Chapter 5
Clinical Manifestations

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Abbreviations

BE	Barrett's esophagus
GEPG	Gastroesophageal pressure gradient
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
ICC	Interstitial cells of Cajal
LES	Lower esophageal sphincter
LPR	Laryngopharyngeal reflux
NSAID	Nonsteroidal anti-inflammatory drug
PUD	Peptic ulcer disease
TNF	Tumor necrosis factor

Esophageal Dysmotility

Clinical Features

Esophageal dysmotility in the setting of diabetes is clinically important because it may be associated with delayed transit of meals and orally administered medications to the stomach. As a consequence, esophageal dysmotility may be associated

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with changes in the absorption of oral drugs, including hypoglycemic agents, and the delayed transit of tablets or capsules may lead to increased risk of mucosal ulceration [1]. In addition, symptoms directly related to dysmotility may be severe and can substantially compromise quality of life. These symptoms include heartburn, chest pain, odynophagia, and dysphagia. However, many are asymptomatic and dysmotility is noted as an incidental finding [2]; the clinical impact of asymptomatic esophageal dymotility remains uncertain but could certainly contribute to the development and severity of gastroesophageal reflux disease (GERD) [3]. Many patients with esophageal dysmotility do not have localizing symptoms to the esophagus and describe symptoms that may be interpreted to originate from the stomach. This discrepancy between observed findings and reported symptoms is thought to be related to disordered esophageal perception through afferent pathways affected by autonomic dysfunction [4, 5]. The extent to which these symptoms correlate with abnormalities in GI motility remains to be elucidated [5].

Pathophysiology

Traditionally, esophageal motility disorders were thought to be based primarily on autonomic neuropathy, a known complication of diabetes that can involve any segment of the gastrointestinal tract, including the esophagus [6, 7]. The pathogenesis of upper gastrointestinal dysfunction is now thought to be multifactorial and while it certainly includes autonomic dysfunction impacting on motor and sensory function, it also appears to involve structural and functional changes in interstitial cells of Cajal, alterations in enteric neuroendocrine function, the impacts of a low-grade chronic inflammatory state, visceral hypersensitivity, decreased nitric oxide synthase expression, and changes in nitrergic neurotransmission, as well as mural fibrosis and changes in wall compliance in the setting of microvascular damage [6–9]. For example, distension has been shown to provoke an exaggerated and uncoordinated motor response in diabetes and both autonomic neuropathy and structural changes in the esophageal wall with increased thickening of the mucosal and submucosal layers were thought to contribute [10]. These latter findings, which impact on esophageal wall function, may reflect disturbed remodeling [11]. It is also possible that changes in the central nervous system might contribute—this will certainly be the case if cerebrovascular events have occurred [12].

Clinical Correlations

Prior studies have documented abnormal esophageal manometry in 46–63% of diabetic patients [4, 5]. Gustafsson and colleagues found no difference in the prevalence of dysmotility between males and females or between those with type I or type II diabetes [13]. However, the occurrence of dysmotility does correlate with the

duration of diabetes [1, 13, 14] with the amplitude of esophageal peristaltic waves and the frequency of effective peristalsis being significantly lower in patients with longer duration of diabetes [1]. Of the various complications of diabetes, the only one that has been found to correlate with the presence of esophageal dysmotility is retinopathy [5, 13]. Esophageal dysmotility can occur with, or independent of, diabetic peripheral neuropathy [3, 13] and its relationship with gastroparesis, surprisingly, is also unclear [4, 13]. Though there is limited data, it does not appear that, at least in the short term, poor glycemic control predisposes to esophageal dysmotility [13].

Dysmotility will impair transit [14] and, while such impaired transit has implications for esophageal stasis, it does not appear to be a sensitive marker of generalized diabetic gastroenteropathy [15]; again reflecting the apparently poor correlation between esophageal dysmotility and other gastrointestinal motor disorders in diabetes.

Manometric Findings

A number of abnormalities have been demonstrated on conventional and high-resolution manometry. Of the various findings described, multi-peaked/multiphasic contractions have been the most consistent [5, 13, 16]. Their occurrence has been attributed to disturbed autonomic input to the esophagus with a relative loss of noncholinergic input and a resultant hypersensitivity to acetylcholine [17]. Other findings have included higher intra-bolus pressure and inhibition of contractile activity on repeated swallows on high-resolution manometry [18], impaired amplitude of peristalsis and ineffective peristalsis [1], and a trend toward an increased incidence of primary esophagogastric outflow obstruction [5].

In one of the most detailed studies, Gustafsson and colleagues defined dysmotility as the presence of one or more of the following on manometry [13]:

- Absence of peristaltic contractions (aperistalsis >0%)
- Mean esophageal peristaltic contraction amplitude <30 or >200 mmHg
- >10% simultaneous, non-propulsive peristaltic waves
- Speed of the peristaltic wave <3 or >6 cm/s in the distal esophagus
- Lower esophageal sphincter (LES) resting pressure <10 or >30 mm Hg

Based on these criteria, esophageal dysmotilty was identified in 66% of type I and 61% of type II diabetics among their diabetic population [13].

Conclusions

Though apparently common in diabetes, the clinical significance of esophageal dysmotility is unclear. Often an incidental finding and correlating poorly with both other motility disorders and diabetic complications, its true impact remains to be

defined in prospective studies. Nevertheless, some affected individuals are symptomatic and it also seems likely that the deficits in peristaltic function which seem to be common in diabetes could exacerbate esophageal injury and symptoms related to gastroesophageal reflux.

Gastroesophageal Reflux Disease and Diabetes

Definition and Clinical Presentation

Gastroesophageal reflux disease (GERD) is defined on the basis of characteristic symptoms and/or esophageal mucosal injury associated with the abnormal reflux of gastric contents into the esophagus [19]. Complications of GERD include erosive esophagitis, esophageal stricture, and Barrett's esophagus (BE); the latter being a major risk factor for esophageal adenocarcinoma.

The cardinal symptoms in GERD patients are heartburn and regurgitation. These symptoms may be severe and, thereby, impact substantially on quality of life [20]. There is some evidence that GERD-related symptoms may differ between diabetics and nondiabetics and that atypical manifestations of GERD may be more prevalent among diabetic patients than among GERD sufferers in the general population. For example, dysphagia and globus sensation have been documented to occur more frequently among type II diabetics with GERD [21]. On the other hand, heartburn was more prevalent among nondiabetics suggesting, perhaps, that the presence of autonomic neuropathy in diabetics may prevent the development of hypersensitivity to acid reflux [21]. Altered pain perception resulting from diabetic neuropathy may also account for higher rates of asymptomatic erosive esophagitis among diabetics [22].

Prevalence

The prevalence of gastroesophageal reflux disease (GERD) in the United States and other Western nations has increased steadily over the past 20 years [23]. Given that both GERD and diabetes have increased in prevalence globally over the same time period, there has been considerable interest in a possible causative role for diabetes in the pathogenesis of GERD [22].

However, an examination of the available literature reveals conflicting data on the prevalence of GERD in diabetic patients. Two large population-based studies utilizing, on the one hand, the Norwegian health survey [24] and, on the other, the United Kingdom General Practice Research Database [25] concluded that the prevalence of GERD was not significantly increased in diabetic patients. A cross-sectional survey among patients with type II diabetes from Korea came to similar conclusions and also noted that the occurrence of GERD in diabetes was not associated with autonomic neuropathy, age, or duration of diabetes [26]. Other studies,

in contrast, had suggested that there was a higher prevalence of abnormal acid reflux [27] and GERD symptoms [28–30] among those with diabetes. However, these studies involved selected populations and may not have controlled for obesity, an independent risk factor for GERD [31], as well as diabetes. A cross-sectional study from Japan among 847 patients with type 2 diabetes reported an overall prevalence of GERD of 31.5% and found that younger age was a significant predictive factor [32].

A recent meta-analysis of nine studies (one conducted in America, one in Europe, and seven in Asia) involving 9067 cases and 81,968 controls identified a significant association between diabetes and risk for GERD [33]. As noted in individual studies from China [34], this association was most pronounced in the Asian studies [33] which contrasts with a systematic review based on studies performed in primary care in the United Kingdom which failed to describe this association [35]. In general, the prevalence of GERD increases with age [23], as does the prevalence of type II diabetes; revealing another confounding factor—age. Ethnicity may also be a factor—in the United States, GERD prevalence was 41.5% among urban African Americans with diabetes in comparison to 20.6% among those without diabetes; among those with diabetes, GERD was much more common in men than in women [36].

In contrast to a somewhat inconsistent association with GERD, in general, the association between diabetes and Barrett's esophagus seems more reproducible. Iyer and colleagues found that type II diabetes was associated with Barrett's esophagus independent of obesity, cigarette smoking, and GERD [37], and Drahos and colleagues using the same database found a marginally increased risk for BE in the absence of GERD among those with the metabolic syndrome [38] which of course includes type II diabetes mellitus. This latter observation is somewhat in keeping with the findings of Rubenstein and colleagues who, though noting an inverse relationship between diabetes and BE, described direct correlations between insulin and leptin levels in the serum and BE, suggesting that it was the metabolic syndrome and, not diabetes, that was the link [39]. Interestingly, Drahos and colleagues also found that there was no increased risk for esophageal adenocarcinoma among those with diabetes [38], a finding that was confirmed in a study from Taiwan [40] but not in a study in the Veterans Administration in the USA [41]. In the latter, an association of diabetes with esophageal adenocarcinoma was independent of obesity; these authors also failed to identify an increased risk for GERD, in the absence of adenocarcinoma, in their predominantly male population [41].

In the single study where it was addressed [42], the prevalence of laryngopharyngeal reflux (LPR) was not significantly increased among patients with type 2 diabetes.

Pathophysiology of GERD in Diabetes

Obesity is not only a risk factor for GERD and its complications but also results in anatomical and physiological changes at the gastroesophageal junction that predispose to and perpetuate pathological acid reflux [43, 44]. These include the

development of hiatal hernias, an increase in the gastroesophageal pressure gradient (GEPG), and the induction of transient lower esophageal sphincter relaxations [43, 44]. In addition, diabetes-induced morphodynamic and biomechanical esophageal remodeling (referred to in the prior section on esophageal dysmotility) has also been proposed to predispose to GERD [45]. Though direct correlations have not been made, it seems likely that the high prevalence of esophageal dysmotility [4, 5, 13] and impaired transit [14, 15] reported in diabetes will impair esophageal clearance and, thereby, increase the duration of acid exposure time and promote esophageal injury. Obesity and the metabolic syndrome are also pro-inflammatory disorders and as such could promote carcinogenesis.

A prospective study of diabetic patients with GERD undergoing bariatric surgery showed that, among patients with morbid obesity, there was an inverse relationship between glycemic control and GERD in that very poor glycemic control correlated with less severe heartburn and lower esophageal acid exposure [46]. Those with poor glycemic control were less likely to have a hiatal hernia [46]. One could also propose that alterations in visceral sensitivity related to the effects of hyperglycemia on neural sensitization might lead to a decrease in the perception of heartburn in patients with very poor glycemic control.

Acute erosive esophagitis has been reported as a complication of severe diabetic ketoacidosis in a child; presumably resulting from repeated vomiting [47].

Conclusions

While a pathophysiological basis for the development of GERD in diabetes can be proposed, the true prevalence of GERD in diabetes remains unclear [2]. Obesity, advancing age, and ethnicity as well as other factors confound the interpretation of many studies but, overall, the increase risk for GERD in diabetes over the general population seems to be small. Nevertheless, there does seem to be a true association between diabetes and Barrett's esophagus, if not esophageal adenocarcinoma.

Esophageal Candidiasis

The prevalence of candida esophagitis is changing in an era of highly active antiretroviral therapy (HAART) and is becoming more prevalent in today's rapidly aging society among nonhuman immunodeficiency virus (HIV)-infected patients. Traditionally, individuals with diabetes were thought to be at higher risk for oral or esophageal candidiasis caused by *Candida albicans*. Poor glycemic control was thought to create favorable conditions for the yeast to grow, increasing the risk of fungal infection. Esophageal candidiasis symptoms include odynophagia, dysphagia with solids, avoidance of oral intake, epigastric pain, heartburn, and nausea [2]. The presence of odynophagia in combination with oral thrush is highly predictive of

esophageal involvement. When severe, esophageal candidiasis may result in complications such as hemorrhage, stenosis, and esophagotracheal fistula. The severity of candida esophagitis may be predicted based on presenting symptoms. Thus, Asayama and colleagues found that odynophagia was an independent predictor of severe (Kodsi endoscopic grades III/IV) candida esophagitis in their study of over 1800 patients. Such strategies may help to identify those at greatest risk for this opportunistic infection and thus avoid the costs involved when employed in unselected populations while ensuring prompt diagnosis and treatment of high-risk individuals [48].

Despite long-held opinion and pathophysiological plausibility, the true risk for esophageal candidiasis in diabetes remains unclear. For example, a recent endoscopic survey of esophagitis and associated risk factors in over 80,000 patients with or without HIV infection failed to define a significant association with diabetes mellitus [49]. It is possible that the past association owed much to poor diabetic control.

Diabetic Gastroparesis

Definition and Clinical Presentation

Gastroparesis is characterized by abnormally delayed gastric emptying and symptoms in the absence of mechanical obstruction [50]. Gastroparesis can occur as a complication of virtually any disease process that has the capacity to induce neuromuscular dysfunction and is, therefore, linked to host of neurological, inflammatory, and endocrinological disorders [51–53]. The most common etiologies of gastroparesis are idiopathic, diabetes, and surgical damage to the vagal nerves and stomach [51]. Gastroparesis is one of the most well-studied and investigated gastrointestinal complications of diabetes mellitus.

The presentation of diabetic gastroparesis is highly variable and extends all the way from being asymptomatic, in the face of a demonstrated delay in gastric emptying rate, to being unable to tolerate any oral intake due to intractable nausea and vomiting.

There is relatively little information on the natural history of the disease. While clinical experience suggests that symptoms and their impact are progressive with relatively minimal symptoms early in the course of the disease, one study from the Adelaide group that examined the clinical course of gastroparesis over a 12-year period found little evidence for progression in either symptoms or gastric emptying delay over this time period [54]. A subsequent study from the same groups over a 25-year period also described a favorable prognosis with gastroparesis not being associated with increased mortality [55]. The National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Consortium followed patients with type 1 and type 2 diabetes and gastroparesis for 4 years and noted, first, that at baseline symptoms were similar in both groups despite the fact that gastric emptying

delay was greater and diabetic control inferior in type 1 patients. Second, symptoms improved in type 2 patients but not in type 1 patients, despite intensive therapy [56]. These latter observations are more reflective of the tertiary referral experience mentioned above and underscore, yet again, the disparity between studies performed in such centers and in the community. Referral bias with a concentration of the most severely affected patients with multiple comorbidities in referral centers may account for our negative impression of the outlook for those diabetics affected by gastroparesis. Typical symptoms include nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal pain or discomfort [50, 57, 58]. Nausea is very common, occurring in virtually all symptomatic patients and may be especially distressing and impact very negatively on quality of life [59]. The problem with these symptoms is, first, their non-specificity—a similar constellation of symptoms may be experienced by those with gastroesophageal reflux disease, peptic ulcer disease, functional dyspepsia, and irritable bowel syndrome to name but a few. Most challenging is the distinction between functional dyspepsia, a very common disorder in the general population [60], and gastroparesis; they share a virtually identical symptomatology and anywhere from 25–30% of patients with functional dyspepsia will demonstrate an, albeit mild, delay in gastric emptying [60–63]. The second problem lies in the relatively poor predictive value of these symptoms for delayed gastric emptying, or, indeed, any other disorder of gastric neuromuscular function [50]. Thus, rapid emptying may result in similar symptoms and gastric retention may be asymptomatic in others, possibly due to afferent dysfunction consequent on vagal denervation [64]. Of the various symptoms listed above, early satiety and postprandial fullness are not only common but seem to correlate well with gastric emptying delay and results of a water load test [65].

Psychological distress is common among subjects with diabetic gastroparesis, appears to be equally common and severe in diabetic and idiopathic gastroparesis, and is a major driver of symptom severity regardless of gastric emptying rate [66]. This observation should encourage great care in the assessment of symptoms in this patient population and, in particular, promote restraint in proposing therapeutic strategies that seek to promote gastric emptying. Not surprisingly, comorbid depression, as well as pain as a prominent symptom, is a poor prognostic indicator [67].

In a study comparing symptoms between those with diabetic and idiopathic gastroparesis, vomiting alone was more prevalent (and more severe) among those with diabetic gastroparesis; symptom severity was otherwise similar between to two groups [59].

The other major clinical issue is the impact of gastroparesis on diabetic control and nutrition. Relationships between blood sugar levels and gastric emptying are complex. On the one hand, taking insulin in conjunction with a meal that is then not emptied will result in hypoglycemia; conversely, hyperglycemia delays gastric emptying [68]. Diabetic patients, therefore, associate episodes of gastroparesis with both hypo- and hyperglycemia [69]. Protracted nausea and vomiting will also disrupt fluid and electrolyte balance—it is no surprise, therefore, that severe exacerbations of gastroparesis are often associated with diabetic ketoacidosis and precipitate recurrent hospital admissions. Caloric intake is also compromised and deficiencies in essential minerals and vitamins will ensue [70].

Prevalence

The prevalence of gastroparesis is difficult to estimate due to the aforementioned weak correlation between symptoms associated with gastroparesis (nausea, vomiting, postprandial fullness, early satiety, bloating, and abdominal pain) and gastric emptying as well as their non-specificity [60–62]. In addition, it is not clear what proportion of diabetic patients with gastroparesis actually seek health care and undergo formal testing of gastric emptying rate [71]. Most studies on the epidemiology of gastroparesis have come from tertiary referral centers utilizing hospital-based databases rather than being based on the general population; not surprisingly, reports from tertiary academic medical centers report high prevalence rates for gastroparesis approximating 40% for type 1 diabetics and ranging from 10 to 20% for type 2 diabetics (10–20%), which is expected to be much higher than the general population [50, 72]. Gastroparesis is, indeed, relatively rare in the general population.

In the community-based study from Olmsted County, Minnesota, USA, the age-adjusted annual incidence of gastroparesis, defined as typical symptoms for more than 3 months and delayed gastric emptying by standard scintigraphy, was 2.4 per 100,000 for men and 9.8 per 100,000 for women [71]. One plausible explanation for the fourfold gender difference is that gastric emptying is, on average, slower in females [73]. Animal studies suggest that diabetes affects the enteric nervous system and, particularly, nitrergic nerves, to a greater extent in females than in males which may also contribute to the greater vulnerability of females to diabetic gastric dysfunction [74]. In a second study from Olmsted County, the cumulative rates of gastroparesis over a 10-year time period was 4.8% in type I diabetes, 1% in type 2 diabetes, and 0.1% among nondiabetic individuals in the general population [75]. The risk of developing gastroparesis among subjects with type 1 DM was, accordingly, increased 30-fold, in comparison to eightfold, relative to age- and sex-matched controls, among those with type 2 diabetes [75]. The incidence of gastroparesis, in diabetes, increases with age and duration of diabetes [69].

The economic impact of gastroparesis-related hospitalizations is significant and on the increase. In the United States, hospitalizations with gastroparesis as the primary diagnosis increased by 158% between 1995 and 2004 [76].

Pathophysiology

In addition to the long-established role of autonomic neuropathy, the pathophysiology of diabetic gastroparesis has recently been shown to be associated with defects at a cellular level in the gastric neuromuscular apparatus. Innovative endoscopic techniques now permit biopsies of gastric muscle and permit the identification of myenteric neurons and interstitial cells of Cajal [77]. This has opened the way to detailed studies of gastric neuromuscular pathology and ultrastructure in gastroparesis. Among the most frequently described abnormalities is damage to, or loss of, interstitial cells of Cajal (ICCs) in the stomach associated with an increase in CD45

and CD68 immunoreactivity, suggesting that cell loss might be a result of inflammation [78]; a process that may be a consequence of loss of anti-inflammatory macrophages [79] and could be mediated by the pro-inflammatory cytokine tumor necrosis α (TNFα) [80]. Though ICC loss occurs in both idiopathic and diabetic gastroparesis, there are differences between the ultrastructure of smooth muscle and nerve cells between these patient groups [81]. Furthermore, loss of ICCs has been shown to correlate with gastric emptying delay but not symptoms, with the latter being more closely linked to the presence of an immune infiltrate in the myenteric plexus [82]. Nitrergic neurons are also affected in diabetic gastroparesis [83–86]; a defect that may have a genetic basic in some subjects [86]. From a therapeutic point of view, it is interesting to note that both insulin [85] and the anti-inflammatory cytokine inteleukin-10 have been shown, in separate studies, to restore ICCs and normalize gastric electrical activity and emptying in an animal model of diabetes [87].

Very recently, there has been considerable interest in the contribution of pyloric dysfunction to gastroparesis and gastroparesis-type symptoms in diabetes. This will be explored further in Chap. 7.

Accelerated Gastric Emptying

Rapid gastric emptying, also known as the dumping syndrome, is associated with an accelerated passage of undigested food into the small intestine [88]. It may occur as a consequence of various surgical procedures in the upper gastrointestinal tract but has also been described in association with type 2 diabetes [89–91], functional dyspepsia, autonomic dysfunction, and gastrin-secreting tumors [88]. The usual symptoms include abdominal discomfort, nausea with or without vomiting, in addition to diarrhea, sweating, abdominal cramps, and dizziness. Symptoms are, therefore, often indistinguishable from those of delayed gastric emptying, which makes a diagnosis on the basis of symptoms alone difficult [50, 72, 89–91]. However, in type 2 diabetes, in contrast to nondiabetics, accelerated gastric emptying has been associated with hyper- and not hypoglycemia [91]; experimental studies have demonstrated a hyperglycemia-mediated increase in ICCs [92]. As the therapeutic approach will be so different, it is critical to define emptying rate by scintigraphy before initiating prokinetic agents, for example.

Conclusions

Upper gastrointestinal symptoms are common in diabetes [93, 94], especially among those with poor control and complication [94, 95]. In some, these symptoms may occur in the context of delayed gastric emptying. While gastroparesis is relatively rare among diabetics studied in the community, it looms large as a clinical problem among those diabetics seen in referral centers. Several factors may drive this

discrepancy—referral bias, psychological comorbidity, more severe and complicated diabetes, and more severe gastrointestinal distress. Symptoms associated with gastroparesis are nonspecific, overlap with other disease entities and syndromes, and correlate poorly with gastric emptying rate. For some, these symptoms are debilitating and impact negatively on glycemic control and nutritional status. Recent work on the pathophysiology of diabetic gastroparesis has shifted from an emphasis on autonomic dysfunction and focused instead on the gastric neuromuscular apparatus and resulted in novel insights of diagnostic and therapeutic import [96].

Peptic Ulcer Disease (PUD)

Definition and Clinical Presentation

Peptic ulcers are usually located in the stomach or proximal duodenum and result from acid peptic injury and mucosal breaches that reach the submucosa. Typical symptoms include epigastric pain, nausea, and vomiting and both duodenal and gastric ulcers may be complicated by hemorrhage, perforation, and fibrosis with the development of gastric outlet obstruction. While it is theoretically possible that autonomic dysfunction with loss of afferent input from the gut could alter or, indeed, reduce symptoms related to PUD in diabetes, there is little data to support this.

Prevalence

In the general population, the lifetime prevalence of PUD has been estimated to be about 5–10% with an incidence rate of 0.1–0.3% per year [97]. However, the prevalence and incidence of PUD are decreasing in the West due to a declining prevalence of *Helicobacter pylori* and changes in other environmental factors, such as cigarette smoking [97]. Along with *H. pylori*, the use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is the main risk factor for the development of PUD and its complications [98].

The relationship between diabetes and peptic ulcer disease, in general, is unclear; one report from Japan in 2002 suggested that the prevalence of peptic ulcer disease in asymptomatic diabetics was between 5.3 and 7.3% [99]; whether diabetes, per se, is a risk factor for the development of PUD in the first instance has not been established. It does appear, however, that diabetes increases the risk for bleeding from peptic ulcers [100]. Furthermore, diabetes is also associated with increased rates of morbidity (increased by 43.3% in one meta-analysis based on 19 individual studies [101]) and mortality (30-day mortality increased by 44.2% in the same meta-analysis [101]) among those with PUD who suffer an upper gastrointestinal hemorrhage [101, 102]. Mortality for those who suffer another complication of PUD, perforation, is also increased [103].

The pathophysiology of peptic ulcer disease and its complications in diabetes are not well understood. Prevalence rates of Helicobacter pylori appear to be increased in type 2 but not type 1 diabetes [104]. In animal studies, diabetic rats displayed delayed healing of gastric ulcers and an increased gastric mucosal susceptibility to stress- and NSAID-induced injury associated with an increased release of pro-inflammatory cytokines and an attenuation of angiogenesis [105, 106]. Diabetic microangiopathy could, thereby, be seen to contribute not only to the assault on mucosal integrity but also to more severe ulcer disease and an inability to halt bleeding [105, 106].

References

1. Kinekawa F, Kubo F, Matsuda K, Kobayashi M, Furuta Y, Fujita Y, et al. Esophageal function worsens with long duration of diabetes. J Gastroenterol. 2008;43:338–44.
2. Boland BS, Edelman SV, Wolosin JD. Gastrointestinal complications of diabetes. Endocrinol Metab Clin N Am. 2013;42:809–32.
3. Horgan JH, Doyle JS. A comparative study of esophageal motility in diabetics with neuropathy. Chest. 1971;6:170–4.
4. Faraj J, Melander O, Sundkvist G, Olsson R, Thorsson O, Ekberg O, et al. Oesophageal dysmotility, delayed gastric emptying and gastrointestinal symptoms in patients with diabetes mellitus. Diabet Med. 2007;24:1235–9.
5. George NS, Rangan V, Geng Z, Khan F, Kichler A, Gabbard S, et al. Distribution of esophageal motor disorders in diabetic patients with dysphagia. J Clin Gastroenterol. 2017;51:890–5.
6. Gatopoulou A, Papanas N, Maltezos E. Diabetic gastrointestinal autonomic neuropathy: current status and new achievements for everyday clinical practice. Eur J Intern Med. 2012;23:499–505.
7. Beaumont H, Boeckxstaens G. Recent developments in esophageal motor disorders. Curr Opin Gastroenterol. 2007;23:416–21.
8. Zhao J-B, Frøkjær JB, Drewes AM, Ejskjaer N. Upper gastrointestinal sensory-motor dysfunction in diabetes mellitus. World J Gastroenterol. 2006;12:2846–57.
9. Zeng YJ, Yang J, Zhao JB, Liao DH, Zhang EP, Gregersen HA, et al. Morphologic and biomechanical changes of rat oesophagus in experimental diabetes. World J Gastroenterol. 2004;10:2519–23.
10. Frøkjaer JB, Brock C, Brun J, Simren M, Dimcevski G, Funch-Jensen P, et al. Esophageal distension parameters as potential biomarkers of impaired gastrointestinal function in diabetes patients. Neurogastroenterol Motil. 2012;24:1016–e544.
11. Frokjaer JB, Andersen SD, Ejskjaer N, Funch-Jensen P, Drewes AM, Gregersen H. Impaired contractility and remodeling of the upper gastrointestinal tract in diabetes mellitus type-1. World J Gastroenterol. 2007;13(36):4881–90.
12. Drewes AM, Søfteland E, Dimcevski G, Farmer AD, Brock C, Frøkjær JB, et al. Brain changes in diabetes mellitus patients with gastrointestinal symptoms. World J Diabetes. 2016;7:14–26.
13. Gustafsson RJ, Littorin B, Berntorp K, Frid A, Thorsson O, Olsson R, et al. Esophageal dysmotility is more common than gastroparesis in diabetes mellitus and is associated with getinopathy. Rev Diabet Stud. 2011;8:268–75.
14. Holloway RH, Tippett MD, Horowitz M, Maddox AF, Moten J, Russo A. Relationship between esophageal motility and transit in patients with type I diabetes mellitus. Am J Gastroenterol. 1999;94:3150–7.

15. Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJ. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. Eur J Nucl Med. 1991;18:229–34.
16. Jorge JX, Panão EA, Simões MA, Borges CI, Delgado FJ, Coelho AC, et al. Esophageal body motility in people with diabetes: comparison with non-diabetic healthy individuals. Diabetes Res Clin Pract. 2012;97:77–81.
17. Loo FD, Dodds WJ, Soergel KH, Arndorfer RC, Helm JF, Hogan WJ. Multipeaked esophageal peristaltic pressure waves in patients with diabetic neuropathy. Gastroenterology. 1985;88:485–91.
18. Roman S, Marjoux S, Thivolet C, Mion F. Oesophageal function assessed by high-resolution manometry in patients with diabetes and inadequate glycaemic control. Diabet Med. 2014;31:1452–9.
19. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–20.
20. Revicki DA, Wood M, Maton PN, Sorensen S. The impact of gastroesophageal reflux disease on health-related quality of life. Am J Med. 1998;104:252–8.
21. Promberger R, Lenglinger J, Riedl O, Seebacher G, Eilenberg W, Ott J, et al. Gastro-oesophageal reflux disease in type 2 diabetics: symptom load and pathophysiologic aspects—a retro-pro study. BMC Gastroenterol. 2013;13:132.
22. Punjabi P, Hira A, Prasad S, Wang X, Chokhavatia S. Review of gastroesophageal reflux disease (GERD) in the diabetic patient. J Diabetes. 2015;7:599–609.
23. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63:871–80.
24. Jansson C, Nordenstedt H, Wallander MA, Johansson S, Johnsen R, Hveem K, et al. Severe symptoms of gastro-oesophageal reflux disease are associated with cardiovascular disease and other gastrointestinal symptoms, but not diabetes: a population-based study. Aliment Pharmacol Ther. 2008;27:58–65.
25. Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Graffner H, Dent J. Natural history of gastro-oesophageal reflux disease diagnosed in general practice. Aliment Pharmacol Ther. 2004;20:751–60.
26. Ha JO, Lee TH, Lee CW, Park JY, Choi SH, Lee JS, et al. Prevalence and risk factors of gastroesophageal reflux disease in patients with type 2 diabetes mellitus. Diabetes Metab J. 2016;40:297–307.
27. Lluch I, Ascaso JF, Mora F, Minguez M, Pena A, Hernandez A, et al. Gastroesophageal reflux in diabetes mellitus. Am J Gastroenterol. 1999;94:919–24.
28. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Sato T, Haruna Y, et al. Gastroesophageal reflux disease related to diabetes: analysis of 241 cases with type 2 diabetes mellitus. J Gastroenterol Hepatol. 2004;19:258–65.
29. Moraes-Filho JPP, Navarro-Rodriguez T, Eisig JN, Barbuti RC, Chinzon D, et al. Comorbidities are frequent in patients with gastroesophageal reflux disease in a tertiary health care hospital. Clinics. 2009;64:785–90.
30. Hirata A, Kishida K, Nakatsuji H, Inoue K, Hiuge-Shimizu A, Funahashi T, et al. High prevalence of gastroesophageal reflux symptoms in type 2 diabetics with hypoadiponectinemia and metabolic syndrome. Nutr Metab (Lond). 2012;9:4.
31. El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. Am J Gastroenterol. 2005;100:1243–50.
32. Ikeda Y, Furukawa S, Sakai T, Niiya T, Miyaoka H, Miyake T, Yamamoto S, et al. Age and prevalence of esophageal reflux disease in Japanese patients with type 2 diabetes mellitus: the Dogo study. Dig Dis Sci. 2016;61:3530–6.
33. Sun X-M, Tan JC, Zhu Y, Lin L. Association between diabetes mellitus and gastroesophageal reflux disease: a meta-analysis. World J Gastroenterol. 2015;21:3085–92.
34. Sun H, Yi L, Wu P, Li Y, Luo B, Xu S. Prevalence of gastroesophageal reflux disease in type II diabetes mellitus. Gastroenterol Res Pract. 2014;2014:601571.

35. El-Serag H, Hill C, Jones BR. Systematic review: the epidemiology of gastro-oesophageal reflux in primary care, using the UK General Practice Database. Aliment Pharmacol Ther. 2009;29:470–80.
36. Natalini J, Palit A, Sankineni A, Friedenberg FK. Diabetes mellitus is an independent risk for gastroesophageal reflux disease among urban African Americans. Dis Esophagus. 2015;28:405–11.
37. Iyer PG, Borah BJ, Heien HC, Das A, Cooper GS, Chak A. Association of Barrett's esophagus with type II diabetes mellitus: results from a large population-based case-control study. Clin Gastroenterol Hepatol. 2013;11:1108–14.
38. Drahos J, Li L, Jick SS, Cook MB. Metabolic syndrome in relation to Barrett's esophagus and esophageal adenocarcinoma: results from a large population-based case-control study in the Clinical Practice Research Data link. Cancer Epidemiol. 2016;42:9–14.
39. Rubenstein JH, Morgenstern H, McConell D, Scheiman JM, Schoenfeld P, Appelman H, et al. Associations of diabetes mellitus, insulin, leptin, and ghrelin with gastroesophageal reflux and Barrett's esophagus. Gastroenterology. 2013;145:1237–44.
40. Cheng KC, Chen YL, Lai SW, Tsai PY, Sung FC. Risk of esophagus cancer in diabetes mellitus: a population-based case-control study in Taiwan. BMC Gastroenterol. 2012;12:177.
41. Dixon JL, Copeland LA, Zeber JE, MacCarthy AA, Reznik SI, Smythe WR, et al. Association between diabetes and esophageal cancer, independent of obesity, in the United States Veterans Affairs population. Dis Esophagus. 2016;29:747–51.
42. Hamdan AL, Jabbour J, Barazi R, Korban Z, Azar ST. Prevalence of laryngopharyngeal reflux disease in patients with diabetes mellitus. J Voice. 2013;27:495–9.
43. Lee Y, McColl KEL. Pathophysiology of gastroesophageal reflux disease. Best Pract Res Clin Gastroenterol. 2013;27:339–51.
44. Fornari F, Madalosso CA, Farré R, Gurski RR, Thiesen V, Callegari-Jacques SM. The role of gastro-oesophageal pressure gradient and sliding hiatal hernia on pathological gastro-oesophageal reflux in severely obese patients. Eur J Gastroenterol Hepatol. 2010;22:404–11.
45. Zhao J, Gregersen H. Diabetes-induced mechanophysiological changes in the esophagus. Ann N Y Acad Sci. 2016;1380:139–54.
46. Lauffer A, Forcelini CM, Ruas LO, Madalosso CA, Fornari F. Gastroesophageal reflux disease is inversely related with glycemic control in morbidly obese patients. Obes Surg. 2011;21:864–70.
47. Uysal S, Kerur B, Shapiro JM, Snelling LK, Quintos JB. Acute erosive esophagitis as a rare complication of severe pediatric diabetes ketoacidosis. J Pediatr Gastroenterol Nutr. 2016;62:e38–9.
48. Asayama N, Nagata N, Shimbo T, Nishimura S, Igari T, Akiyama J, et al. Relationship between clinical factors and severity of esophageal candidiasis according to Kodsis classification. Dis Esophagus. 2013;27:214–9.
49. Takahashi Y, Nagata N, Shimbo T, Nishijima T, Watanabe K, Aoki T, et al. Long-term trends in esophageal candidiasis prevalence and associated risk factors with or without HIV infection: lessons from an endoscopic study of 80,219 patients. PLoS One. 2015;10:e0133589.
50. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of Gastroenterology. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2012;108:18–37.
51. Khoo J, Rayner CK, Jones KL, Horowitz M. Pathophysiology and management of gastroparesis. Expert Rev Gastroenterol Hepatol. 2009;3:167–81.
52. Heetun Z, Quigley EMM. Gastroparesis and Parkinson's disease: a systematic review. Parkinsonism Relat Disord. 2012;18:433–40.
53. Quigley EM. Other forms of gastroparesis: postsurgical, Parkinson, other neurologic diseases, connective tissue disorders. Gastroenterol Clin N Am. 2015;44:69–81.
54. Jones KL, Russo A, Berry MK, Stevens JE, Wishart JM, Horowitz M. A longitudinal study of gastric emptying and upper gastrointestinal symptoms in patients with diabetes mellitus. Am J Med. 2002;113:449–55.

55. Chang J, Rayner CK, Jones KL, Horowitz M. Prognosis of diabetic gastroparesis—a 25-year evaluation. Diabet Med. 2013;30:e185–8.
56. Koch KL, Hasler WL, Yates KP, Parkman HP, Pasricha PJ, Calles-Escandon J, et al. Baseline features and differences in 48 week clinical outcomes in patients with gastroparesis and type 1 vs type 2 diabetes. Neurogastroenterol Motil. 2016;28:1001–15.
57. Vanormelingen C, Tack J, Andrews CN. Diabetic gastroparesis. Br Med Bull. 2013;105:213–30.
58. Bouras EP, Vazquez Roque MI, Aranda-Michel J. Gastroparesis. Nutr Clin Pract. 2013;28:437–47.
59. Parkman HP, Hallinan EK, Hasler WL, Farrugia G, Koch KL, Calles J, et al. Nausea and vomiting in gastroparesis: similarities and differences in idiopathic and diabetic gastroparesis. Neurogastroenterol Motil. 2016;28:1902–14.
60. Koduru P, Irani M, Quigley EMM. Definition, pathogenesis and management of that cursed dyspepsia. Clin Gastroenterol Hepatol. 2017. https://doi.org/10.1016/j.cgh.2017.09.002. [epub ahead of print].
61. Talley NJ, 3rd Locke GR, Lahr BD, Zinsmeister AR, Tougas G, Ligozio G, et al. Functional dyspepsia, delayed gastric emptying, and impaired quality of life. Gut. 2006;55:933–9.
62. Chang J, Rayner CK, Jones KL, Horowitz M. Diabetic gastroparesis-backwards and forwards. J Gastroenterol Hepatol. 2011;26:46–57.
63. Stanghellini V, Tack J. Gastroparesis: separate entity or just a part of dyspepsia? Gut. 2014;63:1972–8.
64. Shin AS, Camilleri M. Diagnostic assessment of diabetic gastroparesis. Diabetes. 2013;62:2667–73.
65. Parkman HP, Hallinan EK, Hasler WL, Farrugia G, Koch KL, Nguyen L, et al. Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. Neurogastroenterol Motil. 2017;29. https://doi.org/10.1111/nmo.12981. [epub ahead of print].
66. Hasler WL, Parkman HP, Wilson LA, Pasricha PJ, Koch KL, Abell TL, et al. Psychological dysfunction is associated with symptom severity but not disease etiology or degree of gastric retention in patients with gastroparesis. Am J Gastroenterol. 2010;105:2357–67.
67. Pasricha PJ, Yates KP, Nguyen L, Clarke J, Abell TL, Farrugia G, et al. Outcomes and factors associated with reduced symptoms in patients with gastroparesis. Gastroenterology. 2015;149:1762–74.
68. Chang J, Rayner CK, Jones KL, Horowitz M. Diabetic gastroparesis and its impact on glycemia. Endocrinol Metab Clin N Am. 2010;39:745–62.
69. Homko C, Siraj ES, Parkman HP. The impact of gastroparesis on diabetes control: patient perceptions. J Diabetes Complicat. 2016;30:826–9.
70. Parkman HP, Yates KP, Hasler WL, Nguyan L, Pasricha PJ, Snape WJ, et al. Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. Gastroenterology. 2011;141:486–98.
71. Jung HK, Choung RS, 3rd Locke GR, Schleck CD, Zinsmeister AR, Szarka LA, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. Gastroenterology. 2009;136:1225–33.
72. Camilleri M, Bharucha AE, Farrugia G. Epidemiology, mechanisms, and management of diabeticgastroparesis. Clin Gastroenterol Hepatol. 2011;9:5–12.
73. Parkman HP, Yates K, Hasler WL, Nguyen L, Pasricha PJ, Snape WJ, et al. Clinical features of idiopathic gastroparesis vary with sex, bodymass, symptom onset, delay in gastric emptying, and gastroparesis severity. Gastroenterology. 2011;140:101–15.
74. Gangula PR, Maner WL, Micci MA, Garfield RE, Pasricha PJ. Diabetes induces sex-dependent changes in neuronal nitric oxide synthase dimerization and function in the rat gastric antrum. Am J Physiol Gastrointest Liver Physiol. 2007;292:G725–33.
75. Choung RS, 3rd Locke GR, Schleck CD, Zinsmeister AR, 3rd Melton LJ, Talley NJ. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. Am J Gastroenterol. 2012;107:82–8.

76. Wang YR, Fisher RS, Parkman HP. Gastroparesis-related hospitalizations in the United States: trends, characteristics, and outcomes, 1995-2004. Am J Gastroenterol. 2008;103:313–22.
77. Rajan E, Gostout CJ, Wong Kee Song LM, Szarka LA, Kashyap PC, Smyrk TC, et al. Innovative gastric endoscopic muscle biopsy to identify all cell types, including myenteric neurons and interstitial cells of Cajal in patients with idiopathic gastroparesis: a feasibility study (with video). Gastrointest Endosc. 2016;84:512–7.
78. Grover M, Farrugia G, Lurken MS, Bernard CE, Faussone-Pellegrini MS, Smyrk TC, et al. Cellular changes in diabetic and idiopathic gastroparesis. Gastroenterology. 2011;140:1575–85.
79. Grover M, Bernard CE, Pasricha PJ, Parkman HP, Gibbons SJ, Tonascia J, et al. Diabetic and idiopathic gastroparesis is associated with loss of CD206-positive macrophages in the gastric antrum. Neurogastroenterol Motil. 2017;29. https://doi.org/10.1111/nmo.13018. [epub ahead of print].
80. Eisenman ST, Gibbons SJ, Verhulst PJ, Cipriani G, Saur D, Farrugia G. Tumor necrosis factor alpha derived from classically activated "M1" macrophages reduces interstitial cell of Cajal numbers. Neurogastroenterol Motil. 2017;29. https://doi.org/10.1111/nmo.12984. [epub ahead of print].
81. Faussone-Pellegrini MS, Grover M, Pasricha PJ, Bernard CE, Lurken MS, Smyrk TC, et al. Ultrastructural differences between diabetic and idiopathic gastroparesis. J Cell Mol Med. 2012;16:1573–81.
82. Grover M, Bernard CE, Pasricha PJ, Lurken MS, Faussone-Pellegrini MS, Smyrk TC, et al. Clinical-histological associations in gastroparesis: results from the Gastroparesis Clinical Research Consortium. Neurogastroenterol Motil. 2012;24:531–9.
83. Rivera LR, Poole DP, Thacker M, Furness JB. The involvement of nitric oxide synthase neurons in enteric neuropathies. Neurogastroenterol Motil. 2011;23:980–8.
84. Ordog T, Takayama I, Cheung WK. Remodeling of networks of interstitial cells of Cajal in a murine model of diabetic gastroparesis. Diabetes. 2000;49:1731–9.
85. Watkins CC, Sawa A, Jaffrey S. Insulin restores neuronal nitric oxide synthase expression and function that is lost in diabetic gastropathy. J Clin Invest. 2000;106:373–84.
86. Gibbons SJ, Grover M, Choi KM, Wadhwa A, Zubair A, Wilson LA, Wu Y, et al. Repeat polymorphisms in the Homo sapiens heme oxygenase-1 gene in diabetic and idiopathic gastroparesis. PLoS One. 2017;12:e0187772.
87. Choi KM, Gibbons SJ, Sha L, Beyder A, Verhulst PJ, Cipriani G, et al. Interleukin 10 restores gastric emptying, electrical activity, and interstitial cells of Cajal networks in diabetic mice. Cell Mol Gastroenterol Hepatol. 2016;2:454–67.
88. Balan K, Sonoda LI, Seshadri N, Solanki C, Middleton S. Clinical significance of scintigraphic rapid gastric emptying. Nucl Med Commun. 2011;32:1185–9.
89. Phillips WT, Schwartz JG, McMahan CA. Rapid gastric emptying of an oral glucose solution in type 2 diabetic patients. J Nucl Med. 1992;33:1496–500.
90. Frank JW, Saslow SB, Camilleri M, Thomforde GM, Dinneen S, Rizza RA. Mechanism of accelerated gastric emptying of liquids and hyperglycemia in patients with type II diabetes mellitus. Gastroenterology. 1995;109:755–65.
91. Bharucha AE, Kudva Y, Basu A, Camilleri M, Low PA, Vella A, et al. Relationship between glycemic control and gastric emptying in poorly controlled type 2 diabetes. Clin Gastroenterol Hepatol. 2015;13:466–76.
92. Hayashi Y, Toyomasu Y, Saravanaperumal SA, Bardsley MR, Smestad JA, Lorincz A, et al. Hyperglycemia increases interstitial cells of Cajal via MAPK1 and MAPK3 signaling to ETV1 and KIT, leading to rapid gastric emptying. Gastroenterology. 2017;153:521–35.
93. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. Arch Intern Med. 2001;161:1989–96.

94. Hammer J, Howell S, Bytzer P, Horowitz M, Talley NJ. Symptom clustering in subjects with and without diabetes mellitus: a population-based study of 15,000 Australian adults. Am J Gastroenterol. 2003;98:391–8.
95. Bytzer P, Talley NJ, Hammer J, Young LJ, Jones MP, Horowitz M. GI symptoms in diabetes mellitus are associated with both poor glycemic control and diabetic complications. Am J Gastroenterol. 2002;97:604–11.
96. Yarandi SS, Srinivasan S. Diabetic gastrointestinal motility disorders and the role of enteric nervous system: current status and future directions. Neurogastroenterol Motil. 2014;26:611–24.
97. Lanas A, Chan FKL. Peptic ulcer disease. Lancet. 2017;390:613–24.
98. Huang JQ, Sridhar S, Hunt RH. Role of helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet. 2002;359:14–22.
99. Sato T, Kitahara F, Nakamura T, Kojima Y, Fujino MA. Peptic ulcer in patients with diabetes mellitus. Nihon Rinsho. 2002;60:1580–4.
100. Peng YL, Leu HB, Luo JC, et al. Diabetes is an independent risk factor for peptic ulcer bleeding: a nationwide population-based cohort study. J Gastroenterol Hepatol. 2013;28:1295–9.
101. Wei F, Lin X. Diabetes increases morbidity and mortality rates in peptic ulcer bleeding: an updated systematic review and meta-analysis. Turk J Gastroenterol. 2016;27:304–11.
102. Leontiadis GI, Molloy-Bland M, Moayyedi P, Howden CW. Effect of comorbidity on mortality in patients with peptic ulcer bleeding: systematic review and meta-analysis. Am J Gastroenterol. 2013;108:331–45.
103. Thomsen RW, Riis A, Christensen S, Nørgaard M, Sørensen HT. Diabetes and 30-day mortality from peptic ulcer bleeding and perforation: a Danish population-based cohort study. Diabetes Care. 2006;29:805–10.
104. Li J-Z, Li J-Y, Wu T-F, Xu J-H, Huang C-Z, Chen D, et al. Helicobacter pylori infection is associated with type 2 diabetes, not type 1 diabetes: an updated meta-analysis. Gastroenterol Res Pract. 2017;2017:5715403.
105. Harsch IA, Brzozowski T, Bazela K, Konturek SJ, Kuharsky V, Pawlik T, et al. Impaired gastric ulcer healing in diabetic rats: role of heat shock protein, growth factors, prostaglandins and proinflammatory cytokines. Eur J Pharmacol. 2003;481:249–60.
106. Brzozowska I, Targosz A, Sliwowski Z, Kwiecien S, Drozdowicz D, Pajdo R, et al. Healing of chronic gastric ulcers in diabetic rats treated with native aspirin, nitric oxide (NO)-derivative of aspirin and cyclooxygenase (COX)-2 inhibitor. J Physiol Pharmacol. 2004;55:773–90.