Characterization of Gastric Antral Motility Disturbances in Diabetes Using a Scintigraphic Technique

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In this study, food distribution in the stomach and gastric antral motor activity in patients with longstanding diabetes have been evaluated. With use of a standard gastric emptying test with an acquisition protocol and a refined Fourier algorithm to analyze the data, antral contractions have been characterized and gastric motility parameters were correlated to gastric retention in 20 diabetic patients with or without gastroparesis and in 10 healthy subjects. The results of this study show that, in longstanding diabetes, gastric emptying retardation is accounted for by a retention of food in the proximal stomach, which is reflected by a prolonged lag phase as well as by a reduction in antral motor activity that is determined by a decrease in the amplitude of the antral contractions. This study demonstrates that scintigraphy can noninvasively characterize abnormalities of food distribution in the stomach and provides information similar to that obtained from manometry.

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Gastric retention of solids has been documented since 1945 in symptomatic and asymptomatic patients with diabetes mellitus (*1,2*). Since its introduction in 1976 for the evaluation of gastric emptying rates in diabetics (*3*), the scintigraphic test has been extensively used to assess gastric emptying abnormalities as well as the effect of various gastrokinetic drugs in diabetic patients with or without symptoms of gastroparesis (*4–9*). Most of these studies have demonstrated a significant delay in gastric evacuation of a solid test meal. By using a manometric technique, some authors have correlated this retardation with a disrupted interdigestive motor complex in the stomach and in the small bowel, as well as a diminution of the fundic motility index and of antral motor activity (*5,8,10*).

Despite the multiple refinements of manometric techniques over the past 10 yr, characterization of postprandial antral motor activity in diabetics has remained limited most probably because of the invasive character of manometry and the nonavailability of the necessary equipment in most medical centers. We have recently shown that a scintigraphic gastric emptying test allows the characterization of gastric antral contractions in healthy subjects (*11*). We have also demonstrated that it is possible to define the compartimentalization of food in the stomach and to quantify emptying from each compartment with radionuclide techniques (*12*).

The purpose of this study was threefold: (1) to investigate food distribution in the stomach in patients with longstanding diabetes; (2) to characterize the antral motility disturbances in those patients and (3) to correlate gastric emptying with antral motor activity.

MATERIAL AND METHODS

Population

We studied 10 diabetic patients with retarded gastric emptying (6 females, 4 males; mean age 36.7 ± 11 yr) and compared their results to 10 diabetics with normal gastric emptying tests (5 females, 5 males; mean age 40 ± 18 yr) and 10 healthy subjects (5 females, 5 males; mean age 43 ± 12 yr). Patient selection was based on type I diabetes of 15 or more years duration and the absence of prior gastrointestinal surgery, peptic ulcer disease, scleroderma or gastric outlet obstruction. In addition, no patient was taking any pharmaceutical but insulin. Four of the 10 patients with a normal gastric emptying test and 6 patients with evidence of delayed gastric emptying had symptoms suggestive of diabetic gastroparesis. Control subjects were free of any gastrointestinal symptoms, had no history of gastrointestinal surgery and were not taking any medication. All subjects had a normal esophageal and gastric endoscopy. The study was approved by our local ethical committee and informed consent was obtained from all patients and subjects.

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Scintigraphic Test Procedure

All controls and patients were studied after an overnight fast of at least 12 hr. Diabetics were given their regular insulin dose 20 min before the test. The scintigraphic test procedure was performed as follows: after ingestion of a standardized test meal consisting of 50 g of scrambled egg labeled with 74 MBq (2 mCi) of ^{99m}Tc-sulfur colloid, two slices of regular white bread and 150 ml of water, each subject and patient were imaged on a dual-headed gamma camera. Simultaneous 1-min anterior and posterior images (128 × 128 pixels) of the stomach were acquired on the 140-keV ^{99m}Tc peak with a symmetric window of 20%. Images were taken every 10 min for 1 hr and every 15 min for the second hour and if needed until 50% of the meal had emptied from the stomach. Anterior dynamic (64 × 64 pixels) frames of 1 sec also were acquired for 4 min at 1, 11, 21, 31, 41, 51, 61, 76, 91, 106, 121 min and until 150 min for 4 patients after meal completion until 50% emptying had occurred.

Data Analysis

Static Images. After correction for technetium decay, regions of interest (ROIs) were drawn around the total, proximal and antral stomach on the static images at each time interval. Gastric counts were determined for each region at each time interval and meal retention percentages were calculated. Total gastric emptying data were analyzed using the power exponential function $y(t) = 1 - (1 - e^{-kt})^{\beta}$. This function permits separate identification of the two emptying phases of a solid meal: (1) the initial delay and variable emptying rate called lag phase (TLAG) and (2) the constant emptying rate (ER). In the equation, y(t) is the fractional meal retention at time t, k is the gastric emptying rate in min^{-1} and β is the extrapolated y intercept from the terminal portion of the gastric emptying curve. The lag phase can be defined as the time at which the second derivative of the fitting function is equal to zero, i.e., TLAG = (1/k) lnβ. This function also allows for determination of the half-emptying time (T1/2) (*12,13*). The parameters k and β were determined by a nonlinear least squares fitting algorithm.

Dynamic Images. In order to allow for precise outlining of the antrum, the 1-sec dynamic images were first reframed in a single 4-min image. A ROI was drawn around the horizontal portion of the stomach between the incisura angularis and the pylorus on each reframed image. A 240-point curve was then generated for each dynamic set of images to generate antral time-activity curves. These curves were first normalized to their respective mean count. The autocorrelation function

$$A(T) = \int C(t).C(t + T)dt,$$

where t is time and T the lag time of the correlation, was then applied to each set of normalized data. This function eliminates background noise and nonperiodical events in the defined time interval. To obtain the frequency (in contractions/min) and amplitude in the time domain (in absolute value) of the cyclical phenomena, the Fourier transform

$$F(\omega) = \Delta t \int A(T).\cos.(\omega T)dT,$$

where ω is the pulsation frequency, was calculated for each dynamic acquisition set (Fig. 1D, left and right). The application of these functions to a normal and to a diabetic antral time-activity curve is shown Figure 1. By analogy to manometric recordings, a scintigraphic antral motility index (SAMI) was also calculated for each time interval by multiplying the frequency of the antral contractions by the amplitude obtained from the Fourier analysis. The average frequency and amplitude for the whole gastric emptying course was calculated for each subject and patient. An average SAMI was also calculated for the 2-hr course of gastric emptying, the duration of the lag phase (determined by the power exponential function) and the constant emptying rate phase.

Statistical Analysis

Statistical analysis was performed using Student's unpaired t-test to compare the percentages of meal retention and antral contraction amplitude, frequency and motility indexes between diabetic patients and healthy controls. Differences were considered significant when $p < 0.05$. A linear correlation analysis was used to determine the relationship between gastric emptying parameters and amplitude and motility indexes.

RESULTS

No significant difference was observed in meal consumption time among the three groups. All patients and healthy controls consumed the test meal within 8 min.

Total and Compartmental Gastric Emptying

Total gastric emptying of solids for healthy subjects, normal diabetics and delayed diabetics are shown in Figure 2a. No significant differences were observed between the healthy controls and the normal diabetics for the total gastric emptying curve at each time interval.

Food distribution in the stomach, however, was different between normal controls and diabetics immediately following meal ingestion. Sixty-four percent of the test meal was retained in the proximal stomach in healthy controls versus 82% in diabetics with normal gastric emptying and 80% in diabetics with gastric retardation (Fig. 2b). Inversely, after meal ingestion, the filling of the antral stomach was greater in the control group when compared to the diabetic groups. Food retention in the proximal stomach was then constantly greater in diabetics with delayed gastric emptying in comparison to normal diabetics and healthy controls.

Antral stomach retention was higher in diabetics with delayed gastric emptying compared to the controls and diabetics with normal gastric emptying after the 20th and 50th min, respectively. Maximal filling of the antrum (Fig. 2c) was obtained at ±20 and 40 min in healthy subjects and normal diabetics. Antral filling in diabetics with delayed emptying reached a plateau at ±30 min with a maximum around 80 min.

Standard Gastric Emptying Parameters

Half-emptying time was almost double in diabetics with delayed emptying (132 ± 17 min; $p < 0.0001$) when compared to controls and diabetics with normal emptying. Although no statistically significant difference was observed between half-emptying times for controls and

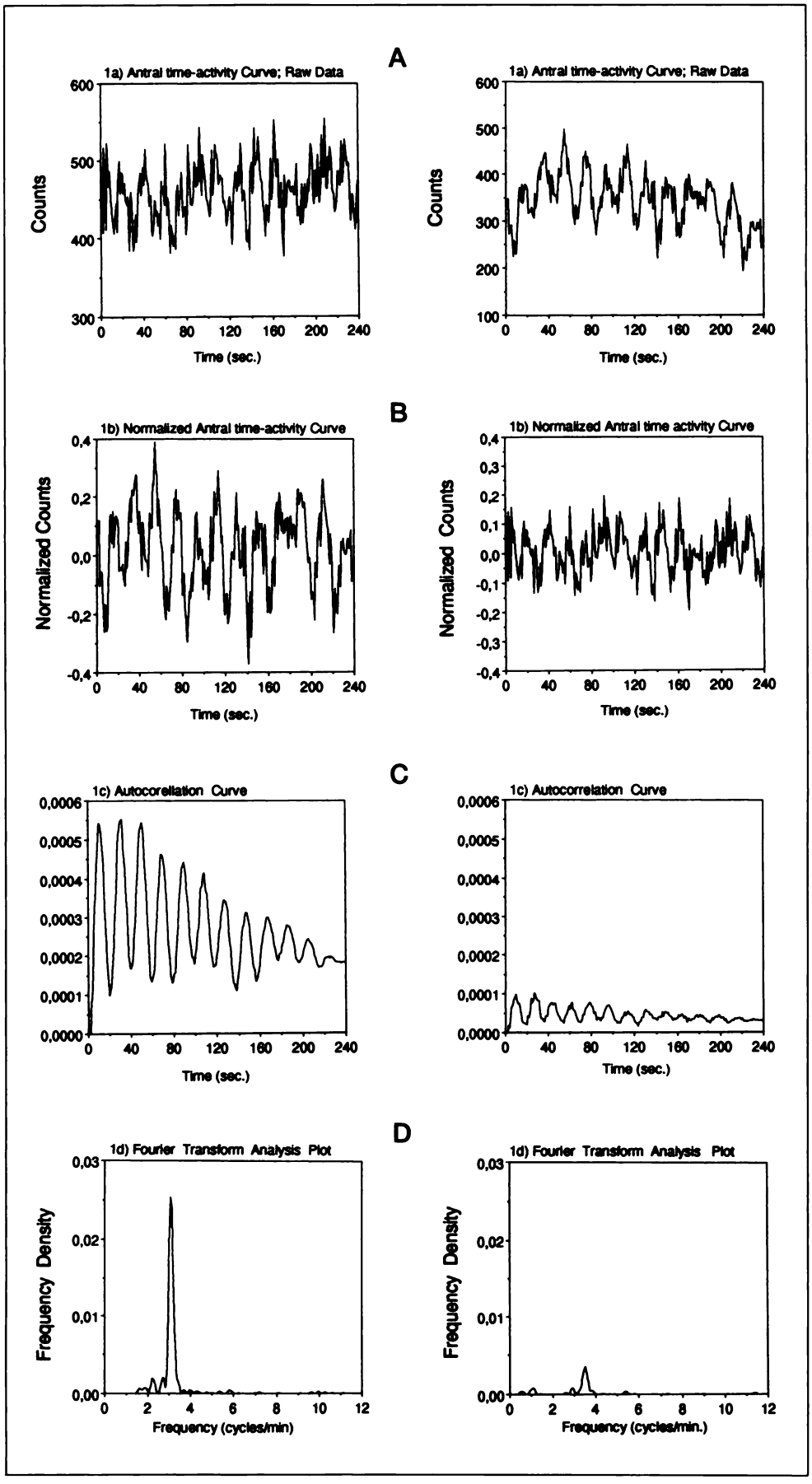

FIGURE 1. A 4-min raw antral time-activity curve (61–65 min) is figured at the top (A) for a healthy control (left column) and a diabetic patient with gastric emptying delay (right column). Data are normalized to their respective mean count (B). The autocorrelation function (C) and the Fourier transform (D) are then applied. Variations of antral counts are lower in the diabetic patient compared to the healthy control (A and B). Frequency of the contractions in the healthy control is about 3 cycles per min; in the diabetic, the frequency is around 3.5 cycles per min. (D). The differences in amplitudes between the antral time-activity curves are highlighted by the Fourier plot.

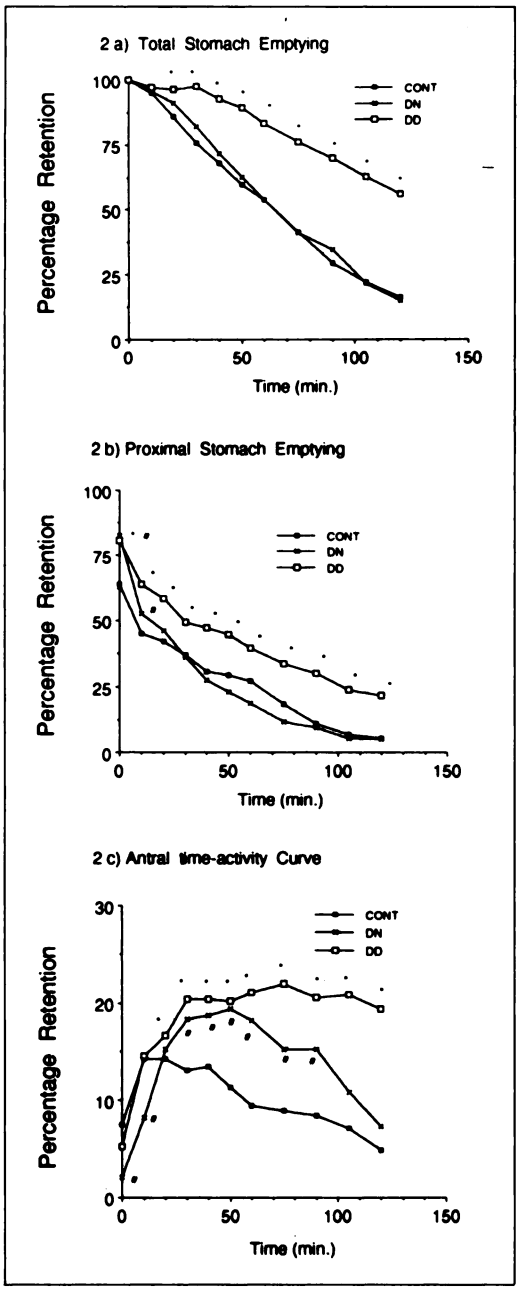

FIGURE 2. Meal retention in the total (a), proximal (b) and antral (c) portions of the stomach in controls (CONT), diabetics with normal gastric emptying (DN) and diabetics with delayed gastric emptying (DD). Half-emptying time is doubled in DD compared to DN and CONT. Retention in the proximal stomach is higher in DD than in CONT and DN after meal ingestion. With time, retention in DN tends to normalize, while it stays delayed in DD. Antral time-activity curves show a significant and retarded accumulation of food for DN and DD, reflected by a prolonged lag phase. *$p < 0.05$ DD versus CONT. #$p < 0.05$ DD versus CONT. °$p < 0.05$ DD versus DN.

normal diabetics (62 ± 11 min versus 65 ± 15 min), the lag phase was significantly prolonged in normal diabetics in comparison to controls (44 ± 12 min versus 25 ± 11 min; $p < 0.001$). The lag phase was significantly longer in the delayed group (75 min ± 28) when compared to controls ($p < 0.0002$) and normals ($p < 0.005$). To maintain a normal gastric half-emptying time, the emptying rate in normal diabetics was higher than that in controls (2.4 ± 1 versus 1.75% ± 0.5%/min; $p < 0.036$). No significant difference in emptying rate was observed between controls and diabetics with delayed emptying.

Antral Motor Activity

Frequency. Antral contractions frequencies were remarkably stable during emptying for the three groups, with a mean of 2.9 ± 0.5, 3.0 ± 0.3 and 3.2 ± 0.3 contractions per minute in controls, normals and diabetics with delayed emptying (Fig. 3a). Although a statistically significant level was reached after 20 min, the frequency of the antral contractions in the delayed group was constantly higher than the frequency in the healthy subjects. No statistical difference was observed between delayed and normal groups and/or controls and normals.

Amplitude. In contrast to the frequency, a striking decrease in the amplitude of antral contractions in diabetics with delayed gastric emptying was seen during the entire gastric emptying course when compared to controls and after the 50th min when compared to diabetics with normal emptying (Fig. 3b). For the three groups, we observed a significant increase in amplitude in the first 30 min when compared to their respective value at time 0.

Motility Index. Despite the higher contraction frequency, the motility index in diabetics with delayed emptying was significantly lower than that in controls at all imaging times. It was also lower than that in diabetics with normal emptying after 20 min (Fig. 3c).

Correlation Between Antral Motor Activity and Gastric Emptying Parameters

In controls, an inverse correlation was found between the lag phase and the motility indices during the lag phase ($r = -0.682$, $p < 0.05$), the constant equilibrium phase ($r = -0.539$) and the total gastric emptying course ($r = -0.587$, $p < 0.05$). In diabetics with normal emptying, a positive correlation was found between the half-emptying time and total gastric emptying motility ($r = 0.621$, $p < 0.05$) and amplitude ($r = 0.699$, $p < 0.05$) indices. A highly significant correlation was observed in diabetics with delayed emptying between half-emptying time and lag phase motility ($r = 0.806$, $p < 0.05$) and amplitude ($r = 0.794$, $p < 0.05$) indexes.

DISCUSSION

Although the actual pathogenesis of diabetic gastroparesis remains uncertain, histologic (*15–17*), physiologic (*18–20*) and pharmacological studies (*5,15*) support the notion that in longstanding diabetes vagal autonomic neuropathy is responsible for both gastric secretory and motor disturbances.

Delayed gastric emptying of solids has been demonstrated by many reports in symptomatic and asymptomatic diabetic patients (*1,2,4–9*). This has been shown to be mainly accounted for by a prolonged lag phase while the emptying rate is preserved (*7,21*). Malagelada, Fox and Camilleri have demonstrated a significant decrease in antral motility indexes in the fasting and fed states with manometry. It has also been suggested that the decrease in antral motor function is mainly accounted for by a diminution in antral contraction amplitude while maintaining antral contraction frequency (*10*).

Our results clearly demonstrate that in diabetic patients with or without symptoms of gastroparesis gastric emptying may be significantly delayed and that this delay is due to retention of food in the proximal stomach and to a reduction in antral motor activity. Retention of the food in the proximal stomach and the consequent late filling of the antrum explain the prolongation of the lag phase that we observed in diabetic patients. This observation also supports our previous point that the lag phase calculated by the power exponential function reflects antral filling (*12*). In addition, the high correlation found between the prolonged lag phase and the half-emptying time in diabetics with gastroparesis confirms the observation of Loo that delayed gastric emptying in diabetics is due mainly to a prolonged lag phase (*7*). Delayed emptying of solids from the proximal stomach may be related to the fact that in diabetes there is a decrease in fundic motor activity (*8*). It could also be due to reduced antral motor activity observed during the lag phase. This has been shown previously using a combined scintigraphic and manometric technique (*22*). Delayed emptying of solids from the proximal stomach might also be accounted for by a hypomotile antrum that is unable to accumulate food coming from the fundus and/or an impairment of proximal-distal stomach coordination regulating the passage of the food between the two compartments.

In contrast to manometric study results (*5,8,10*), we did not observe a decrease in the frequency of antral contractions in our patients. In comparison to controls, we did observe a slight increase in the delayed emptying group and a significant increase in frequency in diabetics with normal emptying after 30 min. This observation is difficult to correlate with the manometric studies of Fox and Malagelada, which were performed in the fasting state and quantified interdigestive motor activity. However, in the fed state, Camilleri demonstrated that 20% of the diabetic patients had a prolonged period of continuous low amplitude antral contractions at a constant frequency of ±3/min. The lower and irregular frequency observed in the other patients in Camilleri's study may be explained by a more severe impairment of antral motility than that present in our patients. Their results may also have been attributable to technical difficulties encountered in the mid eighties to manometrically record contractions with a low pressure. We believe that the relatively high frequency we observed in our diabetic patients reveals the imbalance between the excitatory and inhibitory nerves firing on the antral electromechanical activity due to vagal damage (*23*).

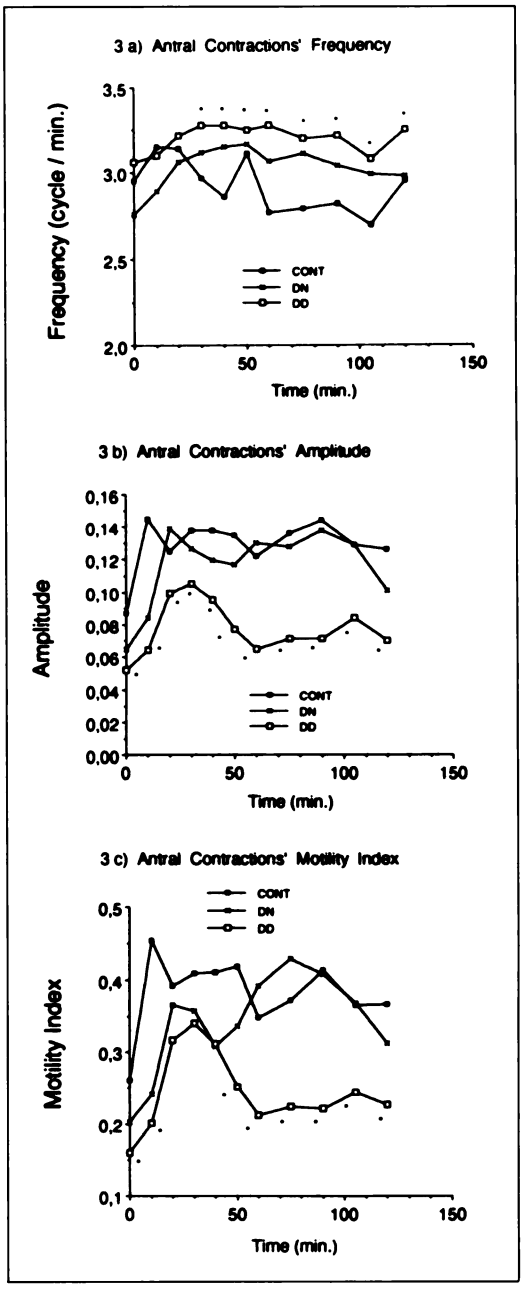

FIGURE 3. Average antral contractions' amplitude (a), frequency (b) and motility indices (c) during the gastric emptying course for controls (CONT), diabetics with a normal gastric emptying (DN) and diabetics with delayed gastric emptying (DD). Although a statistically significant level is obtained for DD only, frequency is higher in DN and DD compared to CONT after 20 min. While starting at different levels, the amplitude increases in all groups for the first 20–30 min. Thereafter a striking decrease is seen in DD compared to CONT and DN. Despite the higher contraction frequency, the motility index is constantly and significantly lower in DD than in CONT at all imaging times than in DN after 20 min. *$p < 0.05$ DD versus CONT. #$p < 0.05$ DD versus CONT. °$p < 0.05$ DD versus DN.

It is generally assumed that antral hypomotility is the major cause of delayed emptying (*24*). However, defective sequencing of contractions along the antropyloric segment, small bowel motility disturbances (*25*) and gastric secretion impairment (*18–20,26*) might also account for delayed emptying of the stomach. While these factors are not specifically addressed in this scintigraphic study, further refinements of our technique should address the first two possibilities mentioned above.

In conclusion, we have been able to quantitate, reproduce and confirm noninvasively diabetic antral motor abnormalities with current computer capabilities, a dynamic radioisotopic gastric emptying procedure and refined spectral analysis of antral time-activity. We have also demonstrated that food distribution in the stomach of diabetic patients is significantly impaired. Scintigraphy appears to be a useful tool in characterizing gastric motility in diabetes and should allow for pathophysiologic evaluation of various gastric motor disorders as well as a better understanding of the effect of gastrokinetic compounds.

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