GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Effects of rehabilitation management on gastric emptying function in older adults with diabetes

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Genet. Mol. Res. 13 (4): 9244-9252 (2014)
Received March 18, 2013
Accepted September 13, 2013
Published January 24, 2014
DOI http://dx.doi.org/10.4238/2014.January.24.5

ABSTRACT. The relationship between gastric emptying dysfunction and blood glucose concentration in elderly with type 2 diabetes mellitus was investigated, and the effect of rehabilitation exercise prescription training on gastric emptying in the geriatric diabetic patients was evaluated. A total of 160 older type 2 diabetic adults and 30 cases of non-diabetic patients were studied with regard to the gastric half emptying time (GET1/2) of solid meals radiolabelled with 99mTc. Eighty delayed gastric emptying diabetic patients were randomly divided into 4 four groups: rehabilitation exercise + mosapride group (N = 20), rehabilitation exercise group (N = 20), mosapride group (N = 20), and control group (N = 20). The level of blood glucose was measured every six months in a two-year follow-up. The solid GET1/2 of regulated blood glycemic control patients showed no statistically

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significant differences from non-diabetic patients (P > 0.05). However, the value for poor blood glycemic control patients exhibited significant statistical differences compared with both non-diabetic (P < 0.01) and regulated blood glycemic control group patients (P < 0.01). It showed that the gastric emptying time improved in the rehabilitation exercise group, mosapride group and rehabilitation exercise group + mosapride group after two years of treatment (P < 0.05). Fasting blood glucose in both rehabilitation exercise group and rehabilitation exercise + mosapride group was significantly decreased. Postprandial blood glucose in the rehabilitation exercise group, mosapride group, rehabilitation exercise group + mosapride group was significantly decreased. High blood glucose level can delay gastric emptying in older type 2 diabetic patients. Gastric emptying and blood glucose control affect each other. It was shown that appropriate rehabilitation exercise combined with prokinetic agent may improve gastric emptying in some geriatric type 2 diabetic patients and help control their blood glucose.

Key words: Elderly; Type 2 diabetes; Rehabilitation management; Gastric emptying; Blood glucose

INTRODUCTION

With the extension of the average human life span and improvement of living standards, the incidence of type 2 diabetes has likewise been increasing. As a chronic lifelong disease, diabetes has had a considerable impact on the physical health and quality of life of patients. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves.

Gastroparesis is defined as delayed gastric emptying resulting from disordered gastric motility without any gastric outlet mechanical obstruction. In patients with long-standing type 2 diabetes mellitus (DM), upper gastrointestinal motility dysfunction is a common phenomenon. Given the combined co-morbid conditions of disordered gastric motility and delayed gastric emptying (De Block et al., 2006; Stevens et al., 2008; Ejskjaer et al., 2009; Hyett et al., 2009; Parkman, 2010; Hejazi et al., 2012), approximately 30 to 50% of DM patients may suffer from a variety of symptoms such as pain, bloating, fullness, early satiety, anorexia, and vomiting (Ma et al., 2009; Szarka and Camilleri, 2010). Delayed gastric emptying among diabetics is closely related to poor glycemic control and cardiac autonomic neuropathy, as well as gastrointestinal hormone changes (Little et al., 2006; Chandrasekharan and Srinivasan, 2007; Mason, 2007; Huang et al., 2009 Borg et al., 2009). The gastroduodenal motor dysfunctions underlying abnormally slow gastric emptying in diabetes include decreased antral contractions, impaired coordination between the antrum and duodenum, increased pyloric contractions and impaired proximal gastric relaxation (Stevens et al., 2011). Acute hyperglycemia could directly repress the migrating motor complex and distal stomach motility in both healthy subjects and DM patients (Kuo et al., 2007; Hata et al., 2009).

Nowadays, in almost every country, the proportion of people over 60 years old is growing faster than any other age group, as a result of both longer life expectancy and declining fertility rates. The number of elderly with diabetes is rapidly increasing worldwide due to increased expectancy (Kim et al., 2012). Diabetes in older adults exhibits a number of characteristics that are different from general cases, including higher and unmanageable postprandial blood glucose. The current pharmacological treatment of diabetic gastroparesis remains unsatisfactory and often disappointing for both the patient and the clinician. Such disturbances may not only cause gastrointestinal symptoms but may also impair glycemic control. How to improve delayed gastric emptying and relieve dyspeptic symptoms in patients with diabetic gastroparesis especially in elderly patients is still a challenge to clinicians.

For all the factors mentioned above, it comes as no surprise that we should make some efforts to better manage delayed gastric emptying. First, we investigated the relationship between gastric emptying dysfunction and blood glucose concentration in older adults with type 2 DM. Second, a survey of blood glucose and gastric emptying function of solid phase meals in 160 cases of older adults with type 2 DM was performed. Meanwhile, by using prokinetic drugs with rehabilitation exercise for delayed gastric emptying patients, we determined the role of health management in delayed gastric emptying older adults with diabetes. Through these studies, we hoped to gain insight into the relationship between glucose regulation and gastric emptying and find the appropriate treatment for older diabetic patients with gastroparesis.

MATERIAL AND METHODS

Patients and treatments

A total of 30 non-diabetic older adults (2 females and 28 males, mean age ± SD of 76.0 ± 4.3 years) from Huadong Hospital outpatient and inpatient departments were enrolled as the control group.

A total of 160 type 2 DM older adults (age ≥65 years, fulfilling the 2002 diagnostic criteria for type 2 DM of the American Diabetes Association, including 51 females and 109 males, mean age ± SD of 77.1 ± 5.2 years) from the Huadong Hospital outpatient and inpatient departments were treated with dietary and/or hypoglycemic medication.

Patients with merging gastrointestinal disease, esophageal or gastrointestinal surgery, acute lung, liver, kidney, and heart diseases, fluid and electrolyte imbalance, or recent gastric motility drug treatment, as well as bedridden invalids or those who were unable to feed themselves or participate in rehabilitation management, were excluded from this study.

The 160 diabetic patients were divided into two groups based on glycemic control: 1) Regulated glycemic control [fasting blood glucose (FBG) ≤7.8 mM, 2-h postprandial blood glucose ≤11.1 mM] group, including 70 cases, among whom 55 were male and 15 were female patients with a mean age of 75.1 ± 4.2 years and duration of 13.4 ± 8.5 years. Among these patients, 3 were treated with only diet control, 57 with oral hypoglycemic drugs, and 10 with insulin. 2) Defective glycemic control (FBG ≥7.8 mM and/or 2-h postprandial blood glucose ≥11.1 mM group, including 90 cases, among whom 64 were male and 26 were female patients with mean age of 79.5 ± 4.2 years and duration of 18.6 ± 9.3 years. Among these patients, 63 cases were treated with hypoglycemic agents and 27 cases with insulin for blood glucose level control.

Delayed gastric emptying diabetic patients for isotopic detection were randomly divided into four groups. Each group had 20 cases: 1) rehabilitation exercise + prokinetic drug intake group, with 5 females and 15 males, mean age of 78.4 ± 7.2 years, 2) rehabilitation exercise group, with 4 females and 16 males, mean age of 79.8 ± 4.1 years, 3) prokinetic drug intake group, with 6 females and 14 males, mean age of 75.4 ± 3.7 years, and 4) control, with 6 females and 14 males, mean age of 75.4 ± 3.7 years.

Mosapride (5 mg tid) was selected as the prokinetic drug. Rehabilitation exercises were conducted, including balanced function test, isokinetic test and training, and spatial position sense proprioceptive training. Patients in each group were routinely treated with antidiabetic drugs [including gliclazide sustained-release tablets (Servier) 30 to 60 mg qd; acarbose tablets (Bayer) 50 mg tid; metformin (Bristol-Myers Squibb Company) 50 mg bid or tid] or insulin (Humulin 70/30).

Gastric emptying assay

1) Test meal: Bread 50 g + porridge 50 g, with 99mTc-labeled ion exchange resin RA-400, total volume of 300 mL, well mixed and eaten within 5 min. Patients should have 8 h fasting and 7 days prokinetic drug withdrawal.

2) Instrument: The Siemen E. CAM System was employed. With patients in a supine position, the probe should cover the whole stomach. A frame was collected every 10 min within 60 s. Patients were continuously observed for 100 min.

3) Image processing: A full region of interest (ROI) of the stomach was drawn and then analyzed with gastric emptying analysis software and mobile correction techniques. ROI at different phases was input into a computer. Through a regression analysis of radioactive counts within each phase, a stomach emptying time-radioactive dose curve was drawn based on a variety of quantitative parameters, including half-time (GET1/2) and the emptying rate of each phase period.

Balance function test

1) Instrument: An mtd-balance function testing and training system was used. The mechanical signal in the sensor was recorded and then converted into digital signals using a computer, for automatic analysis processing.

2) Training and testing methods: Patients took off their shoes and were asked to remain standing on the center of the sensor pattern, with waist upright, hands naturally hanging down, and body stable. Patients could swing around and control the progress of training. The training was conducted two weeks a month, three times a week for 20 min.

Isokinetic testing and training protocol

The BIODEX SYSTEM 3 isokinetic testing system was used for isokinetic testing and training. Briefly, the biodex seatback tilt angle was set to nearly 85°. Patients sat upright, with a hip buckling angle of 110°, and were fixed with two shoulder straps as well as waist and thigh belts. Within the joint activity range, complete resistance exercises of bilateral knee joints were performed with angular velocities of 60, 120, and 180°/s for 10 min each. Sub-

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sequent passive relaxing excises were conducted for another 10 min at the same angles. The trainings were performed two weeks a month, thrice a week for 20 min.

Proprioceptive spatial position sense training

Proprioceptive spatial position sense training was conducted using the passive angle method with the BIODEX SYSTEM 3 training system. Training exercises were performed two weeks a month, two times a week for 4 min.

Blood glucose concentration determination

Blood glucose concentration was measured using the glucose oxidase method (automatic biochemical analyzer). First, 75 g glucose was orally taken in the fasting state, and a blood sample was drawn and used for the for 2-h glucose challenge test. Every six months, fasting and postprandial glucose levels were determined in each patient. Gastric emptying tests at the time of enrollment and a two-year follow-up completion were conducted. Data on gastric emptying time and blood glucose changes were studied.

Statistical analysis

Statistical analysis was performed with the SPSS 17.0 software. All data were reported as means ± standard error. Comparisons of the quantitative index were performed using the paired Student *t*-test, and $P < 0.05$ was considered to be significant.

The study was approved by the Ethics Committee of Huadong Hospital.

RESULTS

Quantitation of isotope-based gastric emptying

The solid GET1/2 of 30 cases of non-diabetic patients was 78.1 ± 19.6 min, compared with the normal value of 97.7 min when setting X+S as the upper limit of normal data. The solid GET1/2 of regulated blood glycemic control patients was 76.5 ± 17.1 min, showing no statistically significant differences from non-diabetic patients ($P > 0.05$). However, the value for poor blood glycemic control patients reached 106.9 ± 29.5 min, exhibiting significant statistical differences compared with both non-diabetic ($P < 0.01$) and regulated blood glycemic control group patients ($P < 0.01$).

When setting the GET1/2 upper limit at 97.7 min, 80 of 160 patients (accounting for 50.0%) revealed delayed gastric emptying, among whom 10 cases were from the regulated blood glycemic control group, accounting for 14.3% and 70 cases from the poor glycemic control group, accounting for 77.8%. The average duration of these 70 cases was 18.1 ± 8.2 years compared with the other 20 poor glycemic control patients with a modest average GET1/2 duration of 18.8 ± 9.2 years. No significant differences were detected ($P > 0.05$).

The gastric emptying times of solid phase GET1/2 after two-year follow-ups exhibited significant ($P < 0.05$) reductions compared with those before in the first, second, and third groups. No statistical difference was found group 4 ($P > 0.05$) (Table 1).

Table 1. Gastric emptying times of each group.

Group	GET1/2 (min)		
	Before	2 years	P
1	103.80 ± 22.24	83.14 ± 14.98	<0.05
2	106.64 ± 25.39	91.82 ± 17.24	<0.05
3	104.46 ± 19.61	91.05 ± 16.35	<0.05
4	101.92 ± 21.83	101.17 ± 22.36	>0.05

Fasting and 2-h postprandial blood glucose changes

Differences in blood glucose levels were investigated before and after treatment in each group of patients. For FBG level, both groups 1 and 2 showed significant differences after 18 months or two years treatments ($P < 0.05$) (Table 2).

Table 2. Differences in blood glucose levels.

Group	FBG (mM)				
	Before	6th month	12th month	18th month	2 years
1	8.61 ± 2.25	8.30 ± 2.20	8.32 ± 2.07	7.34 ± 1.63*	7.31 ± 1.08*
2	8.32 ± 1.99	7.88 ± 1.44	7.56 ± 1.22	7.25 ± 1.47	7.10 ± 0.65*
3	7.90 ± 2.04	7.63 ± 1.24	7.64 ± 1.00	7.57 ± 1.21	7.56 ± 1.41
4	8.14 ± 1.41	7.51 ± 0.95	7.53 ± 1.15	7.62 ± 0.84	7.57 ± 0.46

*P < 0.05 with basal values.

For 2-h postprandial blood glucose levels, all groups showed lower levels than before treatment. Groups 2 and 3 exhibited significant differences after two-year treatment ($P < 0.05$), whereas group 1 showed significant differences ($P < 0.05$) after 18-month and two-year treatment (Table 3).

Table 3. Change of 2-h postprandial blood glucose level.

	2-h postprandial blood glucose level (mM)				
	Before	6th month	12th month	18th month	2 years
1	15.01 ± 1.98	14.50 ± 1.58	14.30 ± 1.30	13.63 ± 1.00$^{\Delta}$	13.43 ± 0.82$^{\Delta}$
2	14.69 ± 2.05	14.27 ± 1.57	14.34 ± 1.20	14.22 ± 1.04	13.70 ± 1.15$^{\Delta}$
3	14.45 ± 2.00	14.24 ± 1.48	14.28 ± 1.63	14.16 ± 1.43	13.46 ± 1.35$^{\Delta}$
4	14.53 ± 2.15	14.34 ± 1.37	13.92 ± 1.23	13.62 ± 1.15	13.62 ± 0.87

$^{\Delta}$P < 0.05 with basal values.

DISCUSSION

Gastroparesis is regarded as the main outcome of diabetes-induced gastrointestinal dysfunction. In the early stage, blood glucose level can directly affect gastric emptying. However, with the development of the disease and local gastrointestinal tissue damage, hyperglycemia may indirectly result in a higher occurrence of gastroparesis. Meanwhile, tissue damage and gastrointestinal digestive disorder will further influence clinical blood glucose control. In this way, a variety of factors interact to produce a vicious cycle, eventually developing into gastroparesis (Friedenberg and Parkman, 2006; Ramzan et al., 2011; Zhou et al., 2011).

Delayed gastric emptying involves the delayed emptying of solids and liquids. Solid gastric emptying is closely related to blood glucose control. Delayed gastric emptying and elevated blood glucose levels interact, leading to a reciprocal causation in type 1 or type 2 diabetic patients and resulting in unmanageable and sustained increases in blood glucose levels, or even worse complications.

In this study, the solid gastric emptying functions of 160 elderly type 2 DM patients were examined using the radionuclide method. The study revealed 80 cases of delayed gastric emptying, accounting for 50.0%. Moreover, 85.7% normal blood glucose control participants showed eligible solid gastric emptying abilities, which is an acceptable limit. However, patients with defective blood glucose control function showed impaired solid gastric emptying abilities, with 77.8% showing an average of up to 106 min of emptying time. This finding indicates that delayed gastric emptying and blood glucose are closely related in elderly patients with DM.

Gastric emptying function and duration of disease are positively correlated in diabetic patients. A longer duration increases the likelihood of delayed gastric emptying function and the occurrence of severe neuropathy. Although we found that the average duration in 70 patients with GET1/2 delay (18.1 ± 8.2 years) and in the other 20 normal GET1/2 cases was similar, the result may be attributed to interference factors such as long duration time of up to 5 years, the degradation of visceral nerve function that may exist in elderly participants, and the small sample that maybe did not represent the effect of the disease on GET1/2.

Diabetes treatments include diet modification, oral hypoglycemic drugs, and insulin therapy. Rehabilitation management therapy for diabetes treatment has drawn considerable attention. Modest exercise is an important factor in the control of blood glucose (Chiasson and Rabasa-Lhoret, 2004) by promoting the production of insulin receptors or improving insulin sensitivity. Regular exercise can promote the use of fatty acids in muscle tissue, reduce the triglycerides in serum, increase the number of high-density lipoproteins, and block the occurrence or development of atherosclerosis (Kelley and Goodpaster, 2001; Turk and Laughlin, 2004). With increasing age and reduced activities, older people may be affected by the changed proportion of fat and muscle tissues and eventually have difficulty in glucose utilization.

Considering the patients' ages (mean age of 77.1 ± 5.2 years) as well as to ensure the proper amount of exercise and to avoid complications caused by excessive movement, we carefully designed specific exercise prescriptions and canceled poorly tolerated treadmill exercises. Following the balance function, isokinetic, and lower limb proprioception tests based on the physical condition of individuals, tolerant feedback, and no severe low blood glucose reaction were found in the majority of patients.

Mosapride, a novel prokinetic drug classified as a 5-HT4 receptor agonist, can promote gastric emptying primarily through the myenteric plexus preganglionic and postganglionic fibers that release acetylcholine. We thus used mosapride as the intervention drug in this study. Diabetic gastroparesis patients are usually believed to have problems in draining solid food into the small intestine (Loo et al., 1984). The isotope-based gastric emptying check is unaffected by stomach shape and is close to the physiological state, aside from being accurate, repeatable, and non-invasive. Thus, this test is considered the "gold standard" of clinical assessment (Abell et al., 2008).

We used the radionuclide method to determine the solid gastric emptying abilities of 80 patients with diabetes in this study. Curative effects were observed compared with the baseline in all three groups studied, namely the rehabilitation exercise with prokinetic drug group, the rehabilitation exercise group, and the prokinetic drug group. Fasting and 2-h postprandial blood glucose levels in the first two groups were reduced, especially in the first group, where significant improvements could be confirmed.

With sustained diabetic duration and development of the disease, patients are exposed to autonomic damage as well as motilin, gastrin, and pancreatic glucagon secretion abnormalities, aside from high blood sugar, electrolyte imbalance combined with atrophic gastritis, and secondary infection. These conditions result in gastric emptying dysfunction and emptying delay, which lead to the irregular absorption of carbohydrates, proteins, or other nutrients and to eventual hyperglycemia or hypoglycemia occurrences. Therefore, routine hypoglycemic drugs or insulin therapies may be mismatched with the peak of postprandial blood glucose, finally resulting in postprandial hyperglycemia.

On the other hand, when gastric emptying function is improved, the stomach and duodenum move coordinately, nutrient absorption normalizes, and peak postprandial blood glucose and insulin secretion synchronize, thus relieving hyperglycemia. The mechanism by which exercise improved glucose metabolism may be related to the fact that movement can promote GLUT4 gene expression in skeletal muscle cells, increase glucose transporter protein 4 level, and promote cellular glucose transport and utilization. By increasing insulin sensitivity, the absorption and utilization of glucose could be improved in the exercise treatment process (Kuhan et al., 2002).

In summary, appropriate rehabilitation exercise with prokinetic drugs can safely and effectively improve gastric emptying function in elderly patients with diabetes. Based on routine hypoglycemic therapy, rehabilitation exercise helps control blood sugar and reduces the incidence of complications, thereby reducing medical expenditures. Rehabilitation exercise is important in stabilizing the condition of diabetics by improving body function. Admittedly, rehabilitation exercise on blood glucose and gastric emptying is just one of the many influence factors. A deeper study on the motilin, gastric electrical activity, and autonomic function of elderly diabetic patients with abnormal gastric emptying has to be conducted in the future.

ACKNOWLEDGMENTS

Research supported by the Huadong Hospital Affiliated with Fudan University. The authors thank the patients who took part in this study.

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