RESEARCH ARTICLE

Early Detection of Diabetic Gastroparesis in Type 2 Diabetes Using Diabetic Peripheral Neuropathy as a Surrogate Marker: A Pilot Study in Rajavithi Hospital

Kitti Chuenyong[1], Attaporn Pornananrat[1], Veerasak Sarinnapakorn[2], Pichit Kuanrakcharoen[3]

[1]Department of Internal Medicine, Gastroenterology Division, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand, [2]Department of Internal Medicine, Endocrinology Division, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand, [3]Department of Radiology, Nuclear Medicine Division Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand

Abstract

Background: Diabetes is a common disease which can lead to many serious complications including diabetic gastroparesis (DG), a chronic disorder of gastric motility which is characterized by delayed emptying of either solids or liquids from the stomach in the absence of mechanical obstruction. DG typically develops in patients with long-standing diabetes, and although it has a low incidence rate, it detracts from sufferers' quality of life and increases rates of mortality and hospitalization. Some studies have shown a strong association between delayed gastric emptying scintigraphy (GES) and cardiovascular autonomic neuropathy; however, no study has been performed of gastric scintigraphy in diabetic patients using diabetic peripheral neuropathy as a surrogate marker. To do enable early detection of DG, our study was designed to detect the prevalence of delayed gastric scintigraphy of patients who had type 2 diabetes with peripheral neuropathy. **Objective:** We aimed to study the prevalence of delayed GES in type 2 diabetic patients with peripheral neuropathy without abnormal symptoms of the upper gastrointestinal (GI) tract. **Study Designs:** This was a pilot, prospective, cross-sectional study. **Methods:** Thirty cases of diabetes with peripheral neuropathy without abnormal symptoms of upper GI tract were sent for examination by GES after patients had ingested a Tc-99m tagged solid meal. **Results:** A total of 29 of 30 patients completed the protocol, and abnormal gastric emptying was found in 13.79% of cases. Other diabetic complications such as nephropathy and retinopathy appeared to be associated with delayed GES; however, these findings were not statistically significant. **Conclusions:** Delayed gastric emptying may be found even in the absence of warning symptoms. This study had limitations because of its small sample size, but it suggested that it may be possible to predict DG using diabetic peripheral neuropathy as a surrogate marker. A study with a larger sample size is required to corroborate our results.

Key words: Delayed gastric emptying, delayed gastric scintigraphy, diabetes gastroparesis, gastroparesis

INTRODUCTION

Diabetes mellitus (DM) is a common disease worldwide.[1] It brings with many serious complications such as neuropathy, vasculopathy, nephropathy, and also gastroparesis,[2] a chronic motility disorder of the stomach characterized by symptomatic delayed emptying of food from the stomach to the small intestine in the absence of mechanical obstruction.[3,4] The most common causes of gastroparesis are diabetes, idiopathic disorders, post-surgery side effects, and medications.[5] Diabetic gastroparesis (DG) is usually clinically silent, although severe DG is one of the most debilitating of all diabetic gastrointestinal (GI) complications.[6] In one cohort study,[7] symptomatic

Address for correspondence:
Kitti Chuenyong, Department of Internal Medicine, Division of Gastroenterology, Rajavithi Hospital, 2 Phayathai Rd, Ratchatewi, Bangkok, Postal Code 10400, Thailand. E-mail: kittich2001@yahoo.com

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DG was found to cause an increase in morbidity and hospitalization.

The prevalence of delayed gastric emptying varies greatly, and in some studies, it has been found in up to 50% of subjects. The incidence of symptomatic DG is probably much lower;[8] a cohort study from Olmsted County revealed a 10-year cumulative incidence of gastroparesis of 5.2% in type 1 DM, 1% in type 2 DM, and 0.2% in controls. Gastroparesis was assumed in the study if patients had at least one of three criteria: Abnormal delayed gastric scintigraphy, presence of gastroparetic symptoms for more than 3 months plus a physician's diagnosis of gastroparesis, and presence of gastroparetic symptoms more than 3 months plus food retention on gastroscopy or upper GI study.[9] Similar results were found by another community-based study that reported the incidence of DG as 2.5 and 9.8/100,000 person-years for men and women, respectively.[10]

Gastric emptying scintigraphy (GES) was first reported in 1966. Since then, it has become the standard modality for the measurement of gastric motility in clinical practice because it provides a physiologic, non-invasive, and quantitative measurement of GE. While GES has been considered the standard for the measurement of GE, there is a lack of uniformity in the performance of the test. The variations mostly come from the methods of analysis such as emptying halftime, rate of emptying (percent per minute), or the percentage of retention at different time points. In 2008, a consensus was reached to use the percentage of retention as the standard GES analysis.[11] Several studies have been conducted to identify a non-invasive parameter for predicting a correlation with gastroparesis, and body mass index (BMI), fasting blood glucose, and hemoglobin A1C values did not demonstrate a reliable correlation; however, investigations concerning cardiovascular (CVS) autonomic regulation have shown striking correlations with DG.[12] Symptoms of DG such as nausea, vomiting, and early satiation have not been successful predictors of delayed GES.[13]

Studies of uncomplicated diabetes and gastroparesis have not succeeded in finding any significantly delayed gastric emptying time.[14,15] To identify high risk of DG, many trials have focused on diabetic autonomic neuropathy and have found a strong correlation between DG and cardiac autonomic neuropathy. All of these studies defined abnormal autonomic dysfunction by evaluating the cardiac autonomic function, which is a late complication of diabetes.[12,16,17] Therefore, the present study aimed to find other better surrogate markers for earlier detection of DG. The correlation between diabetic peripheral neuropathy and DG has never been studied. The main purpose of this study was to look for any association between DG in type 2 diabetes and peripheral neuropathy, and we conducted a pilot, prospective, cross-sectional study of these two conditions.

MATERIALS AND METHODS

The study population consisted of 30 patients from the Endocrinology Clinic, Rajavithi Hospital, who had type 2 diabetes and were over 18 years old [Table 1]. Our inclusion criteria were patients who had type 2 diabetes in accordance with the diagnosis criteria of the American Diabetes Association, had no abnormal GI symptoms, and had been diagnosed by a neurologist as having diabetic neuropathy. Patients known to have any diseases which influenced gastric motility were excluded from our study, together with those who had egg allergy or were pregnant. All medications which affected GES were discontinued 2 weeks before the procedure. All of the participants signed informed consent forms after receiving clear information about the study protocol and the GES procedure. The study protocol was approved by the Ethics Committee of Rajavithi Hospital (Approval number 024/2554).

After enrollment, the patients were interviewed and tested for neurologic signs before undergoing fundoscopy by an ophthalmologist. Blood pressure and pulse rate were recorded both in the supine and upright position. If orthostatic hypotension was detected without obvious causes such as drugs or volume depletion, the patient was presumed to have autonomic neuropathy. The participants had the following tests: Fasting blood sugar, HbA1C, complete blood counts, lipid profile, blood urea nitrogen, creatinine, urine analysis, urine protein creatinine ratio, and urine pregnancy test. All of the data were collected prospectively.

Preparation before the GES consisted the following: food and drink were not allowed after midnight of the night before the procedure; cigarettes and alcohol were stopped at least 24 h before the operation; and drugs such as prokinetics, anticholinergics, opiates, or others which can affect GES were also discontinued at least 2 weeks before the GES. On the day of the GES examination, participants had a blood test for FBS and HbA1C. Our test meal for the GES study was the same kind as used in the study of GES in normal Thai volunteers which was created by our radiologist (P.K.***). The study of normal Thai volunteers' results provided a standard value for the diagnosis of delayed gastric emptying for Thai patients. We did not use the criteria for delayed GE published in 2008[11] because we were concerned that the criteria were influenced by multiple factors and had never been validated in Asian patients. In our study, we defined delayed GE using halftime of GE (T1/2). The normal range of half-time GE in Thai people is not stated in this report. As solid GES is known to be more accurate than liquid GES, the test meal in our protocol was a solid type consisting of one egg with Tc-99m Phylate or Tc-99m SC 1 millisievert, 100 g of rice, and 100 ml of water. After taking the test meal, participants underwent GES.

Performing gastric scintigraphy using Tc-99m Phytate or Tc-99m SC 0.925 millisievert can trigger adverse side effects, but these are minimal, the common ones being nausea, vomiting, and dizziness. The ratio of cancer from exposure

to nuclear radiation from gastric scintigraphy in an entire lifetime is very low. Hence, the International Commission on Radiological Protection has classified this type of diagnosis as having very low risk of complications, especially for people who are exposed to <1 millisievert per year.[18]

In the present study, we defined delayed gastric emptying using halftime of food clearing as mentioned above, since normal values of GES from normal Thai volunteers had been recorded by the radiologist in our team (P.K.***). The prevalence rates of abnormal gastric scintigraphy and other comorbid conditions were reported as percentages.

Statistical analysis

Descriptive results of continuous variables were expressed as mean ± standard deviation and median (25^{th}–75^{th} IQ). Chi-square tests and one-way ANOVA were used to compare categorical and continuous variables in each grading group, and a $P < 0.05$ was set for statistical significance.

RESULTS

A total of 30 type 2 diabetes patients with diabetic peripheral neuropathy without abnormal GI symptoms were included in the study; however, only 29 were successfully scanned with GES, as one of the patients could not finish the test because of hypotension that occurred during the GES process. There were equal numbers of male and female patients in our study, the mean age of participants was 58.92 ± 9.65 years old, and the mean BMI was 24.99 ± 4.25 kg/m^2. Other comorbidities were also recorded as follows: Diabetic nephropathy 33.3%, diabetic retinopathy 23.3%, macrovascular complications (central nervous system and CVS) 13.3%, autonomic neuropathy presumption by the presence of orthostatic hypotension 16.7%, hypertension 40%, and hypercholesterolemia 40% [Table 1].

The laboratory results before receiving gastric scintigraphy revealed mean fasting blood sugar of 135.53 ± 47.61 mg/dL and mean HbA1C of 7.63 ± 1.75%, while mean cholesterol was 178.43 ± 30.42 mg/dL, mean triglyceride was 122.87 ± 50.10 mg/dL, mean high-density lipoprotein was 48 ± 12.53 mg/dL, mean low-density lipoprotein was 114.07 ± 26.91 mg/dL, and mean urine albumin was 491.9 ± 1501.31 mg/day [Table 2].

The overall prevalence of delayed GES in our study was 4 from 29 patients or 13.8%. The prevalence rates of gastric retention by the time points of 30, 60, 90, 120, 180, and

Table 1: Baseline characteristics and comorbidities

Characteristics	*n* (%) or Mean±SD	Median (25^{th}-75^{th} IQ)
Gender: Male	15 (50%)	
Average age at enrollment (y)	58.92±9.65	57.5 (51–64.75)
Height (cm)	159.33±13.01	159 (153.75–164)
Weight (kg)	63.74±13.01	64 (54–72.25)
BMI (kg/m^2)	24.99±4.25	25.05 (25.05–27.29)
BMI category		
Underweight (<18 kg/m^2)	1 (3.3%)	
Normal (18–24 kg/m^2)	12 (40%)	
Overweight (25–30 kg/m^2)	14 (46.7%)	
Obese (>30 kg/m^2)	3 (10%)	
DM duration (y)	5.89±6.38	5.00 (3–6.25)
Total amount of hypoglycemic used	1.43±0.94	1 (1–2)
Insulin used	5 (16.7%)	
DM complications		
Diabetic nephropathy	10 (33.3%)	
Diabetic retinopathy	7 (23.3%)	
Macrovascular involvement (CNS and CVS)	4 (13.3%)	
Orthostatic hypotension at enrollment	5 (16.7%)	
Comorbidities		
Hypertension	12 (40%)	
Dyslipidemia	12 (40%)	

BMI: Body mass index, DM: Diabetes mellitus, CNS: Central nervous system, CVS: Cardiovascular, SD: Standard deviation

Table 2: Baseline monitors and laboratory results

Characteristic	Range (%)	Median (25th–75th IQ)
Systolic blood pressure (mmHg)	136±22.65	137 (123–150.75)
Diastolic blood pressure (mmHg)	77.87±9.25	78 (73–82.75)
Heart rate (beat/minute)	82.10±13.74	81.5 (72–94.5)
Fasting blood sugar (mg/dL)	135.53±47.61	123.5 (109–143.5)
HbA1C (%)	7.63±1.75	7.25 (6.3–8.22)
Cholesterol (mg/dL)	178.43±30.42	176 (159.75–195.25)
Triglyceride (mg/dL)	122.87±50.10	116.5 (87.5–143.75)
HDL (mg/dL)	48.00±12.53	46.5 (40.75–52.25)
LDL (mg/dL)	114.07±26.91	108.5 (92.5–133.5)
Blood urea nitrogen (mg/dL)	13.13±6.07	11.5 (9–15)
Serum creatinine (mg/dL)	1.06±1.00	0.85 (0.7–1.1)
Urine albumin (mg/day)	491.90±1501.31	97.5 (47.5–249.25)
Urine albumin category: *n* (%)		
No microalbuminuria	5 (16.7)	
Microalbuminuria	17 (56.7)	
Macro albuminuria	8 (26.7)	
Serum potassium (mEq/dL)	4.20±0.51	4.2 (3.7–4.6)

HDL: High-density lipoprotein, LDL: Low-density lipoprotein

Table 3: Gastric scintigraphy results

Gastric scintigraphy	Delay time: *n* (%)
Halftime (T½) of gastric emptying	4 (13.8)
Gastric retention at 30 min	0 (0)
Gastric retention at 60 min	3 (10.3)
Gastric retention at 90 min	6 (20.7)
Gastric retention at 120 min	4 (13.8)
Gastric retention at 180 min	5 (17.2)
Gastric retention at 240 min	2 (6.9)

240 min were 0, 10.3, 20.7, 13.8, 17.2, and 6.9%, respectively [Table 3].

We also analyzed the association between delayed gastric emptying time and other comorbidities such as diabetic complications (i.e., retinopathy, nephropathy, macro vasculopathy, and autonomic neuropathy), sex, hypertension, and hyperlipidemia [Table 4]. Females were more numerous than males in the delayed GES group (females = 75% and males = 25%). Diabetic nephropathy and retinopathy were much more frequent in the delayed GES group (both at 50%), while in the normal GES group, nephropathy and retinopathy were found in only 28 and 12% of cases, respectively. Orthostatic hypotension was found in 25% of patients in the delayed GES subjects and in 16% of the normal GES group. Macrovascular complications were at 25 and 12% in the delayed and normal GES group, respectively. Although these conditions were found more frequently in the delayed GES group, none of them showed statistical significance.

The other parameters in our study, such as BMI, blood pressure, duration of diabetic diagnosis, fasting blood sugar, HbA1C, serum lipid, blood urea nitrogen, and creatinine, did not reveal any significant difference between subjects in the delayed and normal GES group [Table 5].

With regard to the side effects resulting from GES, no serious complications were found. Only one participant was unable to finish the procedure, and this was because of hypotension which was caused by diuretics not related to the GES process.

DISCUSSION

DG is a late and uncommon diabetic complication, especially in type 2 diabetes;[9] however, when it occurs, it requires long-term prokinetic treatment, surgery, or mechanical devices and results in a poorer quality of life.[19] DG has also been found to increase hospitalization and morbidity.[7] Our study was designed to achieve early detection of DG using signs of peripheral neuropathy as a surrogate marker.

As there is no test that is specific to the GI autonomic function, evaluation of diabetic CVS autonomic function was employed as a surrogate marker of DG.[20] Koçkar *et al*., 2002,[12] compared gastric emptying using T1/2 in long-standing type 1 and type 2 diabetes and in healthy volunteers. The authors concluded that nephropathy, vasculopathy, and autonomic neuropathy were strongly associated with gastroparesis; however, the definition of gastroparesis in the

Table 4: Subgroup analysis of normal and abnormal GES focusing on other diabetic complications

Characteristic	Delay T½: *n*=4 (%)	Normal T½: *n*=25 (%)	*P*
Gender: Male	1 (25)	13 (52)	0.32
Diabetic nephropathy	2 (50)	7 (28)	0.38
Diabetic retinopathy	2 (50)	5 (20)	0.19
Macrovascular involvement (CNS and CVS)	1 (25)	3 (12)	0.48
Orthostatic hypotension	1 (25)	4 (16)	0.66
Insulin used	1 (25)	4 (16)	0.66
Hypertension	3 (75)	13 (52)	0.39
Dyslipidemia	2 (50)	10 (40)	0.70

GES: Gastric emptying scintigraphy, CNS: Central nervous system, CVS: Cardiovascular

Table 5: Subgroup analysis of normal and delayed GES focusing on baseline characteristics and basic laboratory results

Characteristic	Delay T½	Normal T½	*P*	95% CI
Age	64.25±6.30	57.88±1.85	0.39	−25.59–12.85
Height	153.25±4.13	160.08±1.35	0.20	−5.68–19.34
Weight	51.00±8.29	65.56±2.35	0.18	−10.76–39.89
BMI	21.63±3.22	25.51±0.76	0.32	−6.07–13.84
Systolic blood pressure	134.00±9.63	138.60±4.32	0.68	−23.89–33.09
Diastolic blood pressure	77.25±5.50	78.80±1.66	0.81	−15.18–18.28
Pulse	85.50±7.40	81.00±2.75	0.60	−26.69–17.69
DM Duration (y)	4.33±2.78	6.18±1.36	0.51	−4.81–8.51
Fasting blood sugar	123.25±19.56	139.20±9.87	0.50	−41.54–73.44
HbA1C	7.20±0.96	7.61±0.35	0.71	−2.47–3.29
Cholesterol	166.50±13.62	182.60±5.83	0.34	−24.32–56.52
Triglyceride	119.75±20.38	123.32±10.63	0.88	−56.22–63.36
HDL	57.75±8.42	47.24±2.20	0.30	−36.37–15.35
LDL	112±9.51	116±5.51	0.73	−23.82–31.82
Urine albumin (mg/day)	639.50±541.51	445.68±319.86	0.77	−1777.03–1389.39
Blood urea nitrogen	16.00±5.43	12.28±0.97	0.55	−20.69–13.25
Serum creatinine	1.03±0.15	1.05±0.21	0.93	−0.52–0.57
Serum potassium	4.28±0.35	4.16±0.10	0.76	−1.19–0.95

GES: Gastric emptying scintigraphy, BMI: Body mass index, DM: Diabetes mellitus, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CI: Confidence interval

study was actually the definition of delayed GES, which was different from the definition reported by the 2008 consensus. Darwiche *et al*., 2001,[16] found an association between delayed gastric emptying and cardiac autonomic neuropathy in type 1 diabetes in a study of three groups: Patients with diabetes with CAN; those with diabetes without CAN; and healthy volunteers. The study used ultrasonography to test gastric emptying, however, and this is not a standard test for gastric emptying studies. Punkkinen *et al*., 2008,[17] performed gastric scintigraphy in 27 type 1 diabetes patients with abnormal GI symptoms and found abnormal gastric emptying time for 26% of the patients. Impaired gastric emptying was correlated with cardiac autonomic neuropathy but not with GI symptoms.

The present research was the first study of DG to include type 2 diabetes with diabetic peripheral neuropathy. Our results regarding diabetic complications showed that, among those with diabetic peripheral neuropathy, other complications were less commonly found, for example, diabetic retinopathy was found in only 50% of cases. This implied that diabetic peripheral neuropathy was the diabetic complication with the earliest onset; therefore, it may be the best surrogate marker for screening of DG; it should at least be superior to cardiac autonomic neuropathy.

In our study, the prevalence of delayed GES was 13.8%, lower than that found in a study by Punkkinen *et al*.[17] (26%). The difference may be caused by many factors such as the nature

of the studied population (Type 1 or 2), the definition of delay gastric emptying, and the test meal used in the studies. The obvious difference between our study and that of Punkkinen *et al*. was the stage of diabetes. Our study selected diabetic patients with peripheral neuropathy which occurs earlier than cardiac autonomic neuropathy, and this may explain why our study found a lower prevalence of delayed GES. With regard to using diabetic peripheral neuropathy as a surrogate marker of DG, the data were not strong enough to form any conclusion. Further studies with larger sample sizes should be performed.

Other diabetic complications, especially nephropathy and retinopathy, seemed to be associated with delayed gastric emptying; however, there was no statistical significance, as the sample size was not large enough to enable generalization. As found previously, females predominated in the delayed GES group of our study.

The disadvantages of our study were its small population size, the lack of data in relation to the prevalence of delayed GES in diabetics without peripheral neuropathy to enable comparison, and the interpretation method, which was different from that in the standard guidelines. As mentioned above, we already had a normal value for the Thai standard provided by the study of our colleague (P.K.***), and that is why we used gastric halftime (T1/2) in our study.

For future research into DG, we recommend that a multicenter study is performed with an increased sample size because the prevalence of DG in this study was not as high as we expected. In a study of diabetic patients with abnormal GI symptoms, it would be prudent to exclude other GI disorders which mimic DG, for instance, functional dyspepsia, irritable bowel syndrome, and dyspepsia to get an accurate estimate of the level of DG. Importantly, a case study of the disease's natural history after the diagnosis of delayed gastric emptying time is required to study the exact mechanism of DG.

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