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# Measurement of gastric emptying in diabetes

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ABSTRACT

There has been a substantial evolution of concepts related to disordered gastric emptying in diabetes. While the traditional focus has hitherto related to the pathophysiology and management of upper gastrointestinal symptoms associated with gastroparesis, it is now apparent that the rate of gastric emptying is central to the regulation of postprandial glycemia. This recognition has stimulated the development of dietary and pharmacologic approaches to optimize glycemic control, at least in part, by slowing gastric emptying. With the increased clinical interest in this area, it has proved necessary to expand the traditional indications for gastric emptying studies, and consider the relative strengths and limitations of available techniques. Scintigraphy remains the 'gold standard' for the measurement of gastric emptying, however, there is a lack of standardization of the technique, and the optimal test meal for the evaluation of gastrointestinal symptoms may be discordant from that which is optimal to assess impaired glycemic control. The stable isotope breath test provides an alternative to scintigraphy and can be performed in an office-based setting.

The effect of glucagon-like peptide-1 (GLP-1) and its agonists to reduce postprandial glycemia is dependent on the baseline rate of gastric emptying, as well as the magnitude of slowing. Because the effect of exogenous GLP-1 to slow gastric emptying is subject to tachyphylaxis with sustained receptor exposure, 'short acting' or 'prandial' GLP-1 agonists primarily target postprandial glycemia through slowing of gastric emptying, while 'long acting' or 'non-prandial' agents lower fasting glucose primarily through insulinotropic and glucagonostatic mechanisms. Accordingly, the indications for the therapeutic use of these different agents are likely to vary according to baseline gastric emptying rate and glycemic profiles.



## 1. Introduction

*'We need to learn to measure what we value, not value what we can easily measure'*

[*Marcus Aurelius AD 121-180*]

Traditionally, issues related to disordered gastric emptying in diabetes lay primarily within the domain of the gastroenterologist, with a particular focus on the management of upper gastrointestinal symptoms. More recently there has been a paradigm shift to the domain of the diabetologist, stimulated by the recognition of the pivotal role of gastric emptying as a determinant of glycemia and, consequently, as a therapeutic target to optimize postprandial glycemic control in diabetes. The substantial evolution of concepts related to gastric emptying in diabetes has also dictated the need for reassessment of the indications for, and methods of, assessment of gastric emptying. This review focuses on the inter-relationship between gastric emptying and glycemia, the techniques that can be used to measure gastric emptying, with particular reference to scintigraphy, and the clinical indications for measurement (Fig. 1).

## 2. Evolution of concepts relating to diabetic gastroparesis

Gastroparesis, when defined as delayed gastric emptying occurring in the absence of mechanical obstruction (Camilleri, 2007), is likely to affect 30%–50% (Chang, Rayner, Jones, & Horowitz, 2010; Marathe, Rayner, Jones, & Horowitz, 2013) of patients with long-standing type 1 or type 2 diabetes, although there have not been any true population-based studies. Clinical features of gastroparesis include nausea, vomiting, bloating, abdominal pain and malnutrition, with additional implications for oral drug absorption in general, and specific issues related to matching glucose-lowering therapy with oral intake. Accordingly, disordered gastric emptying should be

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considered in patients with substantial fluctuations in blood glucose i.e. hyperglycemia that is difficult to manage, in addition to unexplained hypoglycemia (Horowitz, Jones, Rayner, & Read, 2006; Lysy, Israeli, Strauss-Liviatan, & Goldin, 2006). It has been suggested that the diagnosis of gastroparesis requires the presence of gastrointestinal symptoms (Abell et al., 2008; Parkman, Hasler, & Fisher, 2004), however, given the clinical relevance of disordered gastric emptying to glycemic control in diabetes, this stipulation seems inappropriate. Furthermore, the relationship between symptoms and the rate of gastric emptying is weak (Bharucha, Camilleri, Forstrom, & Zinsmeister, 2009; Horowitz et al., 1991; Jones et al., 2001; Samsom et al., 2003), and the magnitude of delay in gastric emptying in those with symptoms is often modest or non-existent (Rayner, Samsom, Jones, & Horowitz, 2001; Samsom et al., 2003). Indeed, gastric emptying is abnormally rapid in a sub-set of patients with diabetes (Ariga et al., 2008; Bharucha et al., 2009; Schwartz, Green, Guan, McMahan, & Phillips, 1996), and symptoms in these patients may be indistinguishable from those in patients with gastroparesis. It has been suggested that the absence of symptoms in patients with markedly disordered gastric emptying may reflect an afferent nerve defect (Stevens, Jones, Rayner, & Horowitz, 2013). It is currently uncertain whether a patient who has significant symptoms consistent with gastroparesis, but in whom gastric emptying is 'normal', can be, in the absence of other pathology, considered to have 'disordered gastric emptying'. There is evidence of visceral hypersensitivity in patients with symptoms in the absence of abnormalities of gastric emptying (Kumar, Attaluri, Hashmi, Schulze, & Rao, 2008; Rayner et al., 2000), and acute hyperglycemia may magnify gastrointestinal sensations (Rayner et al., 2001). However, it is also probable that the sensitivity of current techniques in identifying abnormalities in gastrointestinal motor and sensory function is less than optimal.

Gastric emptying of ingested nutrients is modulated through a complex interplay between the extrinsic and enteric nervous systems, smooth muscle cells, immune cells, and the so-called interstitial cells of Cajal (ICC), the 'pace-makers' of the stomach. A balance between excitatory (e.g. acetylcholine and substance P) and inhibitory, neurotransmitters (e.g. nitric oxide) is required for normal gastrointestinal motility (Kashyap & Farrugia, 2010). The pathogenesis of disordered gastric emptying in diabetes has long been attributed to irreversible vagal neuropathy (Camilleri, 2007), however it is clear that the underlying pathophysiology is multi-factorial, with both 'reversible' and 'irreversible' components. Recent reports from the Gastroparesis Clinical Research Consortium have provided important insights into the pathophysiological cellular changes in diabetic gastroparesis (Grover et al., 2011, 2012). This group examined the cellular changes in 40 patients with gastroparesis (diabetic n = 20, idiopathic n = 20) and matched controls. Full thickness gastric biopsies were obtained at the time of placement of a gastric stimulator for those with gastroparesis, and at the time of duodenal switch gastric bypass surgery in controls — an inherent limitation is that the disease group in these studies represents those with severe and debilitating gastroparesis, while those in the control group were likely to be morbidly obese. Pathologic abnormalities were observed in 83% of biopsies from those with gastroparesis, and an increase in immunoreactivity was evident in patients with diabetic gastroparesis—compared with controls, these patients demonstrated a 25% increase in the expression of CD45, a general cell marker for immune infiltrate, within the myenteric plexus. A central finding was loss of the ICC (Grover et al., 2011), confirming findings from earlier, smaller studies (Forster et al., 2005; He et al., 2001). Moreover, in patients with diabetes gastric emptying was slower when the loss of the ICC was greater, and the latter correlated directly with the loss of enteric nerves, supporting the functional significance of this finding (Grover et al., 2012). In contrast, ICC, and enteric nerve, loss did not correlate with symptom severity. Further work is required to explore the cellular mechanisms underlying the attrition of ICC in diabetic gastroparesis. Neuronal nitric oxide synthase (nNOS), which is responsible for the synthesis of nitric oxide, has an important, potentially reversible, role (He et al., 2001; Watkins et al., 2000), while the signaling molecule, carbon monoxide, has emerged as an important neuro-protective defense and modulator of gastrointestinal function, with the potential to be a therapeutic target in gastroparesis

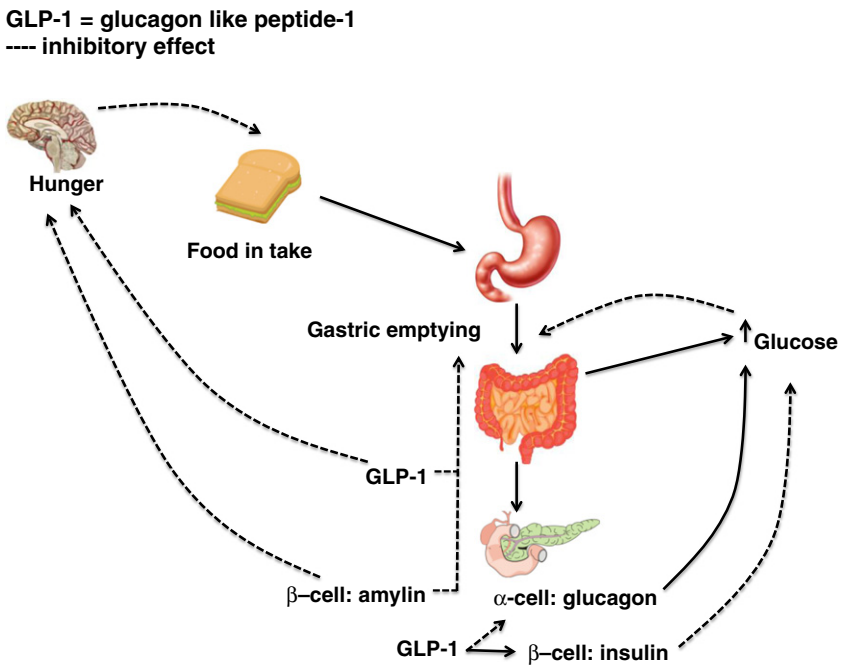


**Fig. 1.** Effects of amylin and GLP-1 on glucose homeostasis. The rate of gastric emptying following a meal is a critical determinant of postprandial glycemia. Ingested nutrients stimulate the release of GLP-1, which slows gastric emptying, promotes satiation and release of insulin, while inhibiting glucagon secretion. Amylin is co-secreted with insulin from pancreatic β cells and acts to slow gastric emptying and promote satiation.