Acta Med. Okayama, 2002
Vol. 56, No. 5, pp. 237-243

Acta Medica Okayama
http://www.lib.okayama-u.ac.jp/www/acta/

Original Article

Diabetic Gastroparesis in Association with Autonomic Neuropathy and Microvasculopathy

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Gastroparesis is a frequent and sometimes life-threatening complication of diabetes mellitus. Autonomic neuropathy seems to be one of the most important mechanisms underlying this entity, together with the other probable pathologies. The present study was performed in order to identify an alternative to gastric scintigraphy as a screening test. The gastric emptying times of 60 subjects (Group 1: 20 insulin-dependent patients, Group 2: 20 non-insulin-dependent diabetes mellitus patients, and Group 3: 20 healthy volunteers) were monitored by gastric scintigraphy. Perception thresholds for cold, heat, and vibration were tested by a quantitative sensory test, and QTc dispersions were calculated from standard electrocardiography recordings. In addition, fasting blood glucose, hemoglobin A_{1c}, and urine β_2-microglobulin and microalbumin concentrations were determined for the patient groups. Funduscopic examination was performed by an independent ophthalmologist. Gastroparesis was determined in both patient groups, regardless of fasting blood glucose and hemoglobin A_{1c} concentrations. A strong correlation was observed between nephropathy, retinopathy, and cardiac autonomic denervation (QTc) and gastroparesis. In conclusion, retinal and renal microvasculopathy parameters and cardiac autonomic function tests may be useful for screening diabetic patients for gastroparesis.

Key words: diabetic gastroparesis, microvasculopathy, autonomic neuropathy

Gastroparesis is a frequent and sometimes life-threatening complication of diabetes mellitus (DM) [1-3]. Gastrointestinal motility abnormalities can cause nausea, vomiting, post-prandial fullness, early satiety, belching, and bloating. They also present a major problem for the regulation of blood glucose, especially in insulin dependent patients, because of the improper digestion and absorbtion of intake [4]. A consortium of pathological processes including hyperglycemia, gastrointestinal hormone changes, myogenic mechanisms, and autonomic neuropathy are the causes of this entity [5-9]. Several studies have been conducted in order to identify a noninvasive method of evaluating patients for gastroparesis, such as a simple screening test similar to gastric scintigraphy [10-19]. Body mass index (BMI), fasting blood glucose, and hemoglobin A_{1c} (HbA_{1c}) values did not demonstrate a reliable correlation [20]. However, investigations concerning cardiovascular autonomic regulation, [21-22] vagal electrical activity, and mesenteric blood flow have shown striking correlations with gastroparesis [23-26].

In this study we investigated the relationship between gastroparesis and diabetic neuropathy, the components of neuropathic insult, and microvasculopathy. The aim of

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this study was to determine a simple screening parameter for diabetic patients with gastrointestinal symptoms in order to accurately diagnose diabetic gastroparesis.

Materials and Methods

The study population consisted of 40 patients with long-standing DM; 20 were insulin-dependent (IDDM, group 1: 13 men, 7 women; mean age 27.15 ± 8.45) and 20 were non-insulin-dependent (NIDDM, group 2: 13 men, 7 women; mean age 51.75 ± 10.11). The diagnostic criteria proposed by the Expert Commitee on the diagnosis and classification of Diabetes Mellitus were used [27]. Prominent symptoms were recurrent nausea, vomiting, post-prandial fullness, early satiety, belching, and bloating without evidence of mechanical obstruction. Exclusion criteria were as follows: presence of any surgical procedures (vagotomy or gastric bypass), metabolic disorders (hypothyroidism, renal failure), cardiac dysfunction (myocardial infarction, angina, valve disease, arrhythmias or cardiac failure in the past or at the present time), rheumatologic conditions (scleroderma, systemic lupus erythematosus), central nervous sytem disorders (cerebrovascular accident, trauma, tumor), infections (Chagas disease, Epstein-Barr virus) and use of any medications (opiates, anticholinergics) within the last 90 days. 20 healthy volunteers served as a control group (Group 3: 13 men, 7 women; mean age 33.5 ± 12.41). Gastric emptying times of all (standing) subjects were quantitated using the geometric mean of the anterior and posterior counts after ingesting a standard test meal consisting of 150 g of scrambled eggs labeled with 99mTc and 150 ml of orange juice labeled with 111In DTPA; the meal was given to the patients in the morning. All subjects underwent quantitative sensory tests for heat, cold, and vibration perception thresholds using a commercial device (WR Case-IV System). QT dispersion was determined by calculating the difference between the longest (QTmax) and the shortest (QTmin) QT intervals within a 12-lead ECG. Since the QT interval alone can vary according to heart rate, it was corrected using Bazett's formula ($QTc = QT/\sqrt{RR}$) to produce QTc intervals. Fasting blood glucose and HbA_{1c} levels, and urine β_2-microglobulin and microalbumin concentrations were determined for each diabetic patient. In addition, Group 1 and 2 patients were examined by an independent ophthalmologist for diabetic retinopathy, and graded from 1 to 4 as being normal, or having background retinopathy, nonproliferative retinopathy, or proliferative retinopathy, respectively. T1/2 for gastric emptying (T1/2 G) was calculated in minutes and the results were first compared between groups, then correlated with the other obtained data separately for each group. An independent samples T-Test was used for comparison of the three groups, and Spearman's Rho and Pearson correlation analyses were performed for the in-group correlations. A commercial statistical analysis program (SPSS 9.02 for Windows) was used for the statistical analysis.

Results

When patient and control groups were compared, T1/2G was found to be significantly lower among controls than in the patient groups (78.48 ± 38.34, 86.93 ± 46.52, 45.59 ± 15.20 for Groups 1, 2, and 3 respectively; $P = 0.001$) (Fig. 1). Both IDDM and NIDDM patients had distal sensorial loss, which was most prominent as regards heat perception (38.83 ± 3.07, 40.57 ± 2.67, 35.18 ± 0.97 for Groups 1, 2, and 3 respectively; $P < 0.001$ for both patient groups). NIDDM patients also demonstrated a significant decrease in vibration sense (7.51 ± 5.33 and 2.52 ± 0.9 for Groups 2 and 3, respectively; $P < 0.001$), which was not significant in the IDDM group (2.85 ± 1.46; $P = 0.4$). QTc dispersion was longer in Group 1 (410.95 ± 47.20 mSec; $P = 0.072$) and significantly longer in Group 2 ($410.40 \pm$

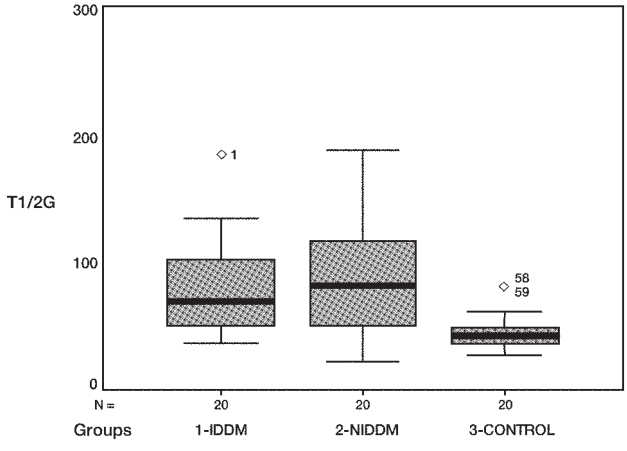

Fig. 1 Gastric emptying time in IDDM and NIDDM patients and healthy controls. T1/2G: Gastric emptying time, given in minutes, Group 1: Insulin-dependent diabetes mellitus (IDDM) patients, Group 2: Non-insulin-dependent diabetes mellitus (NIDDM) patients, Group 3: healthy controls.

39.25 mSec; $P = 0.045$) as compared to controls (390 ± 19.66 mSec) (Table 1). A positive correlation between T1/2G and QTc dispersion was seen among both IDDM and NIDDM patients (correlation coefficient (cc): 0.614, $P = 0.004$ and cc: 0.659, $P = 0.002$, respectively) (Fig. 2A, 2B). There was a strong positive correlation betweeen T1/2G and the grade of retinopathy (cc: 0.715, $P < 0.001$, in IDDM patients and cc: 0.819, $P < 0.001$, in NIDDM patients), urinary β_2-microglobulin concentrations (cc: 0.434, $P = 0.056$, in IDDM patients and cc: 0.774, $P < 0.001$, in NIDDM patients) (Fig. 3A, 3B) and microalbuminuria (cc: 0.567, $P = 0.009$, in IDDM patients and cc: 0.765, $P < 0.001$, in NIDDM patients) (Fig. 4A, 4B).

Discussion

Diabetes Mellitus is associated with peripheral nervous system diseases [28]. The incidence of neuropathy in diabetic patients varies from 10 to 50% according to different studies, and the reported incidence increases with the age of the person with the disease and with the severity of hyperglycemia [29–31]. Other diabetic complications such as retinopathy and nephropathy are seen more frequently in patients with neurologic insult, suggesting a common underlying mechanism [32–33]. A number of different neurologic involvement types are seen in diabetic patients, but to date, no study has yet correlated these clinical entities or the involvement of various peripheral neurologic subsystems (*e.g.*, motor, sensory, and autonomic pathways) with these well-known

Table 1 Threshold for cold, heat, and vibration, and QTc dispersion in Group 1, Group 2, and among controls (Group 3)

	GROUP 1	GROUP 3	*P*-value	GROUP 2	GROUP 3	*P*-value
QTc (mSec)	410.95 ± 47.20	390 ± 19.66	($P = 0.072$)	410.40 ± 39.25	390 ± 19.66	($P = 0.045$)
Cold perception threshol	25.76 ± 4.69	29.8 ± 1.0	($P < 0.001$)	25.42 ± 3.54	29.8 ± 1.0	($P < 0.001$)
Heat perception threshold	38.83 ± 3.07	35.18 ± 0.97	($P < 0.001$)	40.57 ± 2.67	35.18 ± 0.97	($P < 0.001$)
Vibration perception threshold	2.85 ± 1.46	2.52 ± 0.19	($P = 0.4$)	7.51 ± 5.33	2.52 ± 0.9	($P < 0.001$)

QTc dispersion given in mSec, Group 1, IDDM patients; Group 2, NIDDM patients; Group 3, healthy controls.

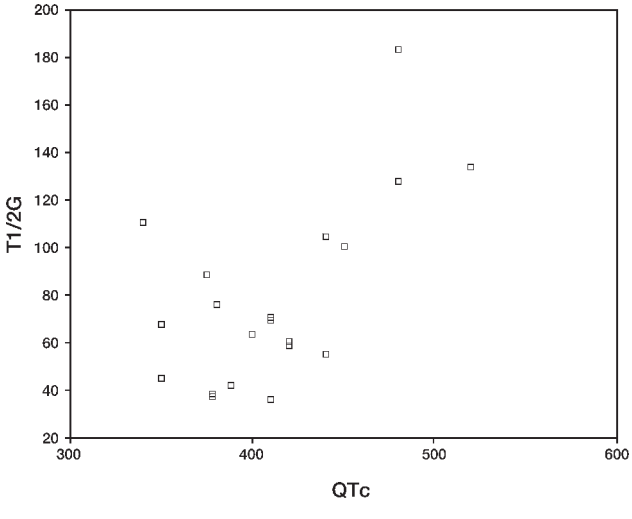

Fig. 2A Correlation between QTc Dispersion and T1/2G in IDDM patients (cc: 0.614, $P = 0.004$). T1/2G, Gastric emptying time, given in minutes; IDDM, Insulin-dependent diabetes mellitus; QTc dispersion given in mSec.

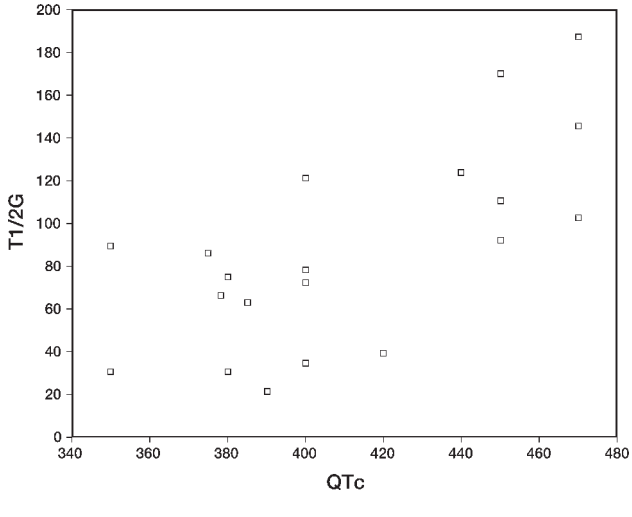

Fig. 2B Correlation between QTc Dispersion and T1/2G in NIDDM patients (cc: 0.659, $P = 0.002$). T1/2G, Gastric emptying time, given in minutes; NIDDM, Non-insulin-dependent diabetes mellitus; QTc dispersion given in mSec.

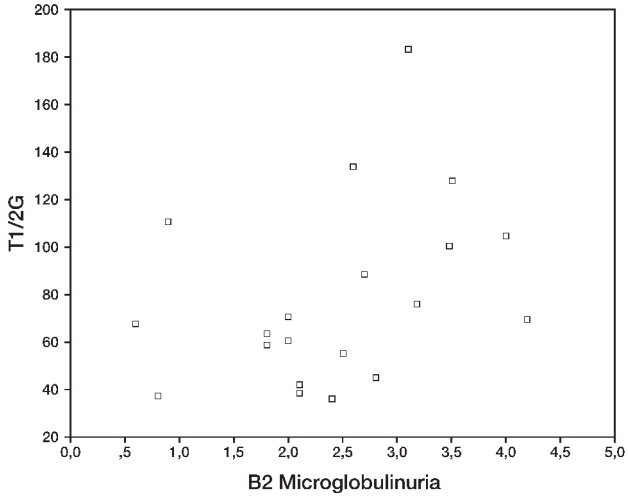

Fig. 3A Correlation between B_2-microglobulinuria and T1/2G in IDDM patients (cc: 0.434, $P = 0.056$). T1/2G, Gastric emptying time, given in minutes; IDDM, Insulin-dependent diabetes mellitus; B2 microglobulinuria given in mg/dl.

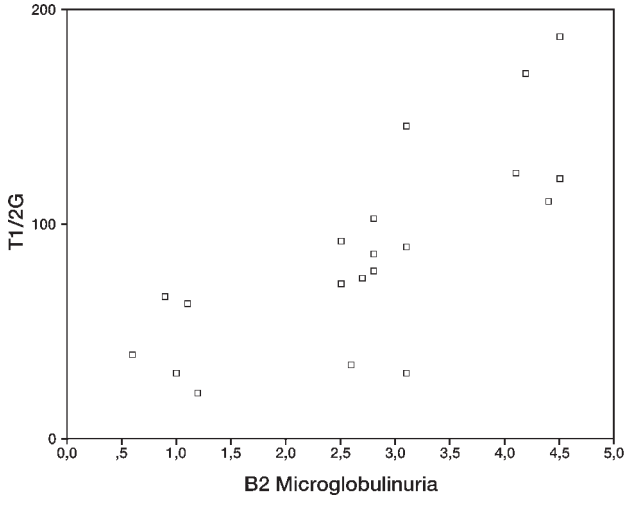

Fig. 3B Correlation between B_2-microglobulinuria and T1/2G in NIDDM patients (cc: 0.774, $P < 0.001$). T1/2G, Gastric emptying time, given in minutes; NIDDM, Non-insulin-dependent diabetes mellitus; B2 microglobulinuria given in mg/dl.

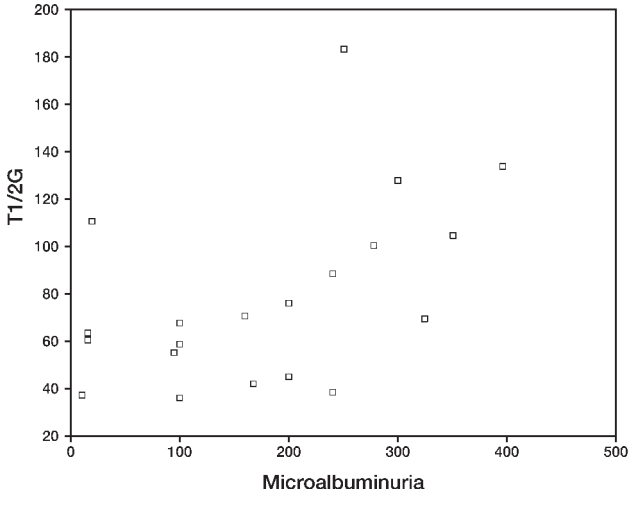

Fig. 4A Correlation between microalbuminuria and T1/2G in IDDM patients (cc: 0.567, $P = 0.009$). T1/2G, Gastric emptying time, given in minutes; microalbuminuria given in mg/dl.

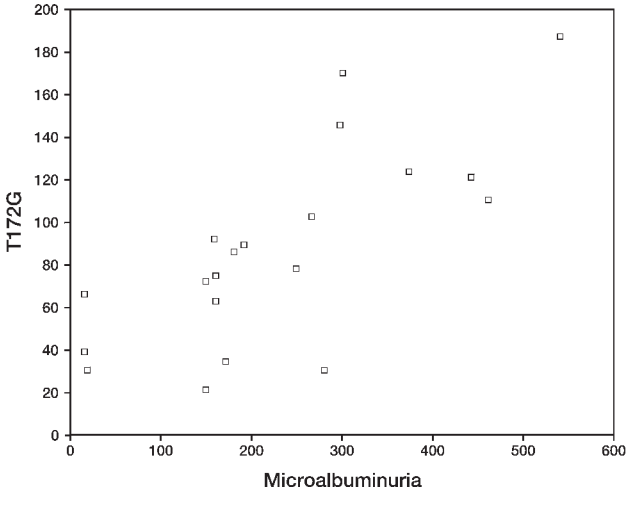

Fig. 4B Correlation between microalbuminuria and T1/2G in NIDDM patients (cc: 0.765, $P < 0.001$). T1/2G, Gastric emptying time, given in minutes; NIDDM, Non-insulin-dependent diabetes mellitus; microalbuminuria given in mg/dl.

non-neurologic complications.

Two major hypotheses have been suggested to explain the neuropathic injury related to DM [34]. The first, the metabolic hypothesis, addresses the accumulation of sorbitol and the concordant decrease in myoinositol, a process leading to functional impairment of Na^+/K^+ ATPase activity [35]. On the other hand, the vascular hypothesis suggests that endoneural microvascular insufficiency is the leading cause of such neuropathic injury [36]. The vascular hypothesis appears to be more

central in recent investigations. Moreover, neither sorbitol accumulation nor myoinositol decrease were identified in a study of sural nerve biopsies of diabetic patients with mild neuropathic symptoms [37].

Results of neurotensiometry studies showed that both IDDM and NIDDM patients enrolled in the present study experienced distal sensorial loss, which was most prominent as regards heat perception. NIDDM patients also had a significant decrease in vibration sensation, a finding that was not observed in the IDDM group (Table 1). This finding may be due to the difference between the mean durations of illness. Moreover, proprioceptive signals are carried by Group1-a neurons, *i.e.*, neurons with the thickest myelin sheaths; this characteristic might provide some protection against the devastating effects of endoneural ischemia and/or hyperglycemia. The role of non-enzymatic glycolisation of extracellular matrix proteins on diabetic vascular disease has been summarized by Brownlee *et al.* [37]. Interaction between advanced glycolisation end products and axonal viability, and the possibility that the myelin sheath provides a physical barrier between the axoplasm and the extracellular fluid (with a high glucose concentration) remain subjects of interest.

In this study, both patient groups showed a lower threshold for cold perception in comparison with controls (Table 1). This finding may be explained by a slowing of blood flow with increased resistivity at the precapillary level; the latter would be caused by microvasculopathy and would be expected to be more prominent at peripheral areas of the body. Circulating blood not only carries the oxygen and metabolites needed for energy production, but it is also the major conductor of heat throughout the body. Decreased temperature, a result of ischemia, may render the autonomic nerve end at the terminal organ much more susceptible to changes in the environment. In the present study, none of the sensorial parameters were in correlation with the presence of gastroparesis. Therefore, autonomic and sensory neuropathy may be shown to progress at different rates and therefore may require different amounts of time to reach a clinically observable threshold.

DM causes not only somatic sensorimotor neuropathy, but also autonomic sensory neuropathy associated with a number of clinical entities such as postural hypotension, cardiac arrhytmia [38], bladder dysfunctions, and gastrointestinal motility disturbances [39–40]. Arildsen *et al.* and Cardoso *et al.* reported that the QT dispersion increased in patients with diabetes mellitus [41, 42]. Landstedt-Hallin *et al.* studied the effects of insulin-induced hypoglycaemia on cardiac repolarization, using QT interval and dispersion measurements in patients with type 2 diabetes; that study revealed that the mean QT intervals and the QT dispersion both increased significantly. It was therefore concluded that significant changes in the repolarization of the heart could be seen during hypoglycaemia in patients with type 2 diabetes, indicating an increased risk of arrhythmia at low blood glucose levels [43]. Darwiche *et al.* and Buysschaert *et al.* reported a strong association between cardiac autonomic neuropathy and gastric vagal neuropathy [22, 44]. Similarly, in our study, QTc dispersions in both patient groups were longer in diabetic patients than in controls (Table 1). The correlation between T1/2 G and QTc dispersion for both patient groups revealed that this clinical parameter may be useful in screening patients for probable future gastroparesis (Fig. 3A, 3B) [45, 46]. Further investigation may lead to determination of a threshold level of QTc dispersion, which would provide an estimation of the individual risk for gastrointestinal motility disorders secondary to autonomic neuropathy.

The most important finding of the present study was the strong positive correlations between retinopathy, urinary β_2-microglobulin, microalbumin concentrations, and gastroparesis (Fig. 3A, 3B, 4A, 4B). The absence of a correlation between gastroparesis and sensory neuropathy renders the situation more intriguing. Retinopathy and nephropathy did correlate with neurologic insult in DM patients [47]. However, to our knowledge, this type of dispersion between the autonomic and somatic modalities of diabetic neuropathy has not been previously discussed in the literature. The renal and retinal pathologies in DM patients are secondary to microvasculopathy. Therefore, autonomic neuropatic complications are also closely related with this pathologic process. Autonomic efferent fibers are the only non-myelinated portion of the nervous system. Together with the finding of "spared" proprioceptive function, this unique characteristic leads to the question of a possible protective effect of the myelin sheath against ischemic injury. Urinary β_2-microglobulin and microalbumin concentrations appear to be candidate screening parameters for gastric motility disorders in diabetic patients, together with QTc dispersion analyses.

In conclusion, retinal and renal microvasculopathy parameters and cardiac autonomic function tests may be useful in the screening of patients for gastroparesis.

Further study will be necessary to determine if these parameters are appropriate first-choice alternatives to the much more expensive and invasive current methods of diagnosing gastrointestinal motility disorders. The possible protective effect of the myelin sheath against axonal injury in DM patients also remains to be investigated.

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