous cell carcinoma – establishment of an esophageal cancer cell line derived from the metastatic tumor in a rat reflux model. Anticancer Res. 2007;27:175–81.
47. Miwa K, Sahara H, Segawa M, Kinami S, Sato T, Miyazaki I, Hattori T. Reflux of duodenal or gastroduodenal contents induces esophageal carcinoma in rats. Int J Cancer. 1996;67:269–74.
48. Pera M, de Bolos C, Brito MJ, Palacin A, Grande L, Cardesa A, Poulsom R. Duodenal-content reflux into the esophagus leads to expression of Cdx2 and Muc2 in areas of squamous epithelium in rats. J Gastrointest Surg. 2007;11:869–74.
49. Kumagai H, Mukaisho K, Sugihara H, Bamba M, Miyashita T, Miwa K, Hattori T. Cell kinetic study on histogenesis of Barrett's esophagus using rat reflux model. Scand J Gastroenterol. 2003;38:687–92.
50. Miwa K, Segawa M, Takano Y, Matsumoto H, Sahara H, Yagi M, Miyazaki I, Hattori T. Induction of esophageal and forestomach carcinomas in rats by reflux of duodenal contents. Br J Cancer. 1994;70:185–9.
51. Bernstein H, Bernstein C, Payne CM, Dvorakova K, Garewal H. Bile acids as carcinogens in human gastrointestinal cancers. Mutat Res. 2005;589:47–65.
52. Goldman A, Condon A, Adler E, Minella M, Bernstein C, Bernstein H, Dvorak K. Protective effects of glycoursodeoxycholic acid in Barrett's esophagus cells. Dis Esophagus. 2010;23:83–93.
53. Hong J, Behar J, Wands J, Resnick M, Wang LJ, Delellis RA, Lambeth D, Cao W. Bile acid reflux contributes to development of esophageal adenocarcinoma via activation of phosphatidylinositol-specific phospholipase Cgamma2 and NADPH oxidase NOX5-S. Cancer Res. 2010;70:1247–55.
54. Peters CJ, Fitzgerald RC. Systematic review: the application of molecular pathogenesis to prevention and treatment of esophageal adenocarcinoma. Aliment Pharmacol Ther. 2007;25:1253–69.
55. Chang CL, Lao-Sirieix P, Save V, De La Cueva MG, Laskey R, Fitzgerald RC. Retinoic acid induced glandular differentiation of the esophagus. Gut. 2006;56:906–17.
56. Jang TJ, Min SK, Bae JD, Jung KH, Lee JI, Kim JR, Ahn WS. Expression of cyclooxygenase 2, microsomal prostaglandin E synthase 1, and EP receptors is increased in rat esophageal squamous cell dysplasia and Barrett's metaplasia induced by duodenal contents reflux. Gut. 2004;53:27–33.
57. Zhang F, Altorki NK, Wu YC, Soslow RA, Subbaramaiah K, Dannenberg AJ. Duodenal reflux induces cyclooxygenase-2 in the esophageal mucosa of rats: evidence for involvement of bile acids. Gastroenterology. 2001;121:1391–9.
58. Byrne JP, Attwood SE. Duodenogastric reflux and cancer. Hepatogastroenterology. 1999;46:74–85.
59. Ling ZQ, Mukaisho K, Yamamoto H, Chen KH, Asano S, Araki Y, Sugihara H, Mao WM, Hattori T. Initiation of malignancy by duodenal contents reflux and the role of ezrin in developing esophageal squamous cell carcinoma. Cancer Sci. 2010;101:624–30.
60. Tselepis C, Morris C, Wakelin D, Hardy R, Perry I, Luong QT, Harper E, Harrison R, Attwood SE, Jankowski JA. Upregulation of the oncogene c-myc in Barrett's adenocarcinoma: induction of c-myc by acidified bile acid in vitro. Gut. 2003;52:174–80.
61. Osugi H, Fukuhara K, Takada N, Takemura M, Kinoshita H. Reconstructive procedure after distal gastrectomy to prevent remnant gastritis. Hepatogastroenterology. 2004;51:1215–8.
62. Fukuhara K, Osugi H, Takada N, Takemura M, Lee S, Taguchi S, Kaneko M, Tanaka Y, Fujiwara Y, Nishizawa S, Kinoshita H. Correlation between duodenogastric reflux and remnant gastritis after distal gastrectomy. Hepatogastroenterology. 2004;51:1241–4.
63. Hashimoto N, Yasuda T, Inayama M, Ho H, Shinkai M, Kawanishi K, Hirai N, Imano M, Shigeoka H, Imamoto H, Shiozaki H. Duodenogastric reflux after choledochoduodenostomy: evaluation by technetium-99m scintigraphy. Hepatogastroenterology. 2007;54:796–8.
64. Lujan-Mompean JA, Robles-Campos R, Parrilla-Paricio P, Liron-Ruiz R, Torralba-Martinez JA, Cifuentes-Tebar J. Duodenogastric reflux in patients with biliary lithiasis before and after cholecystectomy. Surg Gynecol Obstet. 1993;176:116–8.
65. Mearin F, De Ribot X, Balboa A, Antolin M, Varas MJ, Malagelada JR. Duodenogastric bile reflux and gastrointestinal motility in pathogenesis of functional dyspepsia. Role of cholecystectomy. Dig Dis Sci. 1995;40:1703–9.
66. Perdikis G, Wilson P, Hinder R, Redmond E, Wetscher G, Neary P, Adrian T, Quigley E. Altered antroduodenal motility after cholecystectomy. Am J Surg. 1994;168:609–14; discussion 614–615.
67. Takada K, Hamada Y, Watanabe K, Tanano A, Tokuhara K, Kamiyama Y. Duodenogastric reflux following biliary reconstruction after excision of choledochal cyst. Pediatr Surg Int. 2005;21:1–4.
68. Sobala GM, O'Connor HJ, Dewar EP, King RF, Axon AT, Dixon MF. Bile reflux and intestinal metaplasia in gastric mucosa. J Clin Pathol. 1993;46:235–40.
69. Chen SL, Mo JZ, Cao ZJ, Chen XY, Xiao SD. Effects of bile reflux on gastric mucosal lesions in patients with dyspepsia or chronic gastritis. World J Gastroenterol. 2005;11:2834–7.
70. Ladas SD, Katsogridakis J, Malamou H, Giannopoulou H, Kesse-Elia M, Raptis SA. Helicobacter pylori may induce bile reflux: link between H pylori and bile induced injury to gastric epithelium. Gut. 1996;38:15–8.

71. Murakami M, Sugiyama A, Ota H, Maruta F, Ikeno T, Hayama M, Kumagai T, Okimura Y, Kawasaki S. Duodenogastric reflux and helicobacter pylori infection synergistically increase gastric mucosal cell proliferative activity in mongolian gerbils. Scand J Gastroenterol. 2003;38:370–9.
72. Kawai Y, Tazuma S, Inoue M. Bile acid reflux and possible inhibition of helicobacter pylori infection in subjects without gastric surgery. Dig Dis Sci. 2001;46:1779–83.
73. Mathai E, Arora A, Cafferkey M, Keane CT, O'Morain C. The effect of bile acids on the growth and adherence of Helicobacter pylori. Aliment Pharmacol Ther. 1991;5:653–8.
74. Manifold DK, Anggiansah A, Rowe I, Sanderson JD, Chinyama CN, Owen WJ. Gastro-esophageal reflux and duodenogastric reflux before and after eradication in helicobacter pylori gastritis. Eur J Gastroenterol Hepatol. 2001;13:535–9.
75. Taskin V, Sedele M, Saka O, Kantarceken B. The effect of duodenogastric reflux on helicobacter pylori presence and gastric histopathologic changes. Turk J Gastroenterol. 2003;14:239–42.
76. Hermans D, Sokal EM, Collard JM, Romagnoli R, Buts JP. Primary duodenogastric reflux in children and adolescents. Eur J Pediatr. 2003;162: 598–602.
77. Helsingen NJ. Esophagitis following total gastrectomy: a clinical and experimental study. Acta Chir Scand. 1961;273:1–21.
78. Orlando RC, Bozymski E. Heartburn in pernicious anaemia: a consequence of bile reflux. N Engl J Med. 1973;125:522–3.
79. Palmer E. Subacute erosive (peptic) esophagitis associated with achlorhydria. N Engl J Med. 1960;262:927–9.
80. Fein M, Maroske J, Fuchs KH. Importance of duodenogastric reflux in gastro-esophageal reflux disease. Br J Surg. 2006;93:1475–82.
81. Stein HJ, Feussner H, Kauer W, DeMeester TR, Siewert JR. Alkaline gastresophageal reflux: assessment by ambulatory esophageal aspiration and pH monitoring. Am J Surg. 1994;167:163–8.
82. Vaezi MF, Richter JE. Synergism of acid and duodenogastresophageal reflux in complicated Barrett's esophagus. Surgery. 1995;117:699–704.
83. Gotley DC, Appleton GV, Cooper MJ. Bile acids and trypsin are unimportant in alkaline esophageal reflux. J Clin Gastroenterol. 1992;14:2–7.
84. Attwood SE, Ball CS, Barlow AP, Jenkinson L, Norris TL, Watson A. Role of intragastric and intraesophageal alkalinisation in the genesis of complications in Barrett's columnar lined lower esophagus. Gut. 1993;34:11–5.
85. Caldwell MTPLP, Byrne PJ, Walsh TN, Hennesy TPJ. Ambulatory bile reflux monitoring in Barrett's esophagus. Br J Surg. 1995;82:657–60.
86. Wolfgarten E, Putz B, Holscher AH, Bollschweiler E. Duodeno-gastric-esophageal reflux – what is pathologic? Comparison of patients with Barrett's esophagus and age-matched volunteers. J Gastrointest Surg. 2007;11:479–86.
87. Pfaffenbach B, Hullerum J, Orth KH, Langer M, Stabenow-Lohbauer U, Lux G. Bile and acid reflux in long and short segment Barrett's esophagus, and in reflux disease. Z Gastroenterol. 2000;38: 565–70.
88. Champion G, Richter JE, Vaezi MF, Singh S, Alexander R. Duodenogastresophageal reflux: relationship to pH and importance in Barrett's esophagus. Gastroenterology. 1994;107:747–54.
89. Koek GH, Tack J, Sifrim D, Lerut T, Janssens J. The role of acid and duodenal gastresophageal reflux in symptomatic GERD. Am J Gastroenterol. 2001;96:2033–40.
90. Marshall RE, Anggiansah A, Owen WA, Owen WJ. The relationship between acid and bile reflux and symptoms in gastro-esophageal reflux disease. Gut. 1997;40:182–7.
91. Marshall RE, Anggiansah A, Owen WA, Owen WJ. Investigation of gastro-esophageal reflux in patients with an intact stomach: is esophageal bilirubin monitoring a useful addition to pH monitoring? Scand J Gastroenterol. 2000;35:904–9.
92. Wilmer A, Tack J, Frans E, Dits H, Vanderschueren S, Gevers A, Bobbaers H. Duodenogastresophageal reflux and esophageal mucosal injury in mechanically ventilated patients. Gastroenterology. 1999;116:1293–9.
93. Hak NG, Mostafa M, Salah T, El-Hemaly M, Haleem M, Abd El-Raouf A, Hamdy E. Acid and bile reflux in erosive reflux disease, non-erosive reflux disease and Barrett's esophagus. Hepatogastroenterology. 2008;55:442–7.
94. Xu XR, Li ZS, Zou DW, Xu GM, Ye P, Sun ZX, Wang Q, Zeng YJ. Role of duodenogastresophageal reflux in the pathogenesis of esophageal mucosal injury and gastresophageal reflux symptoms. Can J Gastroenterol. 2006;20:91–4.
95. Jiang M, Chen J, Chen F, Yu J, Liang J, Zhang Y, Ou B. Bile and acid reflux in the pathogenesis of reflux oesophagitis in children. J Paediatr Child Health. 2009;45:64–7.
96. Felix VN, Viebig RG. Simultaneous bilimetry and pHmetry in GERD and Barrett's patients. Hepatogastroenterology. 2005;52:1452–5.
97. Monaco L, Brillantino A, Torelli F, Schettino M, Izzo G, Cosenza A, Di Martino N. Prevalence of bile reflux in gastresophageal reflux disease patients not responsive to proton pump inhibitors. World J Gastroenterol. 2009;15:334–8.
98. Hoffman ITA, Ectors N, De Greef T, Haesendonck N, Tack J. Duodenogastro-esophageal reflux in children with refractory gastro-esophageal reflux disease. J Pediatr. 2007;151:307–11.
99. Tack J, Koek G, Demedts I, Sifrim D, Janssens J. Gastresophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both? Am J Gastroenterol. 2004;99:981–8.

100. Hallberg K, Fandriks L, Strandvik B. Duodenogastric bile reflux is common in cystic fibrosis. J Pediatr Gastroenterol Nutr. 2004;38:312–6.
101. Poelmans J, Feenstra L, Tack J. The role of (duodeno)gastroesophagopharyngeal reflux in unexplained excessive throat phlegm. Dig Dis Sci. 2005;50:824–32.
102. Galli J, Calo L, Agostino S, Cadoni G, Sergi B, Cianci R, Cammarota G. Bile reflux as possible risk factor in laryngopharyngeal inflammatory and neoplastic lesions. Acta Otorhinolaryngol Ital. 2003;23:377–82.
103. Richter JE. Duodenogastric reflux-induced (alkaline) esophagitis. Curr Treat Options Gastroenterol. 2004;7:53–8.
104. Marshall RE, Anggiansah A, Manifold DK, Owen WA, Owen WJ. Effect of omeprazole 20 mg twice daily on duodenogastric and gastro-esophageal bile reflux in Barrett's esophagus. Gut. 1998;43:603–6.
105. Menges M, Muller M, Zeitz M. Increased acid and bile reflux in Barrett's esophagus compared to reflux esophagitis, and effect of proton pump inhibitor therapy. Am J Gastroenterol. 2001;96:331–7.
106. Netzer P, Gut A, Brundler R, Gaia C, Halter F, Inauen W. Influence of pantoprazole on esophageal motility, and bile and acid reflux in patients with oesophagitis. Aliment Pharmacol Ther. 2001;15:1375–84.
107. Xin Y, Dai N, Zhao L, Wang JG, Si JM. The effect of famotidine on gastroesophageal and duodenogastro-esophageal refluxes in critically ill patients. World J Gastroenterol. 2003;9:356–8.
108. Orel R, Brecelj J, Homan M, Heuschkel R. Treatment of esophageal bile reflux in children: the results of a prospective study with omeprazole. J Pediatr Gastroenterol Nutr. 2006;42:376–83.
109. Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology. 2001;120:1588–98.
110. Vaezi MF, Sears R, Richter JE. Placebo-controlled trial of cisapride in postgastrectomy patients with duodenogastresophageal reflux. Dig Dis Sci. 1996;41:754–63.
111. Szarszewski A, Korzon M, Kaminska B, Lass P. Duodenogastric reflux: clinical and therapeutic aspects. Arch Dis Child. 1999;81:16–20.
112. Baxter PS, Maddern GJ. Effect of cisapride on gastroduodenal reflux and gall bladder motility in patients with gallstones. Dig Surg. 1998;15:35–41.
113. Chen SL, Ji JR, Xu P, Cao ZJ, Mo JZ, Fang JY, Xiao SD. Effect of domperidone therapy on nocturnal dyspeptic symptoms of functional dyspepsia patients. World J Gastroenterol. 2010;16:613–7.
114. Fountos A, Chrysos E, Tsiaoussis J, Karkavitsas N, Zoras OJ, Katsamouris A, Xynos E. Duodenogastric reflux after biliary surgery: scintigraphic quantification and improvement with erythromycin. ANZ J Surg. 2003;73:400–3.
115. Koek GH, Sifrim D, Lerut T, Janssens J, Tack J. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-esophageal reflux refractory to proton pump inhibitors. Gut. 2003;52:1397–402.
116. Scudamore HH, Eckstam E, Fencil WJ, Jaramillo CA. Bile reflux gastritis. Am J Gastroenterol. 1973;60:9–22.
117. Meshkinpour H, Elashoff J, Stewart H, Sturdevant RA. Effect of cholestyramine on the symptoms of reflux gastritis: a randomized, double-blind, crossover study. Gastroenterology. 1977;73:441–3.
118. Stefaniwsky AB, Tint G, Speck J, Shefer S, Salen G. Ursodeoxycholic acid treatment of bile reflux gastritis. Gastroenterology. 1985;89:1000–4.
119. Buch KL, Weinstein W, Hill TA, Elashoff JD, Reedy TJ, Ippoliti AF, Tedesco FJ, Singh M. Sucralfate therapy in patients with symptoms of alkaline reflux gastritis. A randomized, double-blind study. Am J Med. 1985;79(suppl 2C):49–54.
120. Fukuhara K, Osugi H, Takada N, Takemura M, Ohmoto Y, Kinoshita H. Quantitative determinations of duodenogastric reflux, prevalence of helicobacter pylori infection, and concentrations of interleukin-8. World J Surg. 2003;27:567–70.
121. Takahashi T, Yoshida M, Kubota T, Otani Y, Saikawa Y, Ishikawa H, Suganuma K, Akatsu Y, Kumai K, Kitajima M. Morphologic analysis of gastresophageal reflux diseases in patients after distal gastrectomy. World J Surg. 2005;29:50–7.
122. Zobolas B, Sakorafas GH, Kouroukli I, Glynatsis M, Peros G, Bramis J. Alkaline reflux gastritis: early and late results of surgery. World J Surg. 2006;30:1043–9.
123. Bonavina L, Incarbone R, Segalin A, Chella B, Peracchia A. Duodeno-gastro-esophageal reflux after gastric surgery: surgical therapy and outcome in 42 consecutive patients. Hepatogastroenterology. 1999;46:92–6.
124. Klingler PJ, Perdikis G, Wilson P, Hinder RA. Indications, technical modalities and results of the duodenal switch operation for pathologic duodenogastric reflux. Hepatogastroenterology. 1999;46:97–102.
125. Stein HJ, Kauer WK, Feussner H, Siewert JR. Bile reflux in benign and malignant Barrett's esophagus: effect of medical acid suppression and nissen fundoplication. J Gastrointest Surg. 1998;2:333–41.
126. Elhak NG, Mostafa M, Salah T, Haleem M. Duodenogastresophageal reflux: results of medical treatment and antireflux surgery. Hepatogastroenterology. 2008;55:120–6.