# Delayed gastric emptying is related to cardiovascular autonomic neuropathy in Chinese patients with type 2 diabetes

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## Abstract

***Background and study aims :*** **Delayed gastric emptying (DGE) is the commonest gastrointestinal (GI) complication in type 2 diabetes. We aimed to evaluate the association between DGE and cardiovascular autonomic neuropathy (CAN) in type 2 diabetes.**

***Patients and methods :*** **A total of 71 Chinese patients (39 men and 32 women, aged 60-90 years) and 30 controls (12 men and 18 women, aged 50-79 years) were studied in Nanjing, China. The gastric emptying was assessed by $^{13}$C-octanoic acid breath test (OBT) and gastric emptying ultrasonography (GEU). Cardiovascular autonomic neuropathy (CAN) was assessed by a scoring system being validated before.**

***Results :*** **The diabetic patients, except for a higher plasma glucose level, had similar characteristics compared to the non-diabetic controls. Diabetic patients had higher incidence of DGE and CAN than controls (48.5% vs. 10.7%, p = 0.001). Among diabetic patients with DGE (n = 27), 18 (66.7%) had CAN and 9 (33.3%) did not. Corresponding figures for those without DGE (n = 39) were 14 (35.9%) and 25 (64.1%), respectively (p = 0.014). Diabetes was independently associated with the risk of DGE with odd ratio (95% CI) of 15.6 (1.92, 127.06) (p = 0.010). The presence of diabetes or CAN was independently associated with the half gastric emptying time after adjusting for age, gender, plasma glucose and blood pressure.**

***Conclusions :*** **We found a much prolonged gastric emptying time in Chinese patients with type 2 diabetes as compared to non-diabetic controls. There was a high rate of CAN in diabetic patients, and it was associated with gastric emptying.** (Acta gastroenterol. belg., **2011**, 74, **28-33**).

**Key words** : clinical diabetes, imaging, complication, autonomic neuropathy.

## Introduction

Diabetes mellitus is a systemic disease involving multiple organs. The entire gastrointestinal (GI) tract from the esophagus to the anorectal region can be affected (1). Gastroparesis is the commonest GI complication in type 2 diabetes that occurs in up to 50% of people with long-standing diabetes (2,3). In addition to direct morbidity, gastroparesis can influence glycaemic control by predisposing to unpredictable fluctuations of blood glucose (4,5). We have previously reported a 2.3-fold increase risk of having GI symptoms in Chinese patients with type 2 diabetes as compared to age- and sex- matched normal controls (6). In particular, epigastric fullness was one of the three most commonly reported GI symptoms.

Gastroparesis in diabetic patients are multifactorial (7-9) while autonomic neuropathy is believed to be one of the most important underlying mechanisms (1,8,10). Previously, gastric emptying was commonly assessed by non-invasive gastric emptying ultrasonography (GEU) (11). Recently, $^{13}$C-octanoic acid breath test (OBT) was developed and reported to be an accurate and sensitive tool to diagnose gastroparesis (12-15). In this study, we assessed gastric emptying in 71 Chinese patients with type 2 diabetes and compared them with 30 normal controls. We also studied their cardiovascular autonomic functions with a validated scoring system in Chinese on cardiovascular autonomic neuropathy (CAN). We aimed to : 1) study the scope of problem of gastric emptying based on GEU and OBT, and 2) evaluate the association between CAN and gastric emptying in Chinese. This has the important potential therapeutic implication that for management of diabetic patients with either gastroparesis or CAN, we will need to take the other condition into consideration. Furthermore, clinical outcome prediction may also be linked to the association between CAN and gastric emptying.

## Patients and methods

A total of 71 Chinese patients with type 2 diabetes being diagnosed for 5 years or more were recruited into the study. The diabetic patients were randomly recruited from the Diabetes out-patient clinic in Jiangsu Province Institute of Geriatric, China. Only patients having a reasonable diabetes control according to the Asian-Pacific Type 2 Diabetes Policy Group were eligible to enter the study. Reasonable diabetic control was defined as fasting plasma glucose (PG) level ≤ 7.0 mmol/L, post-prandial PG ≤ 10.0 mmol/L and glycated hemoglobin ($HbA_{1c}$) values stayed within the range of 6.5 to 7.5%. These glycemic parameters were measured within 3 months of starting the study and being documented in their out-

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patients' clinic notes. Another 30 normal subjects were recruited as controls. They were volunteers recruited from the Nanjing community.

The study protocol has been approved by the Ethical Committee, Jiangsu Province Institute of Geriatrics, Nanjing, China. On the day of assessment, demographic data was collected. After sitting for at least 5 minutes, blood pressure (BP) was measured in the right arm using a standard mercury sphygmomanometer. The Korotkoff sound V was taken as the diastolic BP. Only one BP measurement was performed unless the reading was grossly abnormal i.e. < 90/40 or > 180/110 mmHg. Fasting, 2-hour post-prandial PG and $HbA_{1c}$ (in diabetic patients only) were also measured (Bayer DCA 2000).

*Gastric emptying*

The gastric emptying was assessed by $^{13}$C-octanoic acid breath test (OBT) and gastric emptying ultrasonography (GEU). OBT was conducted according to the method described by Ghoos *et al* (16). After a 12-hour overnight fast, all subjects attended the study site in early morning where they were arranged to consume a standard test meal. The test meal consisted of a raw egg mixed with 100 mg $^{13}$C-octanoic acid ($^{13}$C concentration 99%) which was fried as omelet and served with 2 pieces of white bread (total calories ~420 kcal) together with 150 mL plain water. Each test meal was consumed within 10 minutes.

$^{13}$C breath concentration was assessed with the subjects taking normal breath before and every 15 minutes consecutively for 4 hours after the test meal (17 samples for each subject). During the 4 hours of testing, all subjects were confined to the study room. $^{13}$C concentration was measured by Isotope Ratio Mass Spectrometry (Breath MATplus, Finnigan, Germany). The changes of $^{13}$C concentrations at each time point from baseline were analyzed to calculate the half gastric emptying time (GET1/2 i.e. 50% of gastric contents emptied), time of lag phase (Tlag i.e. 5% of gastric contents emptied) and food emptying rate at 60 and 120 minutes (FER60 and FER120 i.e. proportion of gastric contents remained in stomach at 60 or 120 minutes). Delayed gastric emptying (DGE) was defined as GET1/2 > mean GET1/2 of controls + 2 SD.

Gastric emptying by GEU was determined by the cross-sectional area of the stomach. GEU was performed the next day after OBT during fasting state, and 10-min, 20-min, 30-min, 60-min and 120-min after consuming a standard test meal without $^{13}$C. A B-mode ultrasound examination (3.5 MHz transducer) was conducted in subjects lying flat on bed and images were taken of the upper abdomen along the mid line below the sternal xiphoid. Stomach area was measured when abdominal aorta, superior mesenteric vein and stomach were displayed in the same ultrasonic plane. Within 30 minutes of test meal, the largest stomach area was defined as the "full stomach area (FSA)". Food emptying rate at 120-min (FER120) (or at 60-min, FER60) was calculated by the formula :

$$\text{FER120, \%} = [\ (\text{FSA} - \text{stomach area at 120-min}) / \text{FSA}\ ] \times 100$$

*Cardiovascular anutonomic neuropathy (CAN)*

CAN was determined by the following clinical assessments : i) heart rate variability on deep breathing ; ii) heart rate variability on postural change ; iii) movement reflex index ; and iv) BP variability from lying to standing position. These four parameters had been widely studied and reported as reliable tests for CAN (17,18). A scoring system based on these 4 tests had been validated in Chinese and reported by our team previously (19). The total score is highly skewed and ranged from 0 to 4.5 with 0 = normal ; 0.5 = borderline and 1 or above = abnormal (presence of cardiovascular autonomic neuropathy) (19). Significance and strong association between these tests with adverse outcomes related to CAN had also been further evaluated and reported in the literature (20,21).

*Statistical Analysis*

Statistical analysis was performed using SPSS (version 15.0) software on an IBM compatible computer. All results are expressed as mean ± SD, mean (95% confidence interval, CI) or number (percentage) where appropriate. The analysis of variance, paired t-test and Chi-square tests were used for between group comparisons where appropriate. Fisher's exact test was used for group comparison when one or more of the groups had $n < 5$. Pearson age- and sex-adjusted partial correlation coefficient (r) was used to assess linear correlation between CAN scores and half gastric emptying time (GET1/2). Binary logistic regression to predict the risk of DGE and multiple linear regression analysis (stepwise forward) to predict the GET1/2 were performed with age, gender, diabetes (1 = present ; 0 = absent), PG (fasting and post-prandial) levels, BP and CAN (1 = present ; 0 = absent) as independent variables. A p-value $< 0.05$ was considered to be significant.

## Results

Of the 71 Chinese type 2 diabetic patients, there were 39 (54.9%) men and 32 (45.1%) women. Their mean age was 68.2 ± 6.8 years (range : 60-80 years). Of the 30 normal controls, there were 12 (40%) men and 18 (60%) women with mean age of 68.1 ± 6.3 years (range : 60-79 years). Table 1 summarizes the clinical characteristics of these 101 study subjects. Diabetic patients had higher PG values than non-diabetic controls, otherwise, the age, gender and BP were similar between the 2 groups.

Table 2 summarizes the results of gastric emptying assessment by OBT and GEU. By definition, DGE was greater than the mean GET1/2 of controls + 2SD = 82.3 + (23.6 × 2) = 129.5 min. Diabetic patients had

Table 1. — **Clinical characteristics and the comparisons of the 71 patients with type 2 diabetes and 30 normal controls**

| | Controls (n = 30) | Diabetes (n = 71) | p-value |
|---|---|---|---|
| Men:women | 12/18 | 39/32 | 0.17 |
| Age, years | 68.1 ± 6.3 | 68.2 ± 6.8 | 0.952 |
| Diabetes, years | 0 | 11.1 ± 5.2 | < 0.001 |
| Fasting PG, mmol/L | 5.2 ± 0.4 | 6.5 ± 0.9 | 0.019 |
| 2hr PG, mmol/L | 6.5 ± 1.0 | 11.8 ± 3.8 | < 0.001 |
| $HbA_{1c}$, % | / | 6.7 ± 0.5 | / |
| Systolic BP, mmHg | 134.7 ± 18.7 | 142.2 ± 25.8 | 0.102 |
| Diastolic BP, mmHg | 73.0 ± 10.8 | 77.0 ± 11.7 | 0.160 |

PG, plasma glucose ; $HbA_{1c}$, glycated hemoglobin ; BP, blood pressure.

Table 2. — **Gastric emptying assessment by $^{13}$C-octanoic acid breath test (OBT) and gastric emptying ultrasonography (GEU) of the 71 patients with type 2 diabetes and 30 normal controls**

| | Controls | Diabetes | p-value |
|---|---|---|---|
| Gastric emptying : | n = 30 | n = 71 | |
| OBT : | | | |
| GET1/2, min | 82.3 ± 23.6 | 110.1 ± 30.1 | < 0.001 |
| Tlag, min | 13.6 ± 4.8 | 18.9 ± 5.6 | <0.001 |
| *FER60, % | 30.8 ± 5.3 | 22.9 ± 5.2 | < 0.001 |
| ^FER120, % | 72.8 ± 12.5 | 57.5 ± 15.3 | < 0.001 |
| DGE, % (n) | 10.0 (3) | 38.0 (27) | 0.004 |
| GEU : | | | |
| Area of empty stomach, $cm^2$ | 3.81 ± 0.72 | 4.36 ± 0.96 | 0.005 |
| *FER60, % | 40.1 ± 3.3 | 32.1 ± 5.8 | <0.001 |
| ^FER120, % | 86.1 ± 7.1 | 69.1 ± 12.5 | < 0.001 |
| Cardiovascular autonomic neuropathy (CAN) : | n = 28 | n = 66 | p-value |
| CAN score, mean (95% CI) | 0.43 (0.22, 0.64) | 0.98 (0.72, 1.25) | 0.012 |
| With CAN, n (%) | 3 (10.7) | 32 (48.5) | 0.001[f] |
| Without CAN, n (%) | 25 (89.3) | 34 (51.5) | 0.001[f] |

GET1/2, half gastric emptying time (50% of gastric contents emptied) ; Tlag, time of lag phase (5% of gastric contents emptied) ; FER60 and FER120, food emptying rate at 60- or 120-minutes ; DGE, delayed gastric emptying ; CI, confidence interval.

Presence of CAN was defined as CAN score ≥1.

Comparing OBT and GEU on *FER60 and ^FER120 : all p-values < 0.001 among controls and diabetes.

[f]Fisher's exact test.

much prolonged gastric emptying than controls according to both OBT and GEU as assessment methods. The FER60 was constantly ~10% higher and the FER120 ~12% higher as assessed by GEU comparing to that assessed by OBT in both control and diabetic subjects ($p < 0.001$).

Table 2 also summarizes the rate of CAN in both groups of subjects. Diabetic subjects had much higher risk of CAN than controls (48.5% *vs.* 10.7%, $p = 0.001$) as well as a higher CAN score (mean (95% CI) : 0.98 (0.72, 1.25) *vs.* 0.43 (0.22, 0.64), $p = 0.012$). Among diabetic patients with DGE (n = 27), 18 (66.7%) had CAN and 9 (33.3%) had no CAN. The corresponding figures for diabetic patients without DGE (n = 39) were 14 (35.9%) and 25 (64.1%), respectively ($p = 0.014$, Fisher's exact test). Figure 1 shows the distribution of GET1/2 values and the corresponding CAN scores among diabetic patients. The Pearson age- and sex-adjusted partial correlation coefficient (r) between GET1/2 and CAN score was 0.496 ($p < 0.001$).

Table 3 summarizes the results of regression analyses to predict DGE (binary logistic regression) and GET1/2 (linear regression) with age, gender, diabetes, PG levels, BP and CAN as independent variables. The presence of diabetes was independently associated with the risk of DGE with OR (95% CI) at 15.6 (1.92, 127.06) ($p = 0.010$). Other independent variables were not statistically significant and did not enter into the model. The presence of diabetes or CAN was also independently associated with the GET1/2 after adjusting for age, gender, PG and BP. Among the diabetic subjects, duration of diabetes was similar between those with or without DGE (12.1 ± 3.6 vs. 11.6 ± 4.0 years, $p = 0.646$).

## Discussion

Impairment of gastric emptying is well recognized in patients with diabetes (1-4,10). In particular, patients with long-standing insulin-treated type 1 diabetes showed more delayed gastric emptying than those with

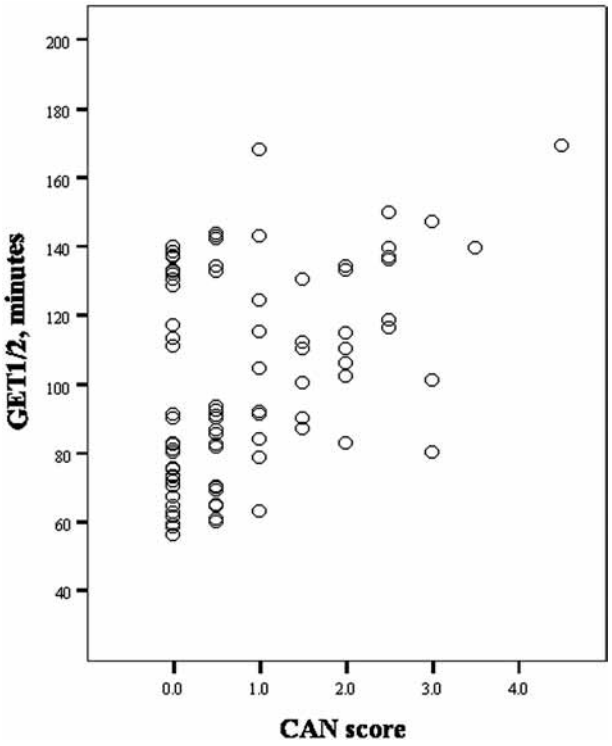


Fig. 1. — Distribution of GET1/2 and corresponding CAN scores in patients with diabetes.

GET1/2, half gastric emptying time (50% of gastric contents emptied) ; CAN, cardiovascular autonomic neuropathy.
Age- and sex-adjusted partial correlation coefficient (r) between GET1/2 and CAN scores : $r = 0.496$, $p < 0.001$.

type 2 diabetes after adjusting gender, $HbA_{1c}$ level, and the rate of neuropathy (22). However, type 2 diabetes is much more common and the impact of DGE on this group of patients cannot be overemphasized. Clinically, patients often present DGE as epigastric fullness, postprandial abdominal bloating, nausea or even vomiting (6,10,23), which impaired their quality of life. Adverse effects on the absorption of oral anti-diabetic agents have also been reported, potentially disturbing the glycemic control of affected patients (2,4,24).

The OBT using solid meal containing $^{13}$C-octanoic acid is considered a useful tool to measure gastric emptying both in physiological and pathological conditions (13-15). Zahn *et al* compared OBT and scintigraphy (99m Technetium-Nanocoll), which was highly accurate but much more expensive than OBT and involving radioactivity (25). They concluded that the OBT represented a suitable method to measure disordered gastric emptying in patients with diabetes due to its highly significant positive correlation to scintigraphy and high validity (25). Ultrasonography to assess gastric emptying is simple and non-invasive (11,26). We found a relatively good precision in subjects with or without diabetes (consistent differences in the FER-60 and FER-120 between the 2 groups) but low validity (much higher FER values) of using GEU to predict gastric emptying in our Chinese subjects as compared to OBT. Obviously, GEU is more operator-dependent hampering its reliability (11). In agreement with other reports (12-15), our results support the use of OBT to assess gastric emptying in both non-diabetic subjects and patients with type 2 diabetes.

DGE in diabetes is multi-factorial. Jones *et al*. reported that the symptom of abdominal fullness and female gender were independent predictors of delayed gastric emptying (27). Effects of glycemic levels on gastroparesis have been widely discussed. In this study, we found an independent association between DGE and the presence of diabetes, while PG level itself did not enter the regression model. On the other hand, acute changes in the blood glucose concentration had been demonstrated to be a major reversible factor on esophageal, gastric, intestinal, gallbladder, and anorectal motility in both healthy subjects and diabetic patients (5). However, while changes in the plasma glucose levels affect gastric motility, $HbA_{1c}$ has been reported not to correlate with gastric emptying (28). Interestingly, duration of diabetes had been reported by some studies to associate, though weakly, with GI motility disorders (29,30). We cannot, however, demonstrate any association between DGE and diabetes duration in our study, which may be partly due to the relatively small sample size.

Table 3. — **Results of regression analyses (stepwise forward) to predict the risk of delayed gastric emptying (DGE) and half gastric emptying time (GET1/2) (as dependent variables) using the following parameters as independent variables : age, gender, diabetes, plasma glucose levels, blood pressure and cardiovascular autonomic neuropathy (CAN)**

| (a) DGE : | | | | |
|---|---|---|---|---|
| | *Binary logistic regression : Nagelkerke $R^2 = 0.249$ | | | |
| | β | S.E. | p-value | OR (95% CI) |
| Diabetes | 2.75 | 1.07 | 0.010 | 15.60 (1.92, 127.06) |
| (b) GET1/2 : | | | | |
| | *Linear regression : $R^2 = 0.329$ | | | |
| | β | S.E. | p-value | |
| Diabetes | 19.89 | 8.09 | 0.017 | |
| CAN | 18.91 | 7.94 | 0.020 | |

OR, odds ratio ; CI, confidence interval.
*Only statistical significant independent variables from the regression models were stated in the above tables.

In the present study, we quantify CAN in our patients with a validated scoring system consisting of four major clinical parameters on movement reflex, heart rate and BP variability under different conditions (19). These assessment tests had been widely studied and reported to be reliable in the evaluation of CAN (17,18,20,21) and help to predict future risk of adverse outcome associated with the presence of CAN in subjects with or without diabetes (31,32). A scoring system based on these 4 tests has been validated in Chinese and reported by our team previously (19). Despite new techniques and novel assessment tools continued to be described, the heart rate and BP variability, and sudomotor assessment remain golden standard in the CAN evaluation (33). Importantly, CAN testing has helped to improve disease recognition and prompted advances in the classification, pathophysiology, and treatment of diabetes and its complications.

Our results have to be interpreted with caution due to the various limitations of the study. Firstly, this was a cross-sectional study and no causal relationship between gastric emptying and CAN could be concluded. Secondly, the sample size was small with the controls tended to be slightly different from the patients such as the male to female ratio. Thirdly, though we excluded those patients with short duration of diabetes (less than 5 years), the diabetes duration remained heterogeneous. Last, but not least, our patients were all Southern Chinese being recruited in Nanjing, China. Our results might or might not be applicable to other parts of China.

In this study, we found a significant correlation between CAN severity and GET1/2, as well as an independent association between the presence of CAN and GET1/2. These suggested that more severe autonomic neuropathy may induce a further delay in gastric emptying. Along this line, morphologic alterations in autonomic nerves on the gut as well as reduction in myelinated axons and neurotransmitters have been demonstrated in animal models of diabetes (34,35). The correlation between gastroparesis and duration of diabetes was also attributed to an increased prevalence of autonomic neuropathy in patients with long-lasting diabetes (10).

In conclusion, we found a much prolonged gastric emptying time in Chinese patients with type 2 diabetes as compared to non-diabetic controls. The delayed gastric motility was demonstrated with both $^{13}$C-octanoic acid breath test and gastric emptying ultrasonography. We also found a high rate of cardiovascular autonomic neuropathy in diabetic patients, and the autonomic neuropathy severity score was directly correlated to the gastric emptying time.

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