Chapter 2
Esophageal Disease in Diabetes Mellitus

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2.1 Esophageal Motility and Diabetes Mellitus

Diabetes mellitus (DM) has multiple clinically important effects on the esophagus. Diabetes results in several esophageal motility disturbances, increases the risk of esophageal candidiasis, and increases the risk of Barrett's esophagus and esophageal carcinoma. Finally, "black esophagus," or acute esophageal necrosis, is also associated with DM. These four entities and their relationship with DM will be reviewed in this section.

Esophageal dysmotility has been shown to be associated with diabetic neuropathy; however, symptomatic esophageal dysmotility is not often considered an important complication of diabetes. Plainly, dysphagia ascribed to diabetic neuropathy should be a diagnosis of exclusion. The effects of blood glucose levels on esophageal motility can be reliably predicted. When blood glucose is increased to 145 mg/dL (physiologic postprandial levels in seen nondiabetic patients),

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peristalsis velocity increases. However, when increased to 270 mg/dL (pathologic level as seen in patients with diabetes), peristalsis slows and lower esophageal sphincter pressures decrease [1, 2].

In general, the manometric effects of diabetes on the esophagus are not specific and mostly related to speed and strength of peristalsis. While various studies have found differing results, the most consistent changes have been the following:

- Lower pressures/amplitude of esophageal body [3].
- Lower esophagus resting pressure was reduced in patients with longer diabetes duration [4].
- Reduced velocity of esophageal contractions. In other words, the time required for a peristalsis to traverse the esophagus is prolonged [5].
- Frequent spontaneous or multiple peaked body contractions [6].
- Incomplete emptying of the esophagus has been demonstrated in barium and radioisotope studies [7, 8].

Again these findings are nonspecific and can be found in variety of other conditions, such as scleroderma, gastroesophageal reflux disease (GERD), alcoholic neuropathy, and intestinal pseudo-obstruction or ileus. Therefore, other causes should be excluded before ascribing esophageal symptoms (dysphagia, chest pain) to diabetic neuropathy. These changes in motility are likely happening silently. In diabetes, the neuropathologic changes in the esophagus include:

- Segmental demyelination (Schwann cell loss) and axonal degeneration of preganglionic parasympathetic fibers of the vagus nerve [8]. This includes both a reduction in motor vagal ganglions and sensory sympathetic ganglions [9].
- Preservation of the myenteric plexus. This differentiates the pathophysiology from that of achalasia and Chagas disease and explains why diabetic neuropathy alone is rarely the cause of dysphagia.

The pathological findings which amount to loss of cholinergic stimulation are consistent with the manometric findings

in the esophagus, which are primarily related to slowed or weakened peristalsis. With preservation of the myenteric plexus, the major regulator of motility in the esophagus, dysphagia is rare. These discoveries were made in historical studies using bethanechol, a cholinergic agent that reliably stimulates the smooth muscle of the esophagus. In achalasia and Chagas disease, bethanechol induced a hypersensitive reaction of the smooth muscles of the esophagus [10], while in diabetics, the hypersensitivity to this drug was not seen [3].

In addition to the autonomic nervous system, via studies mostly in animal models, it is becoming apparent that several parts of enteric nervous system including enteric neurons, interstitial cells of Cajal, glial cells, smooth muscle cells, neurotransmitters, and growth factors are affected by diabetes. Multiple proposed complex mechanisms including oxidative stress, alteration in growth factors, apoptosis, and dysregulation of microRNAs and microbiota have been described [11]. While these discoveries are fledgling, they suggest that therapeutic approaches may need to cover more than one pathophysiologic process to be successful. While there is no therapy beyond the treatment of underlying diabetes, it cannot be overstated that if one is searching for an explanation for dysphagia in a patient with diabetes, diabetes itself is rarely the lone explanation.

2.2 GERD and Diabetes Mellitus

The association between DM and GERD is complex and conflicting. A number of studies have indicated a positive association between GERD and DM, while others have found none. A recent meta-analysis suggests an overall positive association in Western countries [12].

Obesity and concomitant gastroparesis are obvious confounders in this association. Obesity increases intragastric pressure, gastroesophageal gradient, transient lower esophageal sphincter relaxation (TLESR), and esophageal acid exposure, while gastroparesis also increases post-ingestion

transient relaxations of the lower esophageal sphincter (LES), producing a greater number of gastroesophageal reflux episodes. The underlying pathogenesis of DM contributing to GERD is not fully elucidated, but is likely related to reduced acid clearance due to slow, weakened esophageal peristalsis.

The association between DM and gastroesophageal reflux (GER) is well established, but the link between DM and GERD, which requires symptoms or esophagitis, is more complex because sensation may be blunted in diabetics with neuropathy. Asymptomatic gastroesophageal reflux (GER) confirmed by pH studies is significantly more frequent in diabetic patients than in healthy controls [13]. In a cohort of patients with varying duration of diabetes, GER (24 h pH monitoring) and esophageal motility (manometry) disorders worsened with long duration of diabetes [14]. Likewise, high-resolution esophageal manometry studies demonstrated lower esophageal resting pressures in patients with longer duration of diabetes [4].

However, whether these pH and manometry findings translate to clinical symptoms or esophagitis (i.e., GERD) is less obvious. Studies have shown that diabetic patients with neuropathy report significantly more GERD symptoms than those without neuropathy [15–17], yet other studies report that GERD symptoms among patients with diabetes are poorly related to neuropathic complications [18, 19]. One possible explanation for this discordance in symptoms and DM is the presence of concomitant sensory neuropathy. For example, two studies have demonstrated that diabetics with neuropathy have evidence of sensory dysfunction based on delayed or extinguished cortical evoked potentials [20, 21]. These studies indicate that diabetics with afferent nerve damage have increased sensory thresholds for pain or symptoms in the esophagus. Thus, while they may have more acid exposure and less acid clearance, sensory neuropathy may blunt the symptoms. Thus, long-standing diabetics with neuropathy are at higher risk for GERD even if they have no symptoms.

2.3 Barrett's Esophagus, Esophageal Cancer, and Diabetes Mellitus

Diabetes mellitus may be a risk factor for Barrett's esophagus (BE) and esophageal cancer independent of GERD and obesity. In a population-based retrospective case-control study using the General Practice Research Database, a UK primary care database that contains information on more than eight million subjects, type 2 DM was found to be a risk factor for BE, independent of obesity, smoking, or a diagnosis of GERD [22]. On multivariable analysis, diabetes was associated with a 49 % increase in the risk of BE, independent of other known risk factors (odds ratio, 1.49; 95 % confidence interval [CI], 1.16–1.91). In a meta-analysis, including six case-control studies and 11 cohort studies, individuals with DM had a modestly increased risk of EC, in particular adenocarcinoma (summary relative risk [SRR] 2.12, 95 % CI, 1.01–4.46) [23]. These studies suggest that independent of the mechanical effects of obesity and GERD, metabolic pathways related to diabetes itself play a role in the pathogenesis of Barrett's and esophageal carcinogenesis. For example, one theory postulates that elevated insulin concentrations in diabetics lower concentrations of IGF-binding proteins (IGFBPs), which in turn contribute to an upregulated level of insulin-like growth factors (IGFs), which stimulate growth through cellular proliferation and inhibition of apoptosis within the esophageal carcinoma cells [24]. In vitro studies, animal models, and epidemiologic data have demonstrated the role of insulin-like growth factor 1 (IGF-1) in carcinogenesis of the esophagus [25]. The risk appears to be most highly associated with adenocarcinoma, as a recent study failed to demonstrate an association of squamous cell carcinoma and diabetes [26].

Esophageal Candidiasis and Diabetes Mellitus

Diabetes is considered as a risk factor for esophageal candidiasis (EC) because of impaired immunity and stasis of esophageal contents. Most cases are associated with chronically poor

glycemic control. Esophageal colonization with candida is commonplace as it is a normal mouth flora, occurring up to 20 % of normal healthy patients. However, esophagitis requires deeper invasion of the mucosa. It has been demonstrated in multiple case reports that underlying diabetes was the only predisposing factor for the development of candida esophagitis [27]. The pathogenesis is believed to be a combination of:

- Prolonged emptying of the esophagus, allowing for increased colonization.
- Defective cellular immunity (specifically, impaired chemotaxis and phagocytosis) [28, 29].
- Increased fungal virulence in high glucose environments in diabetics. Specifically, *Candida albicans* expresses a surface protein that has significant homology with the receptor for complement factor 3b, which has increased expression in hyperglycemic settings, resulting in competitive binding and inhibition of the complement-mediated phagocytosis [30].
- Increased adherence to diabetic cells due to alteration in the carbohydrate composition of receptors of the epithelium. This has been demonstrated in the buccal mucosa (thrush) in DM and presumed to occur in the esophageal mucosa [31].

The clinical presentation varies from scattered white plaques without symptoms to dense pseudomembranous plaques and erosions with severe odynophagia or dysphagia. The preferred treatment is fluconazole 200–400 mg PO/IV daily for 14–21 days. More severe disease can be treated with an echinocandin or amphotericin B deoxycholate 0.3–0.7 mg/kg. Other oral alternatives include itraconazole 200 mg daily, posaconazole 400 mg b.i.d, or voriconazole 200 mg b.i.d.

2.4 Black Esophagus and Diabetes Mellitus

Black esophagus, or acute esophageal necrosis, is a rare syndrome that arises from ischemic insult from hypotension, corrosive injury from gastric acid, and decreased function of

mucosal barrier in malnourished and debilitated patients. It is most commonly seen in critically ill patients with sepsis, diabetic ketoacidosis, multi-organ failure, massive thromboembolic disease, severe trauma, or malignancy. Diabetes appears to be a risk factor with approximately 24–28 % of patients who develop "black esophagus" having underlying DM [32, 33]. Patients typically present with upper gastrointestinal hemorrhage. Diffuse circumferential black mucosal discoloration in the distal esophagus arising from the GE junction is the hallmark appearance of "black esophagus." The treatment is directed at the underlying cause of the critical illness and control of hyperglycemia. Antacids and parenteral nutrition have been used as supportive measures, but have not been studied singularly [34].

2.5 Conclusion

Diabetes-related esophageal dysmotility does not cause dysphagia, but DM appears to be a risk factor for GERD, Barrett's esophagus, and esophageal carcinoma. Abnormal pH and motility studies do not correlate very well with the GI symptoms of diabetics, possibly due to DM-related sensory dysfunction. Poorly controlled DM is associated with both the white plaques of esophageal candidiasis and the black esophagus of acute esophageal necrosis occasionally seen in the critically ill.

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