Histologic Changes in Diabetic Gastroparesis

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KEYWORDS

• Interstitial cells of Cajal • Gastric emptying • Macrophages • Enteric nerves • Vagus • Smooth muscle

KEY POINTS

- Several key cell types are affected by diabetes leading to gastroparesis.
- Diabetic gastroparesis is associated with damage to the extrinsic innervation to the stomach, loss of key neurotransmitters at the level of the enteric nervous system, smooth muscle abnormalities, loss of interstitial cells of Cajal (ICC) and changes in the macrophage population resident in the muscle wall.
- Macrophages seem to be a key cell type underlying injury to other cell types.
- Targeting macrophages may allow for the development of a disease-modifying strategy for treating diabetic gastroparesis with the potential to markedly change how diabetic gastroparesis is managed.

INTRODUCTION

The cellular abnormalities that lead to diabetic gastroparesis are increasingly being understood. Several key cell types are affected by diabetes, leading to gastroparesis. These changes include abnormalities in the extrinsic innervation to the stomach, loss of key neurotransmitters at the level of the enteric nervous system, smooth muscle abnormalities, loss of ICC, and changes in the macrophage population resident in the muscle wall. This article reviews the current understanding with a focus on data from human studies when available.

EXTRINSIC INNERVATION IN DIABETIC GASTROPARESIS

Diabetic gastroparesis was first described by Dr Kassander in 1958. After the initial description, investigations centered on the role of abnormalities in the extrinsic innervation to the stomach in the causation of diabetic gastroparesis. Both sympathetic

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and parasympathetic abnormalities were described, with increasing evidence over the years for a defect in the vagal innervation to the stomach and indeed the upper gastrointestinal tract.[1] Damage to the vagal innervation of the stomach was shown by a sham feeding test, which takes advantage of the innervation of the pancreas by the vagus. During the cephalic phase of food digestion, stimulation of the vagus results in release of pancreatic polypeptide. Patients with advanced diabetic gastroparesis have a blunted pancreatic polypeptide response as well as reduced gastric secretion in response to sham feeding suggesting vagus nerve dysfunction.[2,3] Abnormalities in vagal innervation of the stomach may contribute to the motor abnormalities seen, including abnormal relaxation of the pylorus. However, the initial histologic report in 1988[4] in 16 diabetic patients of whom 5 had gastroparesis failed to show any histologic defects. In retrospect, this was likely due to the small *n* value and the limited techniques available at that time (hematoxylin and eosin, Gomori trichrome, Luxol fast blue, and Holmes silver stains). In subsequent animal and human studies abnormalities have been described, including abnormalities at a histologic level both in myelinated and unmyelinated nerve fibers of the vagus nerve,[1,5] which were also reported to be smaller in the biobreeding rat model of spontaneous diabetes. Sympathetic nervous system abnormalities have also been described, with changes in the axons and dendrites within the prevertebral sympathetic ganglia.

SMOOTH MUSCLE

In the past relatively, rarely, patients with severe symptoms of diabetic gastroparesis, often unremitting nausea and vomiting, had gastrectomies as a treatment of their symptoms with variable results. An examination of the resected tissue showed evidence of smooth muscle degeneration and fibrosis, with eosinophilic inclusion bodies.[6] In a study of 2 patients with severe diabetic gastroparesis, one had no fibrosis and the other showed fibrosis with the use of a trichrome stain.[7] A study of full-thickness biopsies at the time of gastric stimulation implantation did not show significant fibrosis,[8] suggesting that the fibrosis seen in the earlier studies may represent a more end-stage aspect of the disease.

Nonobese diabetic (NOD) mice are an often used model of diabetic gastroparesis. NOD mice develop a leukocytic infiltrate of the pancreatic islets, resulting in a type 1 type of diabetes. Studies on organotypic cultures from the stomachs of these mice have shown a loss of smooth muscle–derived insulin-like growth factor 1,[9] suggesting that smooth muscle function may be impaired before the onset of overt fibrosis.

ENTERIC NERVES

After the initial discovery that extrinsic nervous system defects are present in diabetic gastroparesis, work on animal models found that the intrinsic nervous system was also affected. Initial work was carried out in rats. Rats made diabetic with streptozotocin[10] showed an increase in vasoactive intestinal peptide-like immunoreactivity in nerve cell bodies and nerve fibers, with no change in level of substance (SP). These changes were reversible with insulin administration.[11] The same rat model also showed evidence for altered enteric nerve ion transport.[12] A study[13] using spontaneously non-insulin-dependent diabetic rats demonstrated depolarization of the smooth muscle membrane potential, an attenuation of nonadrenergic noncholinergic inhibitory neurotransmission, and a reduction in reactivity of adrenoceptors to noradrenaline. Work carried out using spontaneously diabetic biobreeding/Worcester (BB/W) rats showed that the number of neuronal nitric oxide synthase (nNOS)-containing neurons in the gastric myenteric plexus and NOS activity were significantly reduced in