Gastric Myoelectrical Activity in Patients With Diabetes

Role of glucose control and autonomic nerve function

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OBJECTIVE — Gastric myoelectrical activity was studied in diabetic patients using electrogastrography (EGG) to elucidate the relationship between glucose control, diabetic autonomic neuropathy (AN), and gastrointestinal motility.

RESEARCH DESIGN AND METHODS — Cutaneous EGG was recorded during 1 h of fasting and 1 h after the ingestion of a standard meal in 57 diabetic patients and 10 healthy subjects. EGG was measured in 12 diabetic patients after glycemic control for 4 weeks. Diabetic patients were also studied with respect to the presence of gastrointestinal symptoms and AN.

RESULTS — The percentage of dominant electrical frequency (DF) in normal range (the percentage ratio between the power at 2.4–3.6 cycles/min [cpm] and at 1–10 cpm) was significantly lower in patients with AN than in either the control subjects or the patients without AN ($P < 0.01$). The dominant frequency instability coefficient (DFIC) was significantly higher in patients with and without AN than in the control subjects ($P < 0.01$). The postprandial-to-fasting power ratio (PR) was the lowest in patients with AN ($P < 0.01$). Multiple regression analysis revealed that HbA_{1c} levels were independently associated with the DFIC ($R^2 = 0.099$, $P = 0.0170$) and that AN and HbA_{1c} levels were independently associated with the PR ($R^2 = 0.378$, $P < 0.0001$) in diabetic patients. The percentage of normal DF increased and the DFIC decreased significantly after glycemic control in 12 diabetic patients ($P = 0.0409$; $P = 0.0096$, respectively).

CONCLUSIONS — There appears to be an association between improvement in gastric myoelectrical activity and autonomic nerve function. Abnormalities of gastric myoelectrical activity may be partly ameliorated via the improvement of autonomic nerve function, which accompanies glycemic control.

Gastrointestinal motility disorder is common in long-standing diabetes. Impaired gastrointestinal motility is thought to be due to irreversible vagal nerve damage (1). Most patients with diabetic gastroparesis have evidence of both diabetic autonomic neuropathy and peripheral neuropathy (1–3). However, gastrointestinal dysmotility correlates poorly with the presence of autonomic neuropathy (4). Several studies have indicated that hyperglycemia impairs gastrointestinal motor function in patients with diabetes (5) and in normal subjects (6). These findings suggest that irreversible autonomic neuropathy does not always contribute to delayed gastric emptying. In normal subjects, induced hyperglycemia decreased the number of antral pressure waves (7) and stimulated pyloric motility (8). Recently, the use of electrogastrography has provided new insights into the myoelectrical pathophysiology of disordered gastric motility in patients with IDDM (9). However, the effects of glucose control and autonomic nerve function on gastric myoelectrical activity have been poorly understood in patients with diabetes.

We have investigated the roles of glucose control and autonomic nerve function on gastric motility, studied using electrogastrography in diabetic patients with and without autonomic neuropathy.

RESEARCH DESIGN AND METHODS

Subjects

We evaluated 57 diabetic patients (27 men and 30 women, mean age 51.7 years; range 41–69) and 10 healthy control subjects (4 men and 6 women, mean age 52.7 years; range 39–68). Ten patients were insulin dependent and 47 patients were non–insulin dependent. None of the patients or control subjects had a history of gastrointestinal surgery. The serum creatinine concentration was <132.6 mmol/l (1.5 mg/dl) in each subject. Diabetes had been present for an average of 12.7 years (range 1–30) in the diabetic patients. None of the study participants had gastric or duodenal obstructions detectable by an upper gastrointestinal series or endoscopy. No subjects were taking medications known to affect gastrointestinal motility. Each subject gave informed consent to participate in the study. The study methodology was approved by the Joint Committee on Clinical Investigation of the Osaka City University Medical School. The diabetic patients underwent three areas of investigation. They were questioned regarding subjective gastrointestinal symptoms. Their autonomic nerve function was studied using standard noninvasive methods. Finally, an assessment of gastric motility was made using cutaneous electrogastrography (EGG). EGG study was also performed in the 10 healthy control subjects who were receiving no medications and had no evidence of gastrointestinal disease. To investigate the effects of glycemic control on EGG and autonomic nerve function,

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ANOVA, analysis of variance; cpm, cycles per minute; DF, dominant electrical frequency; DFIC, dominant frequency instability coefficient; EGG, electrogastrography; PR, power ratio.

EGG study and autonomic nerve function tests were repeated after 4 weeks of glycemic control in 12 diabetic patients who had had diabetes for 13.9 ± 7.9 years and were under poor glycemic control (fasting plasma glucose, 12.1 ± 2.9 mmol/l; HbA_{1c}, 10.9 ± 2.5%) before the study.

Assessment of autonomic neuropathy

Autonomic nerve function was assessed using standard cardiovascular reflex tests. Parasympathetic function was evaluated by measuring the variation in the R-R interval in the electrocardiogram during deep breathing and the immediate response of the heart rate upon standing (30:15 ratio). Sympathetic function was assessed by recording the fall in systolic blood pressure in response to standing. The following indexes were measured: *1*) the variation of the maximum and minimum heart rate according to R-R interval measured during six deep breaths (maximum:minimum heart rate) (normal ≥15, borderline 11–14, abnormal ≤10), *2*) the ratio of the R-R interval of the 30th beat to the 15th beat after standing (30:15 ratio) (normal ≥1.04, borderline 1.01–1.03, abnormal ≤1.00), and *3*) a drop in systolic blood pressure after standing (normal ≤10 mmHg, borderline 11–29, abnormal ≥30 mmHg). The results were scored as 0 = normal, 1 = borderline, and 2 = abnormal, according to the criteria outlined by Ewing et al. (10). Presence of autonomic neuropathy was defined by a total score of >2.

Assessment of gastrointestinal symptoms

A standard questionnaire was used to assess symptoms indicative of gastroparesis (11): anorexia/nausea, early satiety, gastric fullness/upper abdominal discomfort, and vomiting. Each symptom was scored as 0 = none, 1 = mild (the symptom could be ignored if the patient did not think about it), 2 = moderate (the symptom could not be ignored but did not influence daily activities), and 3 = severe (the symptom influenced daily activities).

Electrogastrographic methods

Electrogastrographic recordings were assessed after an overnight fast. Data were collected for 1 h in the fasting state and then for 2 h after ingestion of a 208-kcal standardized test meal containing 10.2 g of protein, 5.6 g of fat, and 29.0 g of carbohydrate (Okunos-A, Okuno, Tokyo, Japan). All meals were consumed within 4 min.

Table 1—*Clinical characteristics of the subjects*

	Control subjects	Diabetic patients	
		Without autonomic neuropathy	With autonomic neuropathy
Sex (M/F)	4/6	11/13	16/17
Age (years)	52.7 ± 13.2	49.0 ± 16.0	53.8 ± 10.6
BMI (kg/m²)	21.6 ± 3.3	22.7 ± 4.9	20.8 ± 2.5
Type of diabetes (IDDM/NIDDM)	—	4/20	6/27
Duration of diabetes (years)	—	8.3 ± 7.2	15.9 ± 7.5†
Fasting plasma glucose (mmol/l)	4.9 ± 0.5	10.5 ± 4.3*	9.4 ± 3.0*
HbA_{1c} (%)	4.7 ± 0.4	9.5 ± 3.0	9.0 ± 2.5*
Number of insulin-treated patients	—	7	20
Symptom score	0	0.67 ± 1.17	1.64 ± 1.87‡

Data are means ± SD. *$P < 0.01$ vs. control subjects; †$P < 0.01$ vs. diabetic patients without autonomic neuropathy; ‡$P < 0.05$ vs. diabetic patients without autonomic neuropathy.

Two silver–silver chloride bipolar surface electrodes (NM-3125, Nihon Koden, Tokyo, Japan) were placed on cleaned and shaved skin overlying the gastric antrum using ultrasound for localization. A third skin electrode placed adjacent to the recording electrodes was used as a reference lead (12). The subjects were placed in a sitting position to avoid movement.

Electrogastrography was performed using an electromyogram recorder (Neuropack 8, Nihon Koden, Osaka, Japan). All recordings were made at sampling frequencies of 100 Hz. The high- and low-pass filters were set at 0.01 and 0.5 Hz, respectively. After the measurement, the EGG data were digitized and analyzed by computer using a software program (Microsoft Excel, Power Macintosh).

Analysis of electrogastrographic recordings

The percentage of time during which the gastric electrical frequency was normal (2.4–3.6 cycles/min [cpm]) and the number and type of abnormalities recorded were determined. We defined normal gastric slow waves in accordance with previous reports of gastric slow waves in healthy subjects (13). Several parameters were selected to characterize the gastric electrical activity: *1*) the dominant electrical frequency (DF) and the percentages of the DF in the normal frequency range of 2.4–3.6 cpm, the bradygastric range (<2.4 cpm), and the tachygastric range (3.7–10 cpm); *2*) the instability factor of the electrical frequency calculated by the DF instability coefficient; and *3*) the electrical power (amplitude). Because the absolute value of the power is influenced by several factors (skin resistance and electrode distance from the stomach wall), only the postprandial-to-fasting power ratio (PR) was analyzed. DF >10 cpm was separated from tachygastria, since this was assumed to arise from the duodenum or the lung.

A spectrum analysis was performed using a fast-Fourier transformation algorithm of a 256-s window of the raw data. Power spectra of overlapping stretches of the electrical signal for 192 s (75%) were analyzed and displayed as a function of time, yielding frequency and amplitude information over time (14). The first period consisted of the first 256 s of data, while the second included seconds 65–320, and the third, seconds 129–384, and so forth. Thus, each overlapping period included 64 s of new information.

The DF was calculated as the highest peak of the mean fast-Fourier transformation line for a given period. The percentages of the DF in the normal range were defined as the percentages of time when the DF in the normal frequency range was observed in the EGG. The percentages of the DF in the normal range was calculated as the percentage ratio between the number of normal frequency power spectra (2.4–3.6 cpm) and total spectra (1–10 cpm). This parameter is a quantitative assessment of the regularity of gastric slow waves. The instability coefficients were introduced to specify the stability of the DF visible on the running spectra and was calculated as the percentage ratio of the frequency standard deviation to the mean DF. The dominant frequency instability coefficients (DFICs) reflect subtle changes of the gastric slow waves. The PR is the ratio of the power of the postprandial to fasting DF peak.

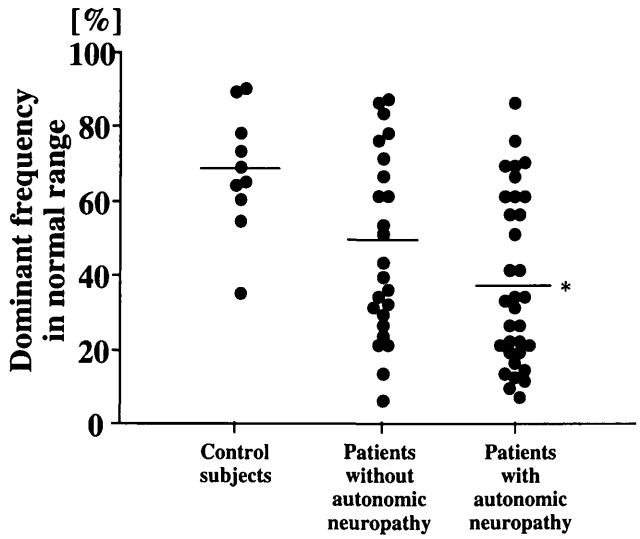

Figure 1—*The percentages of the DF in the normal range in the postprandial periods in control subjects and diabetic patients with and without autonomic neuropathy. The percentage of the DF in the normal range is significantly low in patients with autonomic neuropathy compared with control subjects. *P < 0.01 vs. control subjects.*

Effect of glycemic control on EGG parameters

After four weeks of glycemic control, EGG and autonomic function tests were repeated in 12 hyperglycemic diabetic patients (fasting plasma glucose ≥10 mmol/l and/or HbA_{1c} ≥8.5%). Immediately after the start of this study, each patient received strict diet therapy, and the sulfonylurea or insulin dosage was adjusted once a week according to circadian variations in plasma glucose levels. During the 4 weeks, the mean fasting and postprandial (2-h) plasma glucose levels and HbA_{1c} concentrations decreased significantly (12.1 ± 2.9 vs. 8.3 ± 1.6 mmol/l, $P < 0.01$; 17.2 ± 2.8 vs. 13.7 ± 3.0 mmol/l, $P < 0.01$; 10.9 ± 2.5 vs. 9.7 ± 2.7%, $P < 0.01$, respectively).

Data analysis

Data are expressed as the mean ± SD. Differences among the three groups (the control subjects and the diabetic patients with and without autonomic neuropathy) were tested for significance by a one-way analysis of variance (ANOVA). If the ANOVA showed an overall difference, Scheffé's *F* test was used to compare the means of all possible pairs of groups. Nonparametric ANOVA (Kruskal-Wallis test) was used to assess differences in symptom scores between the two diabetic patient groups. Relationships between the HbA_{1c} concentration and the electrogastrographic variables were examined by linear regression analysis. Relationships between symptom scores and electrogastrographic variables were examined by rank correlation analysis. Multiple regression analysis was used to determine which factors were significantly associated with electrogastrographic variables. Differences in variables before and after glycemic control were analyzed by Wilcoxon's signed-rank test. A value of $P < 0.05$ was accepted as statistically significant.

RESULTS — The clinical characteristics of the subjects are summarized in Table 1. Of the 57 patients, 33 had autonomic neuropathy, 8 had borderline autonomic neuropathy, and 16 had normal autonomic nerve function. The groups did not differ with respect to mean age or BMI. The two diabetic groups had similar fasting plasma glucose levels and HbA_{1c} concentrations. The gastroparesis symptom score was significantly high in patients with autonomic neuropathy as compared with those without autonomic neuropathy.

The percentages of DF in the normal range were significantly lower in diabetic patients with autonomic neuropathy (37.0 ± 4.0%) than in control subjects (66.7 ± 5.2%) ($P < 0.01$) (Fig. 1). No relationship existed between the percentages of DF in the normal range and HbA_{1c} concentrations in diabetic patients ($r = -0.206$, $P = 0.1235$).

The DFIC was significantly high in diabetic patients with (42.4 ± 2.5%) and without autonomic neuropathy (40.8 ± 3.1%) as compared with control subjects (26.2 ± 1.8%) ($P < 0.01$) (Fig. 2). The DFIC was correlated significantly with HbA_{1c} concentrations in diabetic patients ($r = 0.315$, $P = 0.0170$) (Fig. 3).

The postprandial-to-fasting PR was significantly lower in diabetic patients with autonomic neuropathy (1.2 ± 0.1) as compared with control subjects (3.1 ± 0.7) or with diabetic patients without autonomic neuropathy (2.1 ± 0.2) ($P < 0.01$) (Fig. 4). No significant relationship between PR and HbA_{1c} concentrations was found in diabetic patients ($r = 0.175$, $P = 1920$).

Figure 5 shows electrogastrographic running spectrum analysis displays in a

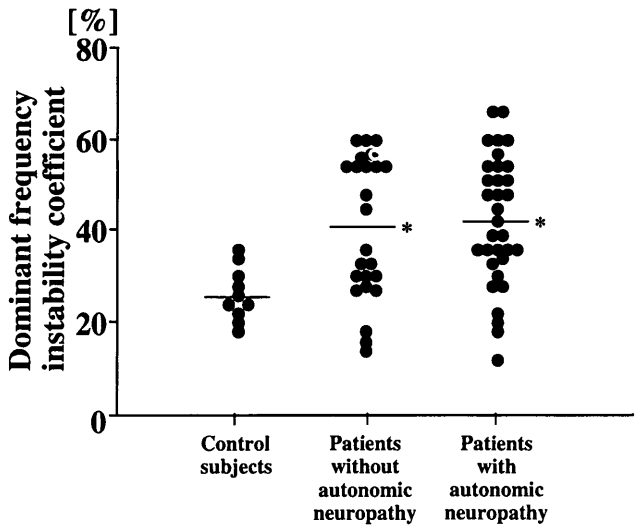

Figure 2—*The DFIC in the postprandial periods in control subjects and diabetic patients with and without autonomic neuropathy. The DFIC is significantly high in patients with and without autonomic neuropathy compared with control subjects.*

control subject and a diabetic patient with autonomic neuropathy. In the control subject, the slow-wave activity showed a dominant frequency of ~3 cpm, which increased in amplitude after meal ingestion (Fig. 5*A*), whereas running power spectral analysis showed an increase in electrical activity in the tachygastric range (5–6 cpm) in the diabetic patient with autonomic neuropathy (Fig. 5*B*).

Multiple regression analysis revealed that HbA_{1c} concentrations were independently associated with the increase in the DF instability index (R^2 = 0.099, P = 0.0170) and that the presence of autonomic neuropathy was independently associated with the decrease in the PR (R^2 = 0.378, $P <$ 0.0001) in all diabetic patients (Table 2).

Of the 57 diabetic patients, 27 had gastrointestinal symptoms. In these patients, gastrointestinal symptom scores were not correlated with any parameter of gastric myoelectrical activity during the study.

Effects of glycemic control on autonomic nerve functions and EGG parameters

Regarding the effects of glycemic control on autonomic functioning, the maximum:minimum heart rate and 30:15 ratios were increased significantly after glycemic control compared with the baseline period (P = 0.0293, P = 0.0079). However, the fall in systolic blood pressure after standing did not change significantly (Table 3). The DFIC and the percentages of the DF in normal range improved significantly after glycemic control compared with the baseline period (P = 0.0096; P = 0.0409, respectively), but the PR did not change significantly (P = 0.0505) (Fig. 6).

CONCLUSIONS — Most investigators believe that gastric motor dysfunction complicates long-standing diabetes in patients with superimposed autonomic neuropathy (1–3). The pathogenesis of diabetic gastroparesis has been attributed to vagal dysfunction. However, many patients with diabetic gastroparesis have no abnormalities on histological examination of the vagal nerve (15). Recently, Jebbink et al. (16) studied IDDM patients with autonomic neuropathy under euglycemic conditions. These patients did not have grossly disturbed myoelectrical activity unless they were symptomatic. Therefore, it is conceivable that autonomic nerve dysfunction may not necessarily involve gastric motor dysfunction in diabetic patients. In the present

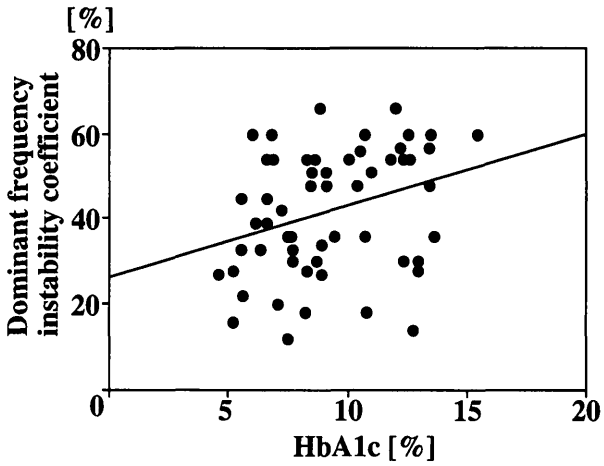

Figure 3—*The relationship between the dominant frequency instability coefficients and HbA_{1c} concentrations in 57 diabetic patients (r = 0.315, P = 0.0170).*

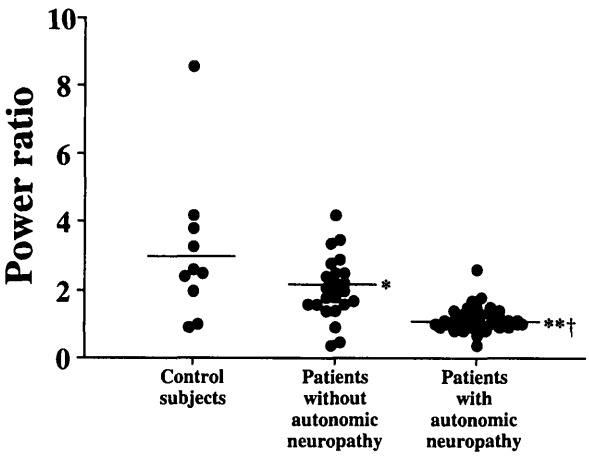

Figure 4—*The postprandial-to-fasting PR in control subjects and diabetic patients with and without autonomic neuropathy. The PR is the lowest in patients with autonomic neuropathy among the three groups. *P < 0.01 vs. control subjects, **P < 0.01 vs. control subjects, †P < 0.05 vs. diabetic patients without autonomic neuropathy.*

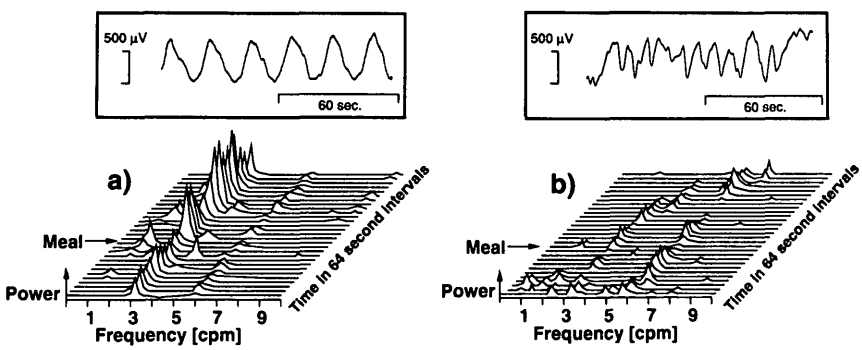

Figure 5—*Representations of the recorded gastric myoelectrical activity (upper panel) and running spectral analysis of ~60 min of the gastric myoelectrical activity. A: a control subject with a normal dominant frequency of electrical activity (3 cpm). B: a diabetic patient with tachygastric dominant frequency of electrical activity (6 cpm).*

Table 2—*Factors associated with EGG parameters*

Independent	Dependent	β	*F* value
Dominant frequency instability coefficient	HbA_{1c}	0.315	6.061
	Duration of diabetes	0.168	
	BMI	0.112	
	Autonomic neuropathy	0.092	
	Age	−0.060	
	Sex	0.060	$R^2 = 0.099$ ($P = 0.0170$)
PR	Autonomic neuropathy	−0.593	30.202
	HbA_{1c}	−0.234	4.708
	BMI	−0.211	
	Age	0.169	
	Sex	0.156	
	Duration of diabetes	−0.138	$R^2 = 0.378$ ($P < 0.0001$)

β, standard regression coefficient; *F* value to enter was set at 4.0 at each step. R^2, multiple coefficient determination.

Table 3—*Effects of glycemic control on clinical parameters*

	Baseline	After glucose control
Fasting plasma glucose (mmol/l)	12.1 ± 2.9	8.3 ± 1.6†
Postprandial plasma glucose (mmol/l)	17.2 ± 2.8	13.7 ± 3.0†
HbA_{1c} (%)	10.9 ± 2.5	9.7 ± 2.7†
Maximum:minimum heart rate	8.3 ± 6.2	9.9 ± 6.8*
30:15 ratio	1.003 ± 0.033	1.015 ± 0.035†
ΔSBP (mmHg)	14.5 ± 15.1	15.2 ± 17.8
Symptom score	1.7 ± 1.3	0.6 ± 1.0†

Data are means ± SD. Maximum:minimum heart rate, ratio of the maximal and minimal heart rate during deep breathing; 30:15 ratio, ratio of R-R intervals at 15th and 30th beats after standing; ΔSBP, fall in systolic blood pressure after standing. *$P < 0.05$; †$P < 0.01$ vs. baseline.

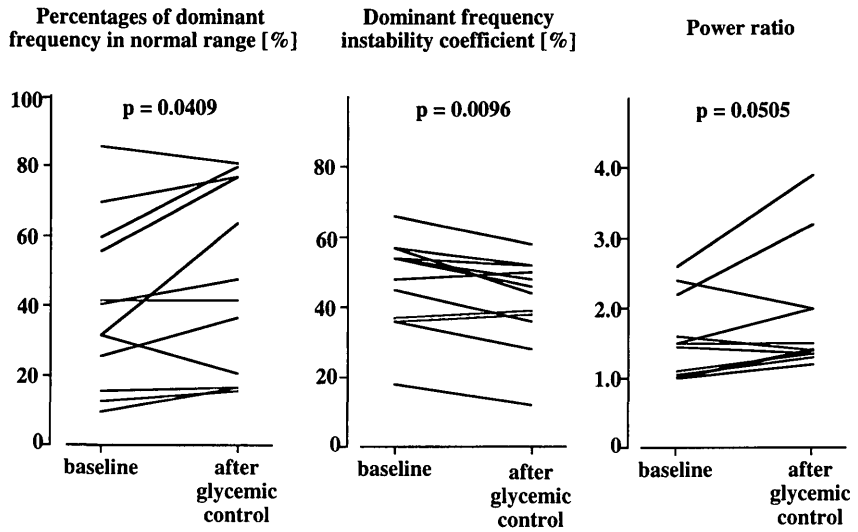

Figure 6—*The effect of glycemic control for 4 weeks on the DFIC, the percentages of the DF in normal range, and the postprandial-to-fasting PR in 12 diabetic patients. The DFIC decreases and the percentages of the DF in normal range increase significantly after 4 weeks of glycemic control compared with baseline period (DFIC, 46.8 ± 3.8 vs. 40.5 ± 3.5%; percentages of the DF in normal range, 39.3 ± 6.9 vs. 47.3 ± 7.8%). The PR tends to increase (but not significantly) after 4 weeks of glycemic control compared with baseline period (1.5 ± 0.2 vs. 1.8 ± 0.2).*

investigation, a decrease in the PR and the percentages of the DF in normal range and an increase in the DFIC were found in patients with autonomic neuropathy. It is therefore likely that the autonomic neuropathy of diabetes contributes to the abnormalities of myoelectrical activity observed in these patients.

Metabolic factors seem to play a dominant role in the impairment of nerve function (17–19). Several studies have demonstrated the importance of serum glucose concentration as a modulator of gastric motility (7–9). Studies in patients with IDDM have shown that gastric myoelectrical activity was not grossly abnormal in the euglycemic state (16). Hyperglycemic clamping has been shown to inhibit gastric slow-wave activity, whereas euglycemic-hyperinsulinemic clamping had no effect on either postprandial antral motility or slow-wave rhythmicity. In fact, in healthy volunteers with induced hyperglycemia, the degree of hyperglycemia correlated with the disruption in the slow-wave rhythm (20). The present study demonstrated that the HbA_{1c} concentration is correlated with the instability of the gastric electrical frequency but not with the PR. In addition, glucose control significantly decreased the instability of the gastric electrical frequency but did not increase the PR in diabetic patients. These findings indicate that glucose control results in improved autonomic nerve function and slow-wave rhythmic activity but not in an increase in the PR that is associated with gastric mechanical activity (21,22). Therefore, it is suggested that hyperglycemia contributed to slow-wave rhythm disruption to some extent via reversible autonomic nerve dysfunction.

The mechanisms by which hyperglycemia inhibits gastrointestinal motility in diabetic patients have not been well defined (23). DeBoer et al. (24) have demonstrated that acute hyperglycemia reduced lower esophageal sphincter pressure, impaired esophageal motility, and reduced plasma pancreatic polypeptide concentrations. Additionally, the inhibitory effect of glucose on the secretion of pancreatic polypeptide that is dependent on a cholinergic pathway is blunted by vagotomy (25). These findings suggest that cholinergic activity is impaired during hyperglycemia. Several investigators have suggested that an increase in the electrical amplitude (power) is associated with gastric mechanical activity (21,22). The results in our study showed that the presence of auto-

nomic neuropathy was independently associated with a reduced power ratio. It is possible that hyperglycemia may influence gastric motility via alteration in vagal activity. The favorable effects of glucose control on the gastric myoelectrical activity may result from increased antral contractility (7), thereby decreasing gastric myoelectrical activity originating in an ectopic pacemaker. It has been suggested that the changes in the gastric myoelectrical activity seen immediately after vagotomy are due to a temporary imbalance between the vagal and sympathetic innervation of the stomach (26).

The absence of a significant relationship between gastroparesis symptoms and gastric electrical activity has several possible explanations. A lack of symptoms in diabetic gastrointestinal motility disorders has been shown to be associated with a visceral afferent neuropathy (27). Gut transit is frequently abnormal in long-standing diabetic subjects. However, symptoms correspond poorly to the actual region of the gut with the abnormal transit. Constipation, however, is associated with prolonged colon transit (28). It is possible that in patients with diabetic gastroparesis, the coexistence of a visceral afferent neuropathy may decrease the occurrence of gastroparesis symptoms. A discrepancy between electrogastrogram data and symptoms has been noted previously (29). Koch and Stern (13) have demonstrated baseline abnormalities in myoelectrical activity in six IDDM patients. Six months of therapy with domperidone led to normalization of all electrogastrogram patterns to 3 cpm, despite a lack of significant improvement in gastric emptying. Furthermore, acute hyperglycemia to 175 mg/dl inhibited postprandial antral motor activity in healthy volunteers, whereas higher levels of plasma glucose at 230 mg/dl were associated with slow-wave rhythm disruption (20). This indicates that motor dysfunction does not require simultaneous disturbance of the electrical pacemaker activity of the stomach. In the present study, we cannot eliminate the possibility of a discrepancy between gastric motor dysfunction and abnormalities in myoelectrical activity because neither gastric emptying nor antral motility was studied directly. Therefore, further confirmation of our observations will require simultaneous measurement of gastric emptying or antral manometry and myoelectrical activity.

In conclusion, both glucose control and autonomic nerve function are important factors in regulating gastric myoelectrical activity. The results also indicate that the change in the gastric myoelectrical activity, especially the gastric slow-wave rhythm disruption, is partly reversible with control of plasma glucose.

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