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Diabetes and the Stomach

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Abnormalities in the function of the stomach in patients with long-standing diabetes mellitus, usually insulin-dependent, may provide difficult management problems. There is a reduced frequency of peptic ulcer disease in diabetics. Gastric atrophy, often with parietal cell antibodies, is common and the frequency of pernicious anemia with its expected intrinsic factor antibodies is increased. Gastric analysis results have been conflicting but generally suggest that long-standing diabetics have lower acid levels than normals, possibly secondary to vagal neuropathy. Gastric atony occurring in a small but sugnificant number of patients with long-standing insulin-dependent diabetes, usually with a clinically apparent peripheral neuropathy, has been associated with upper abdominal discomfort, vomiting, and a clinical picture of gastric outlet obstruction. Various degrees of subclinical delays in gastric emptying are probably present in many asymptomatic patients and, indeed, are underemphasized contributors to poor control of blood sugar levels. Studies utilizing radioactive-labeled physiological meals have demonstrated abnormalities in the gastric emptying of solids, in particular, and sometimes liquids in the latter stages of the disease. Metoclopramide, a dopamine antagonist, which stimulates upper gastrointestinal smooth musculature, results in accelerated gastric emptying; clinical trials have shown that it is capable of alleviating symptoms related to diabetic gastroparesis and with its recent approval and release in this country, it promises improved management of this entity. Another agent, domperidone, a selective peripheral dopamine antagonist with no appreciable side effects, is in this country an investigational drug which has shown clinical efficacy in Europe in improving gastric stasis syndromes.

GASTRIC EMPTYING IN PATIENTS WITH DIABETES MELLITUS

In the pre-insulin era, diabetic gastroparesis was of little interest and the literature is devoid of any mention of that particular neuropathy. Gastric retention in diabetes was first noted by Boas in 1925 [1] and the radiologic picture was described by Ferroir, who conducted the first thorough study of the stomach in diabetics in Paris in 1937 [2]. The focus was on the hypochlorhydria, which was found in 60 percent of 26 patients undergoing gastric analysis. By the use of the then relatively new barium meal study, he described the following abnormalities: "X-ray examination showed that in diabetics, the stomach is generally very chronic, but its motor responses are weaker than normal: contractions are slow, lack vigor and die out quickly. Not infrequently, pyloric incompetence may be found with a hypotonic pyloric sphincter producing rapid evacuation in most cases. Although insulin by itself cannot restore in diabetics the level of secretion that is responsible for the healthy subject, it nevertheless alleviates secretory and motor abnormalities even without resulting in

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hypoglycemia" [2]. The first detailed descriptions of gastric retention secondary to diabetic visceral neuropathy was by Rundles in 1945 [3]. The term "gastroparesis diabeticorum" was coined by Kassander in 1958 where he also indicated that this syndrome could be present in relatively asymptomatic diabetics [4]. The symptom complex of diabetic gastroparesis has been cast in a minor role in the overall clinical picture of diabetes, since it was overshadowed by the life-threatening complications of the primary disease. It is becoming increasingly apparent, however, that alterations in gastric motility can adversely and seriously affect control of the diabetes [5,6].

Early investigators theorized that diabetic gastroparesis was due to a vagal neuropathy, since symptoms were quite similar to those seen after vagotomy [4,5]. Other investigators subsequently made the interesting observation that changes in gastric emptying which were assumed to reflect "autovagotomy" were not reproduced in non-diabetics by surgical vagotomy. There was increasing agreement that the neuropathy was a result of the abnormal metabolism present in unregulated diabetes. An inverse correlation was present between blood sugar levels and gastric motility [6] and it was also noted that peripheral nerve conduction (and presumably autonomic nerve conduction as well) was improved by adequate treatment of the diabetic state. Animal studies showed that normoglycemia prevented and reversed the accumulation of increased sugars at nerve endings and, in doing so, reversed the attendant neuropathy. Recently, myoinosytol metabolism was invoked as a possible important factor in the pathogenesis of diabetic gastroparesis and, indeed, in all of the diabetic neuropathies [7]. This substance is important in lipid synthesis and is essential for the integrity of the nerve unit. Urinary excretion of myoinosytol is increased in diabetics who are under poor control but is reversed when a normoglycemic state is attained. Structural changes have also been reported in the postganglionic sympathetic fibers to the gastrointestinal tract, and these have been correlated with control of the underlying disease [8].

CLINICAL PICTURE

Incidence

There are approximately five million diabetics in the United States. Published incidence figures on gastroparesis vary widely, and this variation reflects diagnostic criteria, populations studied, etc. An earlier review in 1947 demonstrated that of 35 patients with peripheral neuropathy, five had signs of gastric retention [9]. Kassander found six cases of gastric stasis in 27 consecutive diabetic admissions [4], while Ferroir [2] diagnosed gastric stasis in 16 of 27 diabetics. In other published reports, the incidence of gastric motor abnormalities has been reported to vary from 20 to 30 percent [10] to only 35 of 44,000 in a Joslin clinic survey [11]. This variation in reported incidence is explained by the different criteria which have been used in the past to make the diagnosis, the well-known phenomenon that most diabetics with gastroparesis are asymptomatic, and the recognized problems in the quantitation of delayed gastric emptying by radiological techniques.

CLINICAL PRESENTATION

Signs and Symptoms

While an undetermined proportion of diabetics with slow emptying of food are asymptomatic, the usual clinical manifestations, if present, are anorexia, nausea, vomiting, abdominal pain, and a persistent fullness after meals. Acute episodes of

gastric stasis symptomatology often accompany ketoacidosis or, less commonly, occur after a period of "stress" in a non-acidotic diabetic. In case reports of chronic diabetic gastroparesis [3,6,11], many patients have an intermittent course with some symptom-free periods. After multiple relapses, chronic stasis may ensue. In general, gastroparesis is not sex-related and occurs mostly in long-term diabetics, usually in association with other neuropathies [11], particularly a peripheral neuropathy, present clinically or by motor nerve conduction studies. Often other symptoms of autonomic dysfunction, including neurogenic bladder, orthostatic hypotension, impotence, and gustatory sweating are present. Many of those with gastroparesis have concomitant symptoms of diabetic colonic and small bowel dysfunction with constipation and/or diarrhea. In addition, patients often exhibit the ravages of long-standing diabetes, including impaired vision, renal failure sometimes requiring dialysis, and peripheral vascular disease. Long-standing gastroparesis has been associated with the formation of gastric bezoar. The other side of the gastroparesis spectrum involves hypoglycemic tendencies. The presence of stasis has often precluded the usual oral treatment for hypoglycemia. Furthermore, diabetic control is based, in part, on the premise that food, when eaten as prescribed, can be optimally absorbed.

RADIOLOGICAL MANIFESTATIONS

Conventional barium meal investigations, when positive, have revealed a dilated stomach with impaired peristalsis, delayed gastric emptying, and retention of food in the presence of a patulous pylorus [2,3]. These authors have cautioned that changes in symptomatology do not correlate well with changes in the X-ray picture. It was appreciated that radiological abnormalities of esophageal motility were observed in some patients, usually with other evidence of an autonomic neuropathy. Relying on the gastric emptying of barium during a standard upper gastrointestinal series will result in a positive study only in severe cases of diabetic gastric stasis. The majority of patients whose gastric emptying is slow using isotope-labeled solid meals will have a normal barium result. The gastrointestinal series is important to define normal gastric and duodenal anatomy by excluding peptic ulcer disease and obstructing lesions or masses of the antrum, pylorus, or duodenum. Some previous studies have suggested that the rate of gastric emptying can be clinically assessed with the barium burger meal or with some other modification where solid food is mixed with a barium meal. Here the effects of solids upon barium emptying are being studied. The marker, barium, is not fully attached to the meal and empties independently of the solid food particles. Furthermore, the information will be purely qualitative and promotes extensive exposure to radiation.

Gamma Camera and Isotopic Techniques

Previous studies of gastric emptying using saline meals or a modified liquid test meal have shown that emptying is often slower in diabetics. However, studies of gastric emptying, based on the use of a liquid meal, are limited and, if normal, do not mean that emptying of a more natural meal is also normal. Scanning and gamma camera methods, based on the incorporation of gamma-emitting radioactive isotopes in food, offer a means of assessing gastric emptying after ingestion of ordinary meals, but the heterogeneity of such meals may present a problem, as liquids and solids ingested together are not emptied from the stomach at the same rate [12–15]. When an isotope marker of a meal is employed it is, therefore, necessary to

define which component of the meal it represents. In most studies, the solid food component of the meal is the one studied, but, with more sophisticated studies, dual labeling with separate isotopes (usually Technetium and Indium) allows simultaneous assessment of solid and liquid gastric emptying rates. In a study of gastric emptying using a scintiscanning technique, a marked delay in gastric emptying correlated well with the symptoms of gastric stasis and was found more commonly than with conventional radiology using barium.

Impaired gastric emptying of solid food is the first abnormality that occurs and therefore this finding is the most sensitive indicator of diabetic-related effects on gastric motility. Liquid emptying becomes delayed at a later time and reflects a more severe involvement of smooth muscle function accompanying diabetes. Extensive gastric emptying evaluations of diabetic patients with a peripheral neuropathy in a clinic setting using radionuclide techniques have not been performed, but the authors estimate that slow gastric emptying of solids may be detected in at least 75 percent of such a population. Many of these patients would not be symptomatic for gastric stasis, but the impairment in gastric emptying may impact on day-to-day glucose control and estimation of insulin dosage.

Clinical and experimental studies have suggested that the loss of normal vagal innervation of the stomach results in accelerated early gastric emptying. Campbell et al. [16] were unable to identify any rapid early emptying of the liquid marker corresponding to such a pattern. However, an unexpected finding in their patients without gastric stasis was the loss of the solid-liquid differentition. It was implied that the findings indicated that in diabetics without gastric stasis, there may be an abnormality of antral peristalsis for which the usual explanation of "autovagotomy" is not appropriate.

The technique of radionuclide studies to evaluate gastric emptying is not beyond the capability of most hospital nuclear medicine departments. A very convenient meal that we have utilized is that employing a semi-solid meal consisting of an egg-salad sandwich on white bread containing 500 microcuries of ^{99m}Technetium-DTPA

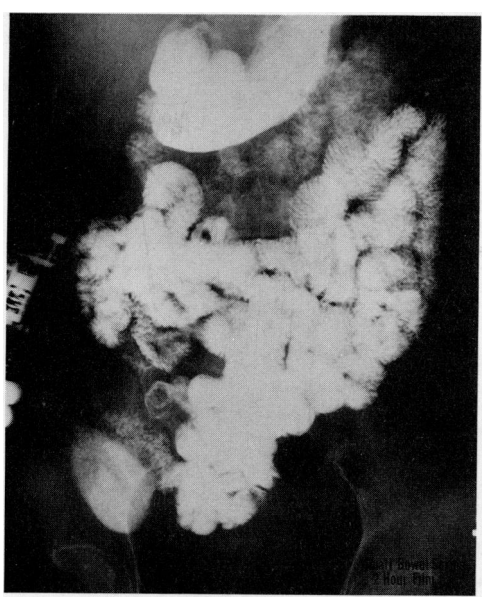

FIG. 1. Upper gastrointestinal series and small bowel follow-through in a 27-year-old juvenile-onset diabetic showing retained barium in the stomach at two hours with some barium also reaching the cecum. The mechanical device at the extreme left is an insulin pump which the patient wears on her belt and which constantly infuses insulin subcutaneously.

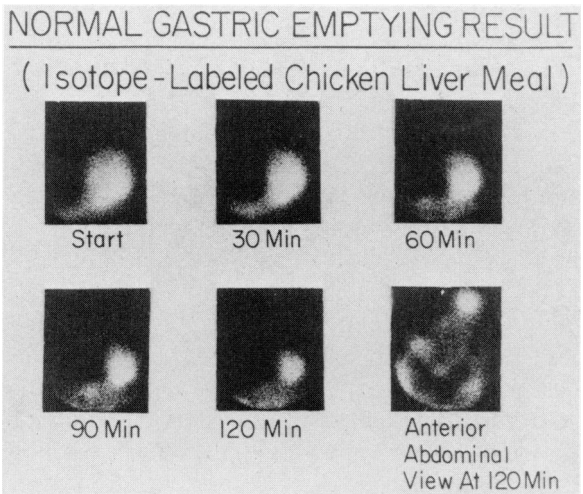

FIG. 2. Normal gastric emptying result after ingestion of an isotope-labeled chicken-liver meal. Radionuclide images of the stomach are shown up to 120 minutes after the meal. A full scan of the anterior abdomen at the termination of the study confirms isotope dispersed throughout the small bowel, with less than 50 percent remaining in the stomach.

(diethylene-triamine-penta-acetic acid) soaked into the bread of the sandwich [17]. This can be ingested along with a small amount of skim milk. Once the normal gastric emptying rate has been standardized using normal individuals, then extrapolations can be made to diabetics and other clinical states.

Figure 1 is a radiograph obtained in a 27-year-old juvenile-onset diabetic with gastric stasis symptoms showing barium in the stomach at two hours after its ingestion and with some gastric dilatation. Figure 2 shows a normal gastric emptying test, using an isotope-labeled solid meal (chicken liver) technique. Emptying occurred linearly over a two-hour period and, as can be appreciated by the final view of the anterior abdomen, significant counts are present in the distal small bowel. Figure 3 shows a diabetic patient with symptoms consistent with gastric stasis and a normal emptying on a previous barium study. There is almost complete retention of an isotope-labeled chicken-liver meal two hours after its ingestion.

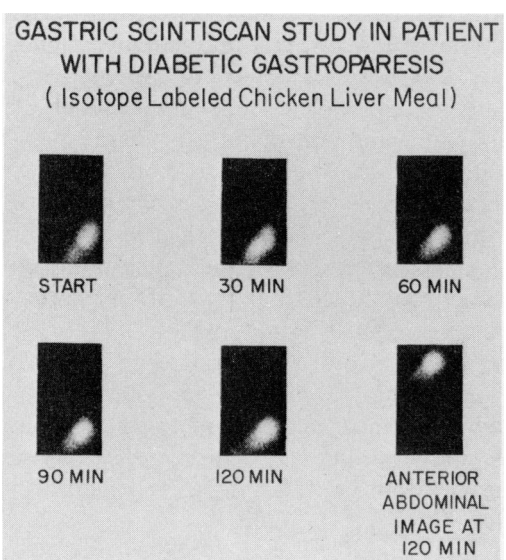

FIG. 3. Gastric emptying study in an insulin-dependent diabetic with gastric retention symptoms utilizing an isotope-labeled chicken-liver meal. The scintiscans show retention of isotope in the stomach, and no isotope is appreciated in the small bowel after 120 minutes.

TREATMENT

It is important to re-emphasize that gastric stasis due to diabetes is partially a diagnosis of exclusion. Standard diagnostic measures, as outlined, are necessary, and of particular importance is the history of other drugs which may have induced symptoms of gastric stasis or, indeed, slowed gastrointestinal motility. Most common offenders in this population are narcotic agents, which are often being taken for the pain of the peripheral neuropathy, as well as various anticholinergics and antidepressants. A standard upper gastrointestinal series, or upper gastrointestinal endoscopy, excludes obstruction of the distal stomach and duodenum without addressing the role of gastrointestinal motility necessarily. Isotope-labeled gastric emptying studies complete the evaluation. Occasionally, the patient may need to be hospitalized because of advancing renal failure which may result in vomiting and confuse the clinical picture, or for acute fluid and electrolyte repletion, as well as diabetic control. Sometimes a better control of blood glucose may be enough to enhance motility toward normal in this type of setting which may be associated with intermittent relapses of diabetic ketoacidosis.

As opposed to this intermittent setting is the more chronically suffering diabetic gastric-stasis patient. Conventional antiemetic therapy is usually not helpful. Previous approaches have been based on the use of the cholinergic agent bethanechol. While its results were unpredictable, there have been some recent pharmacological studies supporting a theoretical role for its use in diabetic gastric-stasis patients [18]. The dose is titrated to relieve symptoms and minimize adverse reactions. A recommended starting dose is 25 mg 15 to 30 minutes prior to meals and at bedtime. In our experience, the result is erratic and not sustained.

At present, the most powerful and well-studied gastric prokinetic in diabetic gastric-stasis syndromes is metoclopramide (methoxychloroprocanamide). This drug, recently approved in this country, is now available orally for the indication of diabetic gastric stasis. It appears to be a potent antiemetic acting centrally, as well as a potent stimulant of upper gastrointestinal smooth muscle acting peripherally [19]. Its mechanism of action is probably threefold: (*1*) It potentiates acetylcholine release and, therefore, promotes cholinergic effects on the musculature of the proximal gut being blocked partially by atropine, but not by vagotomy. It has no effect on gastric acid secretion or fasting serum gastrin. However, unlike conventional cholinergic compounds, it may require some background of cholinergic activity, and this may be the reason why its effects are unpredictable in long-standing diabetic gastric-stasis patients. (*2*) It is a potent dopamine antagonist and, peripherally, opposes dopamine, an inhibitory neurotransmitter of gastrointestinal smooth muscle. (*3*) The antiemetic properties of metoclopramide result from antagonism of central dopamine receptors, as demonstrated by its ability to block the effect of apomorphine on the chemoreceptor trigger zone. Experience with metoclopramide in treating patients with diabetic gastric stasis has shown that it is capable, both parenterally and orally, of accelerating the delayed gastric emptying present in these patients and returning it toward the rate present in normal volunteers [20]. This can be demonstrated on a series of gastric scintiscans from an individual patient (Fig. 4). The drug is most efficacious in decreasing feelings of epigastric fullness, bloating, and pressure, along with nausea and vomiting and anorexia, resulting in improved weight gain and a general sense of "feeling better" in these patients [20] (Fig. 5). This latter effect may be partially centrally mediated.

Side effects are reported in between 10 and 20 percent of the patients, with the

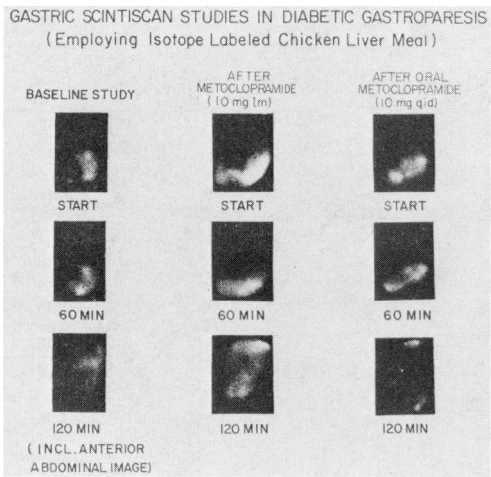

FIG. 4. A series of gastric scintiscans obtained from a diabetic with symptomatic gastric stasis, showing the baseline period, after receiving parenteral metoclopramide (10 mg), and then after a clinical trial of oral metoclopramide therapy. The isotope-labeled chicken-liver preparation is used on this particular occasion, and it can be seen that the slow emptying present during the baseline improved with metoclopramide, both orally and parenterally, consistent with the patient's clinical response while receiving chronic metoclopramide therapy.

most common one being an increased feeling of restlessness and anxiety, which can be improved by decreasing the dose. Other reactions related to its dopamine antagonistic properties include extrapyramidally mediated dystonic reactions, oculogyric crisis, and tremor. It also increases serum prolactin concentrations, sometimes with breast enlargement and tenderness, galactorrhea, and/or amenorrhea.

Because metoclopramide does have some incidence of side effects, a new agent has been developed and is being actively investigated in this country. It is a selective peripheral dopamine antagonist called domperidone, with a wide safety margin. Domperidone has been used successfully in Europe for a number of years and we and others are currently investigating this drug in this country.

Many patients with gastroparesis have been subjected to various surgical drainage

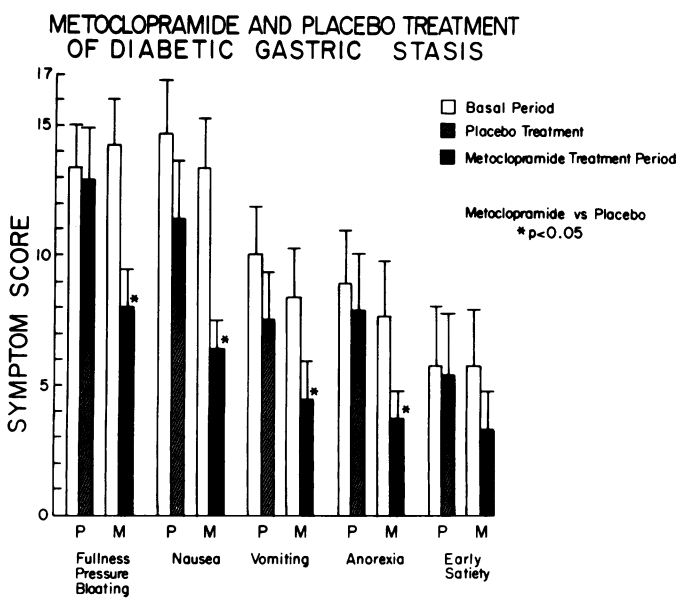

FIG. 5. This figure shows the results of a double-blind clinical trial, in 13 patients with diabetic gastric stasis receiving metoclopramide or placebo in a randomized, double-blind crossover design where each patient received drug and placebo for three weeks. Metoclopramide significantly improved the patients' symptoms of epigastric fullness, pressure and bloating, nausea, vomiting, and anorexia, when compared with the placebo period.

procedures as a "last resort." It is now accepted that surgery is rarely advisable [6] and subjecting these very sick patients to unnecessary surgery is counterproductive and increases their morbidity. One of the reasons for problems after a gastrojejunostomy and/or antrectomy is related to small bowel absorptive abnormalities associated with the patient's visceral neuropathy. The absorptive capacity will be overwhelmed by rapid gastric emptying post-operatively. The absorptive state is already borderline because of impaired motility and bacterial overgrowth. A possible consideration in a severe case is the insertion of a feeding jejunostomy under local anesthesia to sustain adequate nutrition. Another alternative is per oral placement of thin duodenal and jejunal feeding tubes. Feeding with these latter two methods involves the use of a continuous infusion technique using Ensure or another nutritional caloric liquid. This technique is more physiologic and overcomes the malabsorption and/or diarrhea related to bolus ingestions.

DIABETES MELLITUS AND GASTRIC ACID SECRETION

Gastric atrophy, often with parietal cell antibodies, is common in diabetics, and the frequency of pernicious anemia with its expected intrinsic factor antibodies is also increased. These abnormalities are most common in insulin-dependent diabetics. In 200 insulin-dependent diabetic patients, the prevalence of parietal cell antibodies was 28 percent, whereas in 200 diabetics not requiring insulin, the prevalence was 14 percent, and in controls it was only 11 percent. The prevalence of pernicious anemia with intrinsic factor antibodies was 4 percent in the insulin-dependent group, but pernicious anemia was not detected in patients who did not require insulin [21].

The frequency of peptic ulcer disease is reduced in diabetics because of a number of contributing factors. Gastric analysis has given conflicting results but generally suggests that long-standing diabetics have lower acid levels than normals, possibly secondary to vagal neuropathy [22]. Fluctuating metabolic events, such as hyperglycemia and hyperglucagonemia, both of which inhibit gastric acid, might account for the inconsistent results, but it seems likely that the contribution of other peptide hormones may be equally important. For example, gastric inhibitory peptide, an enteric hormone that inhibits gastric acid secretion and stimulates insulin in response to glucose, is released in diabetic patients given oral glucose and may contribute to the low acid levels in the same diabetics [23].

SUMMARY

We have tried to summarize the spectrum of abnormalities that can affect the stomach of diabetic patients. Emphasis is particularly placed on the recent advances in the understanding of gastrointestinal smooth muscle function and, in particular, the way in which the stomach handles solids and liquids. This has allowed improvement in diagnostic tests for gastric emptying disturbances utilizing the role of isotope-labeled test meals, both solid and liquid. This advance in diagnostic accuracy has allowed a better appreciation of the spectrum of gastric emptying disturbances that can be expected in the diabetic population. The other important advance has been the development of the dopamine antagonist metoclopramide, which through its pro-kinetic and anti-emetic properties is a valuable adjunct in the therapy of gastric stasis due to diabetes mellitus.

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