Diabetes mellitus and the stomach

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Abstract

Many patients with diabetes mellitus complain of early satiety and postprandial gastric fullness. In 1945, these symptoms were first found to result from a gastric motor dysfunction which makes the delivery of ingesta into the small intestine, the time of their absorption and the related blood-glucose rise unpredictable. Consequently, insulin or hypoglycaemic agents are administered at inappropriate time points and poor glycaemic control ensues. About 50% of patients with Type I (insulin-dependent) and Type II (non-insulin-dependent) diabetes mellitus are affected. Hyperglycaemia may play an important role in the disorder: gastric emptying was found to be slower in states of induced hyperglycaemia than in euglycaemia. However, significantly reduced blood-glucose concentrations after therapy readjustment were not associated with an increase in emptying rate. Prolonged hyperglycaemia could alter nerve metabolism and contribute to the development of neuropathy. Severity of cardiovascular autonomic neuropathy, but not actual blood-glucose and glycated haemoglobin level, has been found to correlate with the degree of emptying impairment. Drugs enhancing gastric emptying could improve the coordination between insulin administration and the onset of nutrient absorption and thus glycaemic control. Disappointingly, trials to study the long-term effects of such drugs are scarce and their results predominantly negative. In conclusion, many diabetic patients have impaired gastric motor function which could contribute to poor glycaemic control. Evidence suggests that autonomic neuropathy is the main underlying factor. This review aims to offer a critical survey of all the data available at present on these topics. [Diabetologia (2001) 44: 1080–1093]

Keywords Diabetes, gastric motor function, gastric emptying, glycaemic control, hyperglycaemia, autonomic neuropathy, myopathy, symptoms, diagnosis, therapy.

Many patients with diabetes mellitus complain of early satiety and postprandial gastric fullness and discomfort. In 1945 symptoms of this kind were first found to be frequent in 125 patients with diabetic neuropathy and, in 5 patients, to be associated with a prolonged gastric emptying and intestinal transit of barium sulphate [1]. Two years later the same investigators suggested that the disorder accompanied autonomic dysfunction on the basis of observations in another 30 patients with neuropathy [2]. In 1958, the term "gastroparesis diabeticorum" was coined [3]. A large number of publications have appeared since dealing with this complication, its potentially deleterious consequences in particular for glycaemic control, its diagnosis and the therapeutic options available. This review is aimed at critically evaluating the data published on diabetes and the stomach.

Impaired gastric motor function

Gastric emptying. Since diabetic patients' feelings of early satiety and postprandial epigastric fullness were first attributed to delayed gastric emptying [1], the latter disorder was found to prevail in 30 to 60 % of individuals with Type I (insulin-dependent) diabetes mellitus [4–9] and with Type II (non-insulin-dependent) diabetes mellitus [7, 10–15]. In most cases, the emptying of solid meal components is delayed [4, 9, 12, 16] with solids being retained mainly in the proximal stomach [7, 17]. The emptying of liquids in diabetic patients was found to be normal [4, 9, 12, 16, 18] or slower [7, 18, 19] but also faster, mainly in the early phases of the disease, than in healthy individuals [6, 18, 20–23]. Delayed emptying could predispose to gastric bezoar formation: among 3247 patients having undergone oesophago-gastro-duodenoscopies, 14 had a bezoar and of these 7 had diabetes mellitus [24].

A controversy has arisen as to the gastric emptying in patients with Type II diabetes. Ten percent glucose solution has been found to be emptied more quickly in seven of nine patients with recently diagnosed Type II diabetes than in nine healthy subjects [25]. Of the control subjects all were non-Hispanic whites whereas among the patients seven were Hispanic, one Iranian and only one a non-Hispanic white. The ethnic origin cannot be ignored as the same group of authors reported that glucose was emptied significantly more quickly in healthy Hispanics than in healthy non-Hispanic whites [26]. Two further groups of researchers also reported a fast emptying of liquids in Type II diabetes. One study found that 14 of 20 diabetic patients emptied a liquid meal rapidly compared with 15, albeit younger, control subjects [27]. The other study found that 10 diabetic patients emptied a glucose solution, but not solids, more quickly than 12 healthy subjects [22]. In contrast, other investigators have reported that 16 patients with early Type II diabetes emptied glucose solution at a rate similar to 13 healthy subjects [28]. One study even found the emptying of solids to be enhanced: 8 patients with early Type II diabetes emptied a pancake together with a protein drink more quickly on average than 8 matched non-diabetic subjects [23]. However, a closer examination of this study's data reveals that emptying was more rapid in the first postprandial minutes only and much slower thereafter so that the patients' gastric contents at the end of recording were similar to the ones of the non-diabetic subjects.

Receptive relaxation of the fundus and antral motor activity. Fundic relaxation in response to a nutrient drink [29] or to soup ingestion [30] was revealed to be significantly less pronounced in diabetic patients than in control subjects. The fasting tone of the fundus, however, was found to be lower [29] and its compliance in response to intraluminal bag inflation greater than in healthy subjects [31]. In 20 Type I diabetic patients, soup was retained significantly more in the distal stomach than in 20 healthy subjects, i.e., the proximal-to-distal distribution ratio was significantly smaller [32]. A lower proximal gastric retention of liquid compared with healthy subjects was also found in another 20 diabetic patients, in particular in those with cardiovascular autonomic neuropathy (ANP) and symptoms of dyspepsia [18]. In 45 patients with cardiovascular ANP, markedly more of a semi-solid meal was retained in the distal than in the proximal stomach and the proximal-to-distal distribution ratio was significantly smaller than in 32 patients without ANP [33]. Ultrasonography found that the antrum was significantly wider after soup ingestion in Type I diabetic patients than in healthy individuals [34].

These findings are in agreement with observations made manometrically: the postprandial motor activity of the antrum in diabetic patients seems to be characterized by lower contraction amplitudes [17, 35] or a smaller motility index [36] than the one in healthy subjects. In the interdigestive periods of diabetic patients, a prolonged antral phase 2 and/or a less frequently occurring, or even no, phase 3 activity of the migrating motor complex has been observed [35–38] and phase 3 activity has been found to be absent in 6 of 7 patients with severe juvenile-onset Type I diabetes and gastroparesis [39]. A manometric study in the pylorus showed a longer duration of pre- and postprandial contractile activity in 24 diabetic patients with recurrent nausea and vomiting compared with 12 healthy subjects; 14 of the diabetic but only one of the healthy subjects also had episodes of prolonged and intense tonic contractions of the pylorus [40]. All of these peculiarities could contribute to delayed gastric emptying.

The gastric myoelectric slow wave activity as recorded by electrodes placed on the skin of the epigastrium, i.e., the electro-gastrogram, has been found not to differ between euglycaemic Type I diabetic patients with ANP and healthy subjects either in the fasting or in the postprandial state [41]. Furthermore, the electro-gastrogram did not differ between patients with Type I diabetes and healthy subjects during induced hyperglycaemia [42].

Factors potentially underlying impaired gastric motility

Hyperglycaemia. The nature of the changes that result in an abnormal gastric motor function in diabetic patients is still not clear. A crucial role has been ascribed to the prevailing blood-glucose concentrations. In healthy subjects, the rate of gastric emptying was found to be slower in states of induced hyperglycaemia [43–47]. In patients with Type I diabetes the rate of emptying was also found to be slower in in-

duced hyperglycaemia than in euglycaemia [5, 47–55]. In Type II diabetic patients, the emptying of a liquid meal was significantly slower with increasing plasma-glucose concentration and the lag period observed with the emptying of a solid meal, i.e., the period before any ingesta are emptied, longer with higher than with lower plasma glucose [10]. In eight Type I diabetic patients with ANP, a pancake meal was emptied more slowly and the postprandial contractile activity of the antrum was lower in a state of induced hyperglycaemia than in a state of euglycaemia, whereas the emptying of a glucose solution was the same in both conditions [51]. Furthermore, the compliance of the proximal stomach to balloon distension was significantly greater in 10 patients with Type I diabetes during induced hyperglycaemia than during euglycaemia [52]. During insulin-induced hypoglycaemia, by contrast, eight Type I diabetic patients emptied both solids and liquids more quickly than during euglycaemia [53].

It is not clear, however, whether the gastric responses to acute alterations of blood glucose can be extrapolated to the emptying function under the condition of longer lasting hyperglycaemic states. A number of observations argue against long periods of raised blood-glucose concentrations having a decisive role. In patients with Type II diabetes and secondary failure to respond to oral hypoglycaemic therapy, the emptying of a semi-solid meal was recorded before the readjustment of treatment and one week thereafter. After therapy readjustment, all patients had markedly lower blood-glucose concentrations, both fasting and after meal ingestion but the emptying of the meal remained entirely unaffected [54]. In 21 patients with long-standing Type I diabetes, no correlation was found between the emptying of a solid meal and the preprandial plasma glucose [55]. No indications of a relation between emptying rate and preprandial blood-glucose concentrations were found either in studies with 30, 92 and 77 patients, respectively [8, 33, 56]. These observations are therefore in conflict with reports of a slow emptying after the induction of acute hyperglycaemia and argue against a major direct impact of naturally occurring prolonged hyperglycaemic states on gastric motor function.

As to be expected, a significant correlation exists between the rate at which a meal is emptied and the postprandial increase in blood glucose in healthy subjects [57] as well as in diabetic patients [8]: the slower the emptying, the more protracted the blood-glucose rise and, vice versa, the faster the emptying, the earlier and steeper the glucose rise. This highlights the importance of knowing the rate of delivery of ingesta into the small intestine, and thus the beginning of their absorption, for the treatment of diabetic patients.

Autonomic nervous dysfunction. Changes in neural function and polyneuropathy are found in practically all patients suffering from diabetes for more than a few years and can range from subclinical alterations of nerve conduction to life-threatening autonomic dysfunction [58]. Measurable signs of cardiovascular ANP were found in 27% of patients with Type I diabetes at the time of diagnosis [59] and in about 30% of patients who had had diabetes for 10 to 15 years [60]. The prevalence of ANP increases with the duration of the disease [59]. The 10-year survival rate of patients with symptoms of ANP, such as diarrhoea, postural hypotension, gustatory sweating and abnormal heart-rate variability, is markedly lower than the one of asymptomatic subjects both with and without abnormal heart-rate variability [61].

Neuropathy could evolve from prolonged hyperglycaemic states [62], which result in an activation of the polyol pathway, a tissue accumulation of sorbitol and fructose, a myoinositol deficiency and an altered nerve metabolism, but also from a decreased nitric-oxide production and a deficiency in neurotrophic growth factors [63–66]. Changes in nerve metabolism could reduce the density of nerve fibres [67] and lead to a length-related neuropathy of the dying-back type [67, 68] and multifocal ischaemic lesions mainly affecting microvessels [69–71]. By contrast, the absence of prolonged hyperglycaemic states was observed to be associated with a low incidence of neuropathy [72]. In the Diabetes Control and Complications Trial (DCCT) [73], the occurrence of clinical neuropathy over a time span of 6.5 years was found to be 60% lower in those of the 1441 patients who received intensive therapy aimed at maintaining blood-glucose concentrations close to the normal range than in the patients on conventional therapy. Accumulating evidence suggests that the factors involved in the development of neuropathy are interrelated [66].

In mouse models of Type I diabetes, i.e., in mice with streptozotocin-induced and genetic diabetes (non-obese diabetic mice), immuno-histochemistry showed a marked reduction in neuronal nitric-oxide synthase (nNOS) protein expression not resulting from a loss of myenteric neurons. The fact that other neuronal markers, such as synaptophysin, Map-2 and vasoactive intestinal polypeptide, were not significantly lower indicates a selective loss of nNOS expression. In these mice, the emptying of dextrose solution was found to be markedly delayed and the non-adrenergic non-cholinergic relaxation of the pylorus impaired [74, 75]. These changes resemble the defects found in mice with a deletion of the *nNOS* gene (*nNOS-/-*) or treated with a nNOS inhibitor. As both the nNOS expression and pyloric function could be restored to normal by insulin treatment, gastropathy in diabetic mice seems to result from a reversible down regulation of nNOS expression. By contrast, the delay in emptying was not reversed after a 12-h period of insulin-induced normoglycaemia, which indicates that hyperglycaemia was not the cause of im-

paired emptying [74, 75]. The impaired receptive relaxation of the fundus [18, 29, 30, 32–34] was also found to result mainly from an impaired nNOS expression [76].

Another recent study showed that genetically non-obese diabetic mice developed not only delayed gastric emptying but also an impaired electrical pace-making and reduced motor neurotransmission in the stomach [77]. These changes have been related to a greatly reduced number of interstitial cells of Cajal in the tunica muscularis of the corpus and antrum, cells which generate the gastric electrical pace-maker activity and mediate motor neurotransmission [78]. Furthermore, the close associations between these cells and the enteric nerve terminals found in healthy animals were infrequent in diabetic mice [77]. A markedly lower number of interstitial cells of Cajal have also been found in sections from jejunal tissue that appeared normal of a Type I diabetic patient with gastroparesis. The sections showed a reduced presence of mediators of inhibitory neurotransmission, i.e., of vasoactive intestinal polypeptide, pituitary adenylate cyclase-activating polypeptide and nNOS, on the one hand and larger amounts of substance P, a mediator of excitatory neurotransmission, on the other [79] suggesting that a loss of interstitial cells of Cajal and changes in neurotransmission could play a key role in the pathogenesis of diabetic gastroparesis.

Evidence suggests that immunological factors could play a part in the development of ANP. Phospholipid autoantibodies have been found to be present more frequently in the sera of diabetic patients and to correlate with the extent of neuropathy; they could therefore be indicative of ongoing damage to nerves [80]. In patients with Type I diabetes, autoantibodies to nervous tissue structures, in particular anti-sympathetic ganglia and anti-vagus nerve antibodies, have been found to be associated with symptomatic ANP [81]. Autoantibodies against autonomic nervous structures have been found in adolescents with a mean Type I diabetes duration of 6.8 years, who had no signs or symptoms of ANP [82]. Autoantibodies to vagal nerve, cervical ganglia and adrenal medulla targets have been detected frequently in Type I diabetic patients but rarely in healthy blood donors [83].

Although some investigators failed to find clear associations between autonomic nervous and gastric dysfunction [21, 84, 85] and others found that ANP had a poor predictive value for motor dysfunction [14], a number of studies have shown that the gastric emptying of liquid [5, 90], solid [5, 6, 56, 86, 87, 90, 91], semi-liquid [88] and semi-solid [8, 42] ingesta as well as of radiopaque markers ingested with a solid-liquid meal [89] was slower in individuals with cardiovascular ANP than without. The severity of cardiovascular ANP has also been reported to correlate significantly with the degree of gastric motor impairment [5, 6, 56, 87, 90]. Twenty patients with severe cardiovascular ANP emptied an omelette significantly more slowly than 12 patients with mild and 29 without ANP [91] and a significant relation between emptying rate and severity of ANP was also found in 92 Type I diabetic patients [8].

Not only the emptying function but also antroduodenal motor activity, gastric secretory function as well as gastrooesophageal reflux activity could all be affected by ANP. In diabetic patients with both early and definite cardiovascular ANP, the frequency of antroduodenal coordination as well as the frequency and duration of retrograde transpyloric flow episodes following antegrade flow were found to be significantly lower than in healthy subjects [92]. An investigation in 19 diabetic patients showed that those with cardiovascular ANP had a significantly lower gastric secretory response to sham feeding than patients without ANP, although basal and pentagastrin-induced acid secretions did not differ between the two groups [93]. A reduced secretory response to sham feeding has been suggested to be indicative of vagal neuropathy [94]. A study in Type I diabetic patients without symptoms or a history of upper gastrointestinal disease showed that no less than 12 of 31 patients with cardiovascular ANP but only 2 of 19 without cardiovascular ANP had an abnormal 24-h gastrooesophageal reflux activity and that the prevalence of the latter was much higher in patients with ANP than the one to be expected in healthy subjects [95]. The increased prevalence of abnormal reflux can probably be ascribed, at least in part, to the impairment of gastric emptying affecting a large proportion of patients.

Information on the development of ANP and gastric motor and secretory dysfunction over time is scarce. An investigation carried out in 32 patients with Type I diabetes over a 5-year period showed a significant increase in autonomic nervous as well as somatosensory dysfunction [96]. A 10-year follow-up study in 133 Type II diabetic patients showed a massive rise in cardiovascular ANP, which was not related to a deterioration of peripheral neuropathy [97, 98]. In 57 patients with Type I diabetes of more than 10 years' duration, who were studied at the beginning and the end of a 9-year period, the prevalence of cardiovascular ANP increased together with gastroparesis [99]. The association between ANP and impaired gastric motor and/or secretory function could be closer than thought as there is still no validated technique available to assess gastrointestinal autonomic nervous function.

Gastrointestinal myopathy. Some evidence suggests that impaired gastric motor function could also be due to an intestinal myopathy or to a concurrence of myopathy and a dysfunction of the neural structures

governing motor and secretory activity. A post-mortem study in – alas – only five patients with Type I diabetes found polyneuropathy including inflammatory changes in autonomic ganglia and unmyelinated nerves as well as a severe loss of myelinated fibres in the vagal nerves and in the sympathetic trunks as well as a focal hyaline degeneration of the smooth muscle in many viscera [100]. In contrast, no morphological abnormalities in either the gastric wall or the abdominal vagus were found in 16 patients with long-standing diabetes [101]. In an animal model resembling human Type I diabetes, i. e., in spontaneously diabetic biobreeding/Worcester rats, the response of gastric circular muscle strips to direct myogenic stimulants was found to be significantly impaired [102]. The fact that the acetylcholine release from the animals' gastric myenteric plexus in response to transmural electrical stimulation and that the voltage-dependent calcium-ion entry into the muscle strips were intact suggests an impairment of smooth muscle function resulting from an altered intracellular signal transduction. In four patients with long-standing Type I diabetes and gross ANP, who had undergone partial gastrectomies as a last remedy for their intractable vomiting, histopathology of the removed parts of the stomach showed evidence of smooth-muscle degeneration and fibrosis with eosinophilic inclusion bodies ("M-bodies"). This suggests that the patients' gastroparesis was due to a myopathy rather than to denervation, because denervation does not cause intestinal smooth-muscle atrophy [103].

Diagnostic approaches

History taking. How does a physician find out whether a diabetic patient complaining of early satiety, epigastric fullness, belching and vomiting or devoid of any of these symptoms but with therapy-resistant poor glycaemic control has an impaired gastric motor function? The indispensable first step, a thorough history taking, can yield important clues. The occurrence and course of symptoms and their relation to the composition, volume, frequency and timing of meals needs to be ascertained. Eating habits, self-imposed dietary restrictions or peculiarities, appetite, stool frequency and consistency as well as patterns of alcohol intake need to be understood and information gained on undergone operations, traumata and illnesses, in particular of peptic ulcer and gastro-oesophageal reflux disease and other gastrointestinal affections. Furthermore, the presence of malignancies and electrolyte imbalances has to be explored.

Symptoms. Some authors have highlighted the paucity of symptoms associated with slow gastric emptying or the poor relation between such symptoms and the

emptying rate [5]. One study suggested that this supposed symptom paucity resulted from an impaired visceroception [104]. This explanation is supported by the observation made in 89 patients with Type I diabetes and 481 with Type II diabetes as well as in 635 healthy subjects that the occurrence and spectrum of gastrointestinal symptoms in the three groups did not differ [105]. Similar observations were made in a study carried out in 1262 residents of Olmsted County, Minnesota, in which symptom questionnaires were sent to patients with Type I and with Type II diabetes as well as to two age-stratified and sex-stratified random samples of non-diabetic subjects [106]. The prevalence of most symptoms referable to the upper gastrointestinal tract, in particular dyspepsia, nausea and vomiting, was found to be similar in subjects with and without diabetes.

There have been studies, however, which reported that diabetic patients with slow gastric emptying complained of a greater number of symptoms referable to the gastrointestinal tract than patients with normal emptying [6] and that symptoms of dyspepsia predicted, in a linear regression model, delayed emptying [90]. More recently it was observed that upper gastrointestinal symptoms were significantly more prevalent in 110 patients with long-term Type I diabetes than in 210 control subjects matched for age and sex; moreover, patients with HbA_{1c} values in the highest quartile had significantly more symptoms than the others [107]. In one of two further studies with similar results, 489 diabetic patients reported a significantly greater number of gastrointestinal symptoms than 200 matched healthy subjects. Further, patients with neuropathy had significantly more symptoms than those without neuropathy and their symptoms correlated only with neuropathy and not with metabolic control or any other complications [108]. The second study carried out in 483 diabetic patients and 422 matched subjects, found that the patients had a significantly higher overall prevalence and greater number of upper gastrointestinal symptoms than the control subjects [109]. Thus, a paucity of symptoms hinting at impaired gastric motor function does not seem to be characteristic of diabetic patients

Assessment of gastric emptying

What are the means available to assess the net effect of gastric motor function, the emptying of the ingesta?

Fluoroscopy. A fluoroscopic examination can provide information about obstructive lesions, food retained even after a prolonged fast and the stomach's shape and size. If the stomach is hypotonic, it will lengthen with the intake of barium sulphate and the antrum will appear funnel shaped. Although gastric

contractions and the transport of barium into the small intestine can be detected, quantitative information cannot be obtained.

Radiopaque markers. Spheres of a diameter of 1.4 mm and a specific gravity of about 1 are emptied at a rate similar to radiolabelled liver [110], whereas larger spheres tend to be retained until the occurrence of a phase 3 of the interdigestive migrating motor complex [111]. However, even small spheres are not suited for assessing emptying as the feedback mechanisms, which depend on receptors responding to the composition of the chyme delivered to the small intestine, do not come into play [112, 113].

Scintigraphy. Scintigraphic techniques are, at present, the ones best suited and documented for clinical use. Ideally, the measurement of the emptying of solid and liquid meal components, which can be different, is done simultaneously. However, as meals comprise mainly solids and solids tend to be retained over prolonged periods of time, the assessment of the emptying of liquids might not be absolutely necessary. When gamma-scintillation-camera time is scarce, the use of a semi-solid meal is advisable. A semisolid meal is emptied, after a very short lag phase during which the first part of the ingesta is ground down by the antrum and thus becomes ready for delivery to the duodenum, at a similar rate to that of solids after the lag phase [114, 115]. Consequently, the time needed for an investigation is considerably shorter than for a solid meal. The meal employed should be palatable and include more than 1260 kJ, that is, enough to challenge feedback regulation by the small intestine. The blood-glucose concentration immediately before the recording should be measured as it might influence the emptying rate. Scintigraphy also allows the distribution of the meal between fundus, corpus and antrum at various time points after ingestion to be assessed. Techniques have also been developed for evaluating the amplitude and propagation velocity of antral contractions [114–118]. The radiation burden is less than half of the burden resulting from a plain radiography of the abdomen, so that the application of the technique for children and repeat studies to evaluate treatment effects are feasible.

Tracer techniques. These techniques record, at given time points after the consumption of a labelled meal, the concentrations of a tracer substance in the breath or blood under the assumption that it is rapidly absorbed from the small intestine but not the stomach, that its disappearance from the blood is constant and that there is little or no tracer recirculation from other bodily pools. The emptying of a solid meal can be measured after mixing it with octanoic acid labelled with the radioactive ^{14}C or better the stable isotope ^{13}C [57, 119].

Real-time ultrasonography. Several sonographic techniques have been developed to record emptying indirectly. One assesses the volume contained in the antrum as indicated by the cross-sectional area at time points before and after the ingestion of a liquid, semi-solid, solid or solid-liquid meal [120–125]. The emptying time is defined as the point at which the antral volume has returned to its preprandial value. Another procedure determines the volume of the entire stomach, at regular intervals after a liquid meal, by sampling cross sections at multiple sites [126]. However, volume determination is difficult because of the stomach's complex configuration and the unavoidable presence of gas in the fundus and superimposed viscera. A less time-consuming approach is to record the emptying and the intragastric distribution of a liquid meal using sagittal and oblique frontal sections of the proximal and the distal stomach, respectively [127]. Superior in accuracy and precision to the above-mentioned procedures is a technique which permits, although not in real time, the three-dimensional assessment of the intragastric distribution and emptying of a soup meal [128]. However, it has not yet been validated against scintigraphy and using it with a solid meal could be difficult.

More sophisticated techniques such as impedance epigastrography [129], impedance tomography [15] and magnetic resonance imaging [130] have also been shown to reliably record gastric emptying. At the time being, they could be useful in the research setting but cannot be recommended as tools in clinical practice.

Treatment of impaired gastric emptying

Dietary modification

Emptying delays of a lesser extent could be combated by advising the patient to eat 6 to 8 small meals per day instead of adhering to the classical meal sequence [131]. As semi-solids are emptied more readily than solid ingesta, the meals should be of a soft consistency [132]. Controlled trials in the efficacy of such dietary modifications, however, are lacking.

To improve glycaemic control, various diabetes associations recommended diets high in fibre and complex carbohydrates and low in fat. An open crossover study in 10 patients with Type I diabetes showed that the consumption of a high-fibre and low-carbohydrate diet for 4 weeks enhanced the peripheral glucose disposal and decreased the basal insulin requirements but did not alter glycaemic control [133]. In 15 patients with Type II diabetes, the addition of 15 g guar gum to the daily diet for 48 weeks resulted in an improvement of long-term glycaemic control, postprandial glucose tolerance and lipid concentrations [134]. The effect of an increased fibre intake was also

evaluated in a randomised crossover study: 13 patients with mild Type II diabetes ate, for 6 weeks, two diets of identical macronutrient and energy content supplemented with either 8 g of soluble and 16 g of insoluble fibre or 25 g soluble and 25 g insoluble fibre. After the high-fibre diet, fasting and postprandial blood-glucose concentrations as well as the meal-evoked insulin concentration were significantly lower than after the moderate-fibre diet but there was only a tendency towards better glycaemic control [135].

The mechanisms involved in the generation of the above-mentioned effects are not known. Studies in small numbers of healthy individuals suggest that meals rich in fibre are emptied more slowly from the stomach than meals with a low fibre content [136, 137]. Accordingly, in 12 obese patients with poorly controlled Type II diabetes, a supplementation of the diet with 20 g guar gum and 10 g wheat bran for two months resulted in a slowing of the emptying of solids and liquids and an improvement of metabolic control [138]. In another study, seven Type II diabetic patients emptied a meal supplemented with 5 g sodium alginate significantly more slowly than a fibre-free meal and the increases in their postprandial blood glucose were lower [139]. However, not the amount but the nature of the fibre, in particular its particle size, seems to play the critical role: in 12 healthy subjects, a rice pudding was emptied more slowly when coarse bran was added and not fine bran [140]. Furthermore, the addition of ispaghula husk with a particle size smaller than 0.2 mm or of plastic particles 1 to 2 mm in size did not slow the emptying of the rice pudding, whereas the addition of unprocessed bran 2 to 5 mm in particle size resulted in a significant slowing [141]. Thus, patients with fast emptying could benefit from a high intake of coarse bran but it does not seem likely that a high-fibre diet is beneficial for patients with delayed emptying.

Treatments aimed at accelerating gastric emptying

Drugs which enhance gastric emptying might improve the coordination between the time point at which the ingesta reach the small intestine and thus the onset of absorption on the one hand and of insulin administration on the other. In fact, a series of acute and open-label investigations or in the effects of such agents suggested that the employment of such drugs could be beneficial. Controlled trials, however, in particular controlled trials on long-term effects, are scarce and their results mostly negative.

Metoclopramide. Metoclopramide acts as an antagonist at dopamine$_2$- but also at 5-hydroxytryptamine$_3$-receptors in the myenteric plexus. Its acceleratory effect on gastric emptying is thought to be due to a facilitation of cholinergic excitatory neurotransmission, possibly through an agonistic effect at 5-hydroxytryptamine$_4$-receptors [142, 143].

Acute studies in the effects of metoclopramide yielded ambiguous results. A solid-liquid meal was emptied faster after 10 mg metoclopramide intramuscularly than at a baseline recording by only 7 of 12 diabetic patients [144]. In a crossover double-blind study in 9 patients, 10 mg metoclopramide intravenously (i. v.) enhanced the emptying of a doughnut breakfast containing radiopaque markers markedly but not significantly [145]. In an open-label investigation in 10 diabetic patients with cardiovascular ANP and symptoms of slow emptying an i. v. bolus of metoclopramide but also a regimen of 10 mg metoclopramide orally four times a day (q.i.d.) for 2 weeks accelerated the emptying of solids, so that the latter was similar to the one of 10 non-diabetic patients [16]. In another open-label study in patients with slow emptying, 10 mg metoclopramide i. v. and orally accelerated the emptying of a liquid meal, whereas 10 mg metoclopramide orally concluding the administration of 10 mg three times a day (t.i.d.) for one month failed to enhance emptying [19].

Two placebo-controlled double-blind studies evaluated the effects of metoclopramide administered for longer periods of time (Table 1). In a crossover trial, 8 of 9 Type I diabetic patients with gastroparesis emptied a mixture of orange juice and normal saline faster after 3 weeks of metoclopramide than before, whereas after placebo this was the case in 5 of 9 patients. However, all patients had less or no vomiting while on metoclopramide but continued to vomit when on placebo [146]. A crossover trial in 19 patients also showed that metoclopramide for 8 weeks had the same effect on the emptying of solids and liquids as placebo [20].

Domperidone. Domperidone acts as an antagonist at dopamine$_2$-receptors in the myenteric plexus [147]. Because domperidone does not penetrate into the central nervous system, its effects are confined to the periphery. An acute double-blind placebo-controlled trial showed that 10 mg domperidone i. v. enhanced the emptying of a semi-solid meal in all of six diabetic patients with symptomatic gastroparesis but had no effect in six healthy subjects [148]. In a double-blind study in 12 Type I diabetic patients with cardiovascular ANP, a single oral dose of 40 mg domperidone accelerated the emptying of both solids and liquids significantly more than placebo did [149]. Subsequent to the acute study, the patients took 20 mg domperidone t.i.d. for 35 to 51 days. After that period and a single dose of 40 mg domperidone, the emptying of solids was the same as for the placebo in the study's acute phase, but liquids were emptied faster [149]. No effects on the emptying of solids were observed either in six Type I diabetic patients who had taken 20 mg domperidone q.i.d. for 6 months [150].

Table 1. Placebo-controlled, double-blind long-term trials carried out to assess drug effects on gastric emptying in diabetic patients. q. i. d., four times a day; t. i. d., three times a day

Authors [Reference]	Agent	Design	Patients [n]	Treatment duration	Dosage	Recording technique	Ingesta studied	Superiority over placebo
Snape et al. 1982 [146]	Metoclo-pramide	Crossover	9	3 week	10 mg q. i. d.	Scintigraphy	Liquid	No
De Caestecker et al. 1989 [20]	Metoclo-pramide	Crossover	19	8 week	10 mg t. i. d.	Scintigraphy	Solid/Liquid	No/No
Mansi et al. 1995 [122]	Levosul-piride	Crossover	40	4 week	25 mg t. i. d.	Ultrasono-graphy	Semi-solid	Yes
Melga et al. 1997 [123]	Levosul-piride	Parallel group	20 and 20	6 months	25 mg t. i. d.	Ultrasono-graphy	Semi-solid	Yes
Horowitz et al. 1987 [156]	Cisapride	Parallel group	10 and 10	4 week	10 mg q. i. d.	Scintigraphy	Solid/Liquid	Yes/Yes
Havelund et al. 1987 [158]	Cisapride	Crossover	14	4 week	10 mg t. i. d.	Scintigraphy	Solid/Liquid	No/No
De Caestecker et al. 1989 [20]	Cisapride	Crossover	19	8 week	10 mg t. i. d.	Scintigraphy	Solid/Liquid	No/No
Dutta et al. 1999 [157]	Cisapride	Parallel group	15 and 14	2 week	10 mg t. i. d.	Scintigraphy	Solid	Yes
Stacher et al. 1999 [159]	Cisapride	Crossover	23	8 week	10 mg q. i. d.	Scintigraphy	Semi-solid	No

One study investigated the effects of a single-masked oral medication of 20 mg domperidone q. i. d. for 4 weeks on symptoms indicative of gastroparesis. Of 287 diabetic patients, 208 responded with a decrease in symptom frequency and intensity. These 208 individuals were included in a 4-week double-blind withdrawal study, during which they received either 20 mg domperidone q. i. d or placebo. Patients on placebo became significantly more symptomatic than those on domperidone [151].

Levosulpiride. Levosulpiride, the levorotatory enantiomer of sulpiride, acts as a selective antagonist at dopamine$_2$-receptors in the myenteric plexus [152]. Its effects were evaluated in two double-blind placebo-controlled investigations, a crossover study with 4-week and a parallel-group study with 6-month treatment periods [122, 123]. In both studies, levosulpiride significantly accelerated emptying (Table 1).

Cisapride. Cisapride is thought to promote gastric emptying mainly by acting as a partial agonist at 5-hydroxytryptamine$_4$ receptors in the myenteric plexus and thereby facilitating cholinergic excitatory neurotransmission [142, 143]. In uncontrolled single-dose investigations in diabetic patients, the agent was found to accelerate emptying [145, 153], but the results of studies extending over longer periods of time have been ambiguous [154, 155].

Placebo-controlled double-blind trials on the long-term effects of cisapride are few and the numbers of patients included often small (Table 1). In one study, 20 patients with Type I diabetes emptied solids and liquids significantly faster after an oral dose of cisa-

pride than after placebo. A subsequent parallel-group trial in the same patient group showed that the 10 individuals who had taken cisapride over 4 weeks emptied solids and liquids significantly faster than the 10 who had taken placebo [156]. In a parallel-group double-blind trial, 15 gastroparetic patients who had received cisapride for a fortnight emptied a rice cake significantly faster than at a basal recording, whereas there was no significant change in 14 patients who had received placebo [157]. Two double-blind crossover trials in 14 and 19 patients showed that cisapride for four [158] and 8 weeks [20], respectively, did not affect gastric emptying and symptoms any more than placebo. A double-blind crossover trial in 23 patients with Type I diabetes showed that the effects of cisapride administered over 8 weeks on the emptying of a semi-solid meal, glycaemic control and symptoms were the same as for patients on placebo [159].

Erythromycin. The macrolide antibiotic erythromycin mimics the effects of the polypeptide motilin on gastrointestinal motor activity probably by binding to motilin receptors [160]. In an acute double-blind crossover investigation in 10 Type I diabetic patients with gastroparesis, 200 mg erythromycin i. v., but not placebo, significantly accelerated the emptying of both solids and liquids [161]. After a subsequent 4-week period, during which all patients received 250 mg erythromycin orally t. i. d., the acceleratory effect was much less [161]. In an open study on 12 diabetic patients with gastroparesis, the emptying of solids and liquids was enhanced not only by i. v. erythromycin but also by the agent's oral medication for 3 weeks [162]. A placebo-controlled double-blind

crossover study in 10 Type I diabetes patients with gastroparesis showed that single oral doses of 250 and 1000 mg erythromycin significantly accelerated the emptying of a solid meal [163]. In 12 Type I diabetic patients, the antroduodenal motor activity as recorded by an ambulatory manometric technique was improved, both in the fasting state and following a high-caloric meal, after 250 mg erythromycin t. i. d. over 2 weeks [164].

Treatments aimed at delaying gastric emptying

The reports of an accelerated emptying of liquids in patients with Type II diabetes [22, 25, 27] suggested that agents which slow emptying could delay and reduce the postprandial blood-glucose increases and thus improve glycaemic control [165].

Cholecystokinin. In healthy subjects, both i. v. infusions of physiological doses of cholecystokinin octapeptide and the stimulation of endogenous cholecystokinin release, as evolving after the ingestion of lipid-containing long-chain triglycerides, were shown to delay emptying and to reduce postprandial plasma-glucose and insulin increases [166]. Similarly, in seven patients with Type II diabetes and accelerated emptying, cholecystokinin octapeptide not only delayed the emptying of glucose solution but also reduced the ensuing blood-glucose increase [165]. In six Type II diabetic patients, the trypsin/chymotrypsin inhibitor POT II, which increases plasma-cholecystokinin concentrations, delayed the emptying of a glucose-protein solution and reduced the increase in postprandial plasma glucose [167].

Glucagon-like peptide-1. This peptide stimulates insulin secretion by improving the insulinotropic action of glucose and by suppressing glucagon secretion, which leads to an inhibition of hepatic glucose production and a decrease in blood-glucose concentrations [168]. In nine healthy subjects and eight patients with poorly controlled Type II diabetes, i. v. infusions of the peptide delayed the emptying of a liquid meal and reduced the postprandial plasma-glucose increase [169, 170]. In a double-blind crossover study in six patients with poorly controlled Type II diabetes, glucagon-like peptide-1 injected subcutaneously (s. c.) over 3 weeks reduced the postprandial plasma-glucose increase significantly more than did placebo [171].

Amylin. The peptide amylin is co-secreted with insulin by the pancreatic beta cells in response to nutrient stimuli and is deficient in patients with Type I diabetes and elevated in patients with early Type II diabetes; its main action is to inhibit postprandial glucagon secretion [172]. In Type I diabetic patients, the amylin analogue, pramlintide, administered s. c. for a fortnight

reduced postprandial as well as 24-h plasma-glucose concentrations [173, 174]. Two large placebo-controlled double-blind parallel-group trials showed that pramlintide injected t. i. d. and q. i. d. over 4 weeks improved glycaemic control in patients with Type I diabetes [175] and in patients with Type II diabetes using insulin [176]. Because single s. c. or i. v. doses of pramlintide were found to slow the emptying of both solids and liquids [177, 178], as did 5 days of pramlintide t. i. d. [179], these results were attributed to that decelerative effect. However, most diabetic patients do not have enhanced but delayed emptying, so that pramlintide's effects on glycaemic control might not result from its action on the emptying function.

Conclusion

Gastric motor activity is impaired in many patients with both Type I and Type II diabetes. The resulting delayed emptying at least of solid meal components but also a rapid initial emptying of liquids could account for a mismatch between the time of absorption and the related blood-glucose increase on the one hand and the insulin or hypoglycaemic agent administered on the other and so for poor glycaemic control. Evidence indicates that the degree of ANP, rather than an increased blood-glucose concentration or gastric myopathy, is the main underlying factor. The development of therapeutic agents for the long-term treatment of impaired gastric motor function still has a long way to go.

Sources. This review is based on the personal knowledge of publications as well as on publications identified using Medline. The search terms were "diabetes mellitus", "gastric motor function", "gastric emptying", "gastroparesis", "glycaemic control", "hyperglycaemia", "hypoglycaemia", "diabetic complications", "autonomic neuropathy", "myopathy", "symptoms", "prokinetic agents", "metoclopramide", "domperidone", "cisapride", "erythromycin", "motilin", "sulpiride", "cholecystokinin", "POT II", "glucagon-like peptide-1", "amylin" and "pramlintide". The searches were last updated on 23 February 2001. Data in abstract form were included only if published not earlier than 1999.

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