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Colonic Transit Time in Diabetic Patients - Comparison with Healthy Subjects and the Effect of Autonomic Neuropathy

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Constipation and the use of laxatives are relatively common in patients with diabetes mellitus. However, the mechanisms responsible for the constipation are unclear. Even though autonomic neuropathy is regarded as one of the important mechanisms of constipation, it requires further clarification. In addition, the colonic function in diabetic patients requires further investigation. The aim of this study was to compare the colonic transit time between patients with diabetes mellitus and healthy subjects, and correlate it to the presence of cardiovascular autonomic neuropathy. The colonic transit time was measured by a noninvasive, radio-opaque marker method, and the presence of cardiovascular autonomic neuropathy was evaluated by the beat-to-beat variation and the orthostatic hypotension. Constipation was defined by the Rome II criteria. The mean total colonic transit time of the 28 diabetic patients (34.9 $\pm$ 29.6 h, mean $\pm$ S.D.) was significantly longer than that of the 28 healthy subjects (20.4 $\pm$ 15.6 h, $p<0.05$). Among the diabetic patients, 9/28 (32%) had constipation and 14/28 (50%) had cardiovascular autonomic neuropathy. The diabetic patients with constipation showed longer total, left and recto-sigmoid colonic transit times than those without constipation. However, the mean colonic transit time of diabetic patients with and those without cardiovascular autonomic neuropathy was similar. In conclusion, other mechanisms than the mere presence of cardiovascular autonomic neuropathy might be more relevant to the development of constipation in patients with diabetes mellitus.

Key words: Colonic transit time, autonomic neuropathy, diabetes mellitus

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INTRODUCTION

Gastrointestinal (GI) motility disturbances including esophageal motor dysfunction, gastroparesis, constipation and diarrhea, are common in patients with diabetes mellitus.[1-3] A German study reported that constipation was the most common complaint among the upper and lower GI symptoms in patients with type 2 diabetes.[4] In addition, the prevalence of constipation and the use of laxatives was reported to be higher in those with type 1 diabetes than those without in a recent community-based U.S. study.[5]

However, few studies have investigated the colonic motility in patients with diabetes. However, those results were controversial. The mechanisms of constipation in diabetes mellitus are unclear, although several mechanisms have been proposed.[6-8]

Among them, autonomic neuropathy, which is a complication of long-standing diabetes mellitus, has been widely accepted as the culprit.[9] It may lead to an absence of a postprandial gastrocolonic response, a reflex that should be present in healthy people, resulting in severe constipation in diabetic patients. Recently, several recent studies[10,11] showed that an acute change in the blood glucose concentration also had a major effect on the GI motor function in healthy subjects. In particular, acute hyperglycemia inhibited both the gastrocolonic and ascending component of the peristaltic reflex,[12] although this finding was not confirmed by another study.[13] Poor glycemic control has the potential to cause constipation in diabetic patients. However, despite all the suggested mechanisms, there is a lack of basic information on the colonic motor function in diabetic

patients. Simple measurements of the colonic transit time using radio-opaque markers are a noninvasive way of evaluating the colonic motor function.

Therefore, this study measured the colonic transit time in patients with diabetes mellitus and healthy subjects and attempted to determine if the colonic transit time differs according to the presence of the autonomic neuropathy affecting the cardiovascular system.

MATERIALS AND METHODS

Subjects

Twenty-eight patients with diabetes mellitus were recruited from the outpatient clinic of the endocrinology department of our hospital, and 28 healthy volunteers, mostly hospital workers, were also recruited. The fasting serum glucose levels of all healthy subjects were identified to be less than 110 mg/dL and they had no GI diseases or symptoms. The diabetic patients were older and heavier than the healthy subjects (Table 1). Among the 28 diabetic patients, 27 had type 2 and one had type 1 diabetes. Eighteen were treated with oral hypoglycemic agents, six with insulin and four were treated with both insulin and oral hypoglycemic agents.

Written informed consent to participate this study was obtained from all patients and healthy subjects. The ethical committee and institutional review board of our institution approved the study protocol. The exclusion criteria were followings: 1) subjects with acute symptoms or the current use of drugs known to alter gastrointestinal motility, 2) women taking birth control pills or using an intrauterine device within the last six months, and 3) a BMI $> 30\,kg/m^2$. Obese subjects were excluded because the colonic transit might be altered in this condition.[14]

Methods

The bowel habits, stool frequency, GI symptoms such as diarrhea or constipation, smoking habit, and the consumption of alcohol or coffee were assessed by a standard questionnaire. Constipation was defined as a "stool frequency < 3 times per week" or "lumpy or a hard sensation of stool passing" according to the Rome II criteria.[15] The body weight and height were measured by a Body Composition Analyzer (InBody 3.0^{TM}; Biospace, Seoul, Korea). All women capable of childbearing were confirmed to have a negative serum pregnancy test (Gravindex; Testpack^{TM}, Abbott, IL, USA) before the study. The average glycated hemoglobin (HbA_1c) levels and fasting serum glucose concentrations were measured by an Ion capture assay (IMX, Abbott, IL, USA) and glucose oxidase method (7600110, Hitachi, Japan), respectively. The normal values of HbA_1c and fasting serum glucose levels in our laboratory were less

Table 1. Baseline Characteristics and Results of the Colonic Transit Times of Diabetic Patients and Healthy Subjects

	Diabetics (n=28)	Control (n=28)
Age (years)	53 ± 11*	37 ± 5
Gender (M/F)	14/14	14/14
BMI (kg/m^2)	25.0 ± 2.7*	22.8 ± 2.4
Colonic transit times (h)		
Total	34.9 ± 29.6*	20.4 ± 15.6
Right	6.1 ± 6.7	6.1 ± 7.0
Left	14.4 ± 14.2*	7.2 ± 1.3
Recto-sigmoid	14.5 ± 15.7*	7.2 ± 1.5

Mean ± SD, t-test for means and chi-square test for frequencies.
*$p<0.05$.

than 6 percent, and 60-110 mg/dL, respectively.

The colonic transit time was measured using radio-opaque markers. The subjects ingested one capsule containing 20 radio-opaque markers (Kolomark^{TM}, M.I.Tech., Pyongtaik, Korea) in the morning at 24-hour intervals for 3 consecutive days and two simple abdominal radiographs were taken at the supine position on the 4th and 7th day. The subjects were asked to avoid unusually intensive physical activity and live their average daily life during the study. The localization of markers on the abdominal films relied on identifying the bony structures, as suggested by Arhan, et al.[16] The markers located to the right of the vertebral spinous processes above a line from the fifth vertebrae to the pelvic outlet were assigned to the right colon. The markers to the left of the vertebral spinous processes and above an imaginary line from the fifth lumbar vertebrae to the anterior superior iliac crest were assigned to the left colon. Markers inferior to a line from the pelvic brim on the right and the superior iliac crest on the left were judged to be in the rectosigmoid colon and rectum. The total and segmental colonic transit times were calculated by 1.2 × the sum of markers in the entire or segmental colon.[17,18]

Cardiovascular autonomic neuropathy was judged in diabetic patients by 1) a beat to beat variation during forced respiration and 2) orthostatic hypotension, as described in previous-studies.[6,19] The patients were asked to breathe deeply at a rate of six breaths/minute, the inspiration lasting for four seconds, the expiration for six seconds.[20] From the breathing cycle with the maximal heart rate variation, the longest (R-Rmax) and the shortest R-R interval (R-Rmin) were determined and the difference, R-Rmax − R-Rmin, as well as the quotient, R-Rmax/R-Rmin (E/I ratio), were calculated. The orthostatic hypotension was defined as a drop in a systolic pressure of more than 30 mmHg when standing up. None of the patients were taking any medications known to interfere with the cardiovascular reflexes.

Statistical analysis

Data analysis was performed using a statistic package SPSS/PC window 11.0 program (Statistical Package for the Social Science, SPSS Inc., Chicago, IL, USA). The data is expressed as a mean ± standard deviation (SD). The Student's t-test, Mann-Whitney U test, chi-square test, and Fisher's exact test were used in the analysis where appropriate. A p value < 0.05 was regarded as 'significant'.

RESULTS

The mean total colonic transit time of the 28 diabetic patients was 34.9 ± 29.6 hours (h), which was significantly longer than that of the 28 healthy subjects (20.4 ± 15.6 h, $p < 0.05$). In particular, both the left and rectosigmoid colonic transit times were significantly longer in the diabetic patients than in the healthy subjects (Table 1). 6/28 (21%) diabetic patients had longer total colonic transit times than the 95th percentile of the healthy subjects (52.6 h).

Among the 28 diabetic patients, 14 (50%) had cardiovascular autonomic neuropathy, and 9 (32%) met the criteria for constipation. Among the 14 diabetic patients with cardiovascular autonomic neuropathy, 5 (36%) had constipation (not significantly different compared to those without cardiovascular autonomic neuropathy: 4/14 (29%)) and among the 9 diabetic patients with constipation, 4 (44%) had cardiovascular autonomic neuropathy (not significantly different than those without constipation 10/19 (53%)). There were no significant differences in the total and segmental colonic transit times between the diabetic patients who had cardiovascular autonomic neuropathy and those who did not (Table 2). However, the diabetic patients who had constipation showed a significantly longer total, left and recto-sigmoid colonic transit time than those who did not (Table 3).

The age, gender ratio, BMI, mean HbA_{1C} level, and the duration of diabetes in the diabetic patients with and without cardiovascular autonomic neuropathy, and in those with and without constipation, were similar except that the duration of diabetes was significantly longer in the diabetic patients with cardiovascular autonomic neuropathy than those without (10 years vs. 6 years,

Table 2. Comparison of the Baseline Characteristics and Colonic Transit Times in Diabetic Patients According to the Presence of Cardiovascular Autonomic Neuropathy

	Autonomic neuropathy	
	Positive (n=14)	Negative (n=14)
Age (years)	54 ± 9	52 ± 13
Sex (M/F)	8/6	6/8
BMI (kg/m^2)	25.2 ± 2.8	24.7 ± 2.8
DM duration (years)	10 ± 6*	6 ± 5
Hb A_{1C} (%)	7.5 ± 1.5	7.9 ± 1.9
Constipation (+/-)	9/5	10/4
DM complications		
Neuropathy (+/-)	3/11	7/7
Retinopathy (+/-)	9/5	12/2
Nephropathy (+/-)	6/8	10/4
Colonic transit times (h)		
Total	39.6 ± 37.1	30.2 ± 20.0
Right	6.7 ± 7.4	5.6 ± 6.2
Left	15.6 ± 16.7	13.1 ± 11.6
Recto-sigmoid	18.3 ± 20.9	10.7 ± 6.9

Mean ± SD, NS, not significant.
t-test for means and chi-square test for frequencies.
*$p<0.05$.

respectively, $p < 0.05$).

There were no significant differences in the total and segmental colonic transit times between males and females in the diabetic patients as well as in the healthy subjects. The total and segmental colonic transit times did not show any significant correlation with age, BMI, mean HbA_{1C} level, the duration of diabetes and R-R interval (Table 4).

DISCUSSION

These results showed that the mean colonic transit time of the diabetic patients, which was measured by the radio-opaque marker method, was significantly longer than that of the healthy subjects. This was similar to another radio-opaque marker study[7] that also showed that the colonic transit time was significantly elongated in their diabetic patients compared to the control subjects. The difference in the colonic transit time between diabetic patients and healthy subjects in this study was mainly due to the influence of the diabetic patients with constipation. The colonic transit times of the diabetic patients who did not have constipation were similar to those of the healthy subjects.

In the diabetic patients who were consecutively recruited from the outpatient clinic of the endocrinology department of our hospital, 9/28 (32%) had met the symptom criteria of constipation and 6/28 (21%) had a longer total colonic transit times than the 95th percentile of healthy subjects (52.6 h). Whether or not these frequencies (32% and 21%) are higher than in an age- and gender-matched general population is unclear. However, several epidemiological studies[4,5] have suggested that the constipation is

Table 3. Comparison of the Baseline Characteristics and Colonic Transit Time in Diabetic Patients According to the Presence of Constipation

	Constipation	
	Positive (n=9)	Negative (n=19)
Age (years)	51 ± 9	54 ± 12
Sex (M/F)	5/4	9/10
BMI (kg/m^2)	25.4 ± 3.1	24.7 ± 2.6
DM duration (years)	8 ± 5	8 ± 7
Hb A_{1C} (%)	7.1 ± 1.2	8.0 ± 1.9
DM complications		
ANP (+/-)	4/5	10/9
Neuropathy (+/-)	4/5	6/13
Retinopathy (+/-)	7/2	5/14
Nephropathy (+/-)	5/4	11/7
Colonic transit times (h)		
Total	61.0 ± 34.1*	22.2 ± 17.1
Right	8.1 ± 7.0	5.2 ± 6.5
Left	25.7 ± 16.1*	9.0 ± 9.5
Recto-sigmoid	26.2 ± 21.3*	8.1 ± 8.3

Mean ± SD, NS, not significant; ANP, autonomic neuropathy.
t-test for means and chi-square test for frequencies.
*$p<0.05$.

Table 4. Correlation Coefficients (r values) between the Colonic Transit Times and the Clinical Variables

	Colonic transit times (h)			
	Total	Right	Left	Recto-sigmoid
Age (years)	0.001 (0.998)	0.173 (0.379)	0.067 (0.735)	-0.041 (0.836)
BMI (kg/m^2)	-0.222 (0.256)	0.082 (0.679)	-0.253 (0.194)	-0.318 (0.099)
Disease duration (years)	0.074 (0.709)	0.260 (0.181)	0.076 (0.702)	-0.014 (0.946)
HbA_{1C} (%)	-0.198 (0.323)	-0.241 (0.226)	-0.162 (0.420)	-0.069 (0.731)
$R\text{-}R_{max}/R\text{-}R_{min}$	-0.161 (0.431)	0.004 (0.984)	-0.151 (0.460)	-0.270 (0.182)

Pearson' correlation coefficients: r values.
Parentheses indicate p values.

more frequent in patients with diabetes mellitus than in non-diabetic subjects.

A colonic motility dysfunction in diabetic patients may be primarily due to an abnormality in the autonomic neural control.[8,19,21] The cholinergic system appears to be disturbed in diabetic patients whose major complaint is constipation, since the gastrocolonic response is abnormal in these condition.[9] Two previous studies[6,8] showed that the colonic transit was slower in the diabetic

patients with cardiovascular autonomic neuropathy compared with the group without cardiovascular autonomic neuropathy. However, in this study, no significant difference in the colonic transit time between diabetic patients with cardiovascular autonomic neuropathy and those without was found. The reasons for this discrepancy are uncertain. The different characteristics of our diabetic patients from previous studies and a comparatively small sample size of this study can be considered, which warrant future studies with a larger sample size. However, it should be noted that the correlation between the GI motility and cardiovascular autonomic nerve function is relatively poor.[19] Probably, the insensitivity of the methods used to evaluate the cardiovascular autonomic neuropathy in this study might have affected the interpretation of these results. A MIBG (metaiodobenzylguaninidine) scan might be a better alternative method of evaluating the cardiovascular autonomic neuropathy more correctly.[22] The reasons for this poor correlation may be that the tests for the cardiovascular autonomic nervous function failed to adequately assess the extrinsic neural supply to the abdomen and therefore provided no direct information on the integrity of the intrinsic nervous system of the gut, the myenteric plexus.[23] This might require a separate test of the abdominal vagal function such as the plasma human pancreatic polypeptide response to a modified sham feeding.[24,25]

In this study, there were no differences in age, gender ratio, BMI, mean HbA_{1C} level, and the duration of diabetes between the diabetic patients with constipation and those without. However, according to Ko, et al.,[26] the duration of diabetes was associated with the presence of lower GI symptoms. Clouse and Lustman[27] reported that the GI symptoms occurring in diabetic patients were poorly related to neuropathic complications such as peripheral or autonomic neuropathy and rather they were associated with combined psychiatric illnesses such as anxiety or depression. This study did not measure the lifestyle, dietary habits such as the fiber intake or psychiatric illness. Future studies are required to determine if those factors are more relevant to the constipation observed in diabetic patients than the presence of autonomic neuropathy.

Noninvasive measurements of the colonic transit time by a radio-opaque marker method also provide information on the segmental colonic transit time. In this study, the prolonged colon transit in diabetic patients, compared to healthy subjects, and particularly in diabetic patients with constipation, compared with those without constipation, was due to a slow transit in the left and recto-sigmoid colon. These results corroborate those of a previous study,[9] which demonstrated decreased postprandial colonic myoelectrical activity of the distal colon in diabetic patients. Delayed transit in the distal colon in our diabetic patients, particularly those with constipation is not necessarily a specific finding in diabetics, since idiopathic constipation is characterized by either exaggerated reservoir functions of the ascending and transverse colon or an impairment of the propulsive function in the descending colon.[28]

Recently, it was demonstrated that the blood glucose concentration itself has a major impact on the GI motility: marked hyperglycemia appears to affect every region of the gastrointestinal tract.[29,30] Sims, et al.[12] suggested that hyperglycemia blunted mechanoreceptor-mediated gastrocolonic responses and the ascending contractions in healthy volunteers, although another study[13] did not support their results. This study found no correlation between the Hb A_{1C} concentrations, a marker used to assess the long-term glycemic control, and the colonic transit times in our diabetic patients. Since all our diabetic patients were being treated for their diabetes at the time of the study, the effect of acute or marked hyperglycemia or poor glycemic control on the colonic transit time could not be evaluated.

One of the limitations of this study was that the healthy subjects were not age- and BMI- matched to the diabetic patients. The diabetic patients were older and heavier than the healthy subjects. However, since the colonic transit time did not correlate with age or BMI in healthy volunteers of our previous study[31] and in other studies,[32,33] and all obese (BMI > 30) diabetic patients or healthy subjects were excluded in this study, the effect of age and BMI on this study results appears to be negligible.

In conclusion, the colonic transit time was

longer in patients with diabetes, particularly those who had constipation, than in healthy subjects. However, the presence of the cardiovascular autonomic neuropathy had no affect on the colonic transit time. The mechanisms of constipation in diabetes mellitus need to be further investigated.

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