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作成者（著者）	Suzuki, Takeshi / Komatsu, Fumiya / Takemoto, Ikutaka / Kijima, Sho / Sasaki, Yosuke / Urita, Yoshihisa
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Original Article

Influence of Gastric Emptying on the Outcome of the 75-g Oral Glucose Tolerance Test

Takeshi Suzuki[1] Fumiya Komatsu[1] Ikutaka Takemoto[2]
Sho Kijima[2] Yosuke Sasaki[2]* and Yoshihisa Urita[2]

[1]Department of General Medicine and Emergency Care, Toho University Graduate School of Medicine, Tokyo, Japan
[2]Department of General Medicine and Emergency Care, Toho University Omori Medical Center, Tokyo, Japan

ABSTRACT

Introduction: The 75-gram oral glucose tolerance test (75-g OGTT) is a widely used procedure and is considered the gold standard for diagnosing diabetes. Variations in gastric emptying result in the false estimation of the OGTT. The aim of this study was to determine whether altering gastric emptying affects the postprandial insulin and glucose response to 75 g of glucose.

Methods: Eighty-two diabetic patients without medication (42 women and 40 men; age range: 30-84 years; average: 62 years) without any abdominal symptoms were recruited into this study. The ^{13}C-acetate breath test was performed to assess gastric emptying. After an overnight fast, patients received 75 g of anhydrous glucose in 225 mL of water, which contained 100 mg of ^{13}C-acetate. Breath samples were collected at 10-min intervals for 180 min.

Results: There was a positive correlation between serum insulin at 30 min and $^{13}CO_2$ excretion at 30, 60, and 90 min but no relationship between $^{13}CO_2$ excretion and serum insulin at 90 min or later. An inverse correlation was found between serum glucose and $^{13}CO_2$ excretion. The homeostasis model assessment for insulin resistance did not correlate with $^{13}CO_2$ excretion, except at 90 min.

Conclusions: Hyperglycemia at an early phase after an oral glucose load should depend on gastric emptying and that at a late phase should be influenced by glucose metabolism, specifically glucose oxidation. Gastric emptying was a great determinant of not only rapid insulin response but also delayed insulin response.

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KEYWORDS: glucose tolerance test, gastric emptying, ^{13}C-acetate breath test, insulin response, insulin resistance

Introduction

It has been over 100 years since the first report of the oral glucose tolerance test (OGTT) by Janney and Isaacson.[1] Currently, the OGTT is a widely used procedure and is considered the gold standard for diagnosing diabetes. Although the plasma glucose and insulin responses during this test reflect the ability of pancreatic β-cells to secrete insulin and the sensitivity of tissues to insulin,[2] postprandial glycemia is influenced by various factors. Plasma glu-

*Corresponding Author: Yosuke Sasaki, 6-11-1, Omorinishi, Ota-ku, Tokyo, 143-8541, Japan, tel: +81–3–3762–4151
e-mail: yousuke.sasaki@med.toho-u.ac.jp
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cose does not increase unless the contents of the stomach move to the small intestine. Oral intake sometimes gives us a delusion that everything that is administered orally should be rapidly absorbed from the digestive tract and elevate plasma glucose levels. However, 2%-20% of carbohydrates escape absorption in the small intestinal.[3] Based on this fact, the digestion and absorption of carbohydrates may affect the results of OGTTs. Digestion and absorption start after gastric emptying. Delayed gastric emptying is caused by autonomic neuropathy, which results from poor glycemic control, and is a major complication of diabetes.[4,5] When glucose metabolism, including insulin resistance and insulin secretion, is assessed using the OGTT, the prerequisite condition is that there is little difference in gastric emptying and digestive and absorptive function. Variations in gastric emptying can result in the false estimation of the OGTT results. For example, delayed gastric emptying makes the postprandial glucose level lower than expected. Interestingly, gastric emptying is delayed, even in healthy individuals, when the plasma glucose levels are artificially elevated.[4,5] This suggests that delayed gastric emptying can be interpreted as an appropriate physiological response to hyperglycemia because a slower delivery of nutrients can avoid further increases in plasma glucose levels. Therefore, a response to an oral glucose load should depend on the individual, even in diabetic patients. However, it is difficult to evaluate gastric emptying and insulin secretion at the same time during the OGTT. We propose a new method of measuring gastric emptying and glucose tolerance at the same time to assess the influence of gastric emptying on the outcome of OGTT. The aim of this study was to determine whether altering gastric emptying affects the postprandial insulin and glucose response to 75 g of glucose.

Materials and Methods

A standard 75-g OGTT was performed in 82 diet-controlled patients with diabetes (42 women and 40 men; age range: 30-84 years; average: 62 years) without abdominal symptoms. Patients treated with antidiabetic drugs, including alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, biguanide, glinide, thiazolidinediones, sulfonylurea, and sodium-glucose co-transporter-2 inhibitors, were excluded from this study. None of the patients had a history of proton pump inhibitor, H2-receptor antagonist, antibiotic, steroid, or nonsteroidal anti-inflammatory drug use for at least 6 months before the investigation. Patients who previously underwent partial gastrectomy were also excluded from the study. Informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of Toho University Omori Medical Center (Permit Number: 17-64).

Breath test with the 75-g OGTT

After an overnight fast, patients received 75 g of anhydrous glucose in 225 mL of water, containing 100 mg of ^{13}C-acetate (Cambridge Isotope Laboratories, Tewksbury, MA), in the sitting position. Breath samples were collected from the mouth in breath collection bags (Model 20; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) at baseline and 10-min intervals for 180 min. ^{13}C was measured as the $^{13}CO_2/^{12}CO_2$ isotope ratio and expressed as delta (Δ) over baseline per mille (‰). Gastric emptying was expressed as the time of peak excretion (T_{max}), which is closely correlated with the scintigraphy half-emptying times.[6] The Δ values and Δ over baseline values were converted to the percentage of ^{13}C recovered per hour (%dose/h) and the cumulative percentage of administered dose of ^{13}C recovered over time (cumulative %dose), based on body surface area (BSA) and assumed CO_2 production V_{CO2} as follows[7]:

(%dose)/h = Δ‰ × V_{CO2} × 0.01123 × 10/(A × APE/MW)

where the molecular weight (MW) is 60, V_{CO2} is 300 BSA・mmol/h, BSA is 0.024265 × weight 0.5378 × height 0.3964 m^2, dose (A) is 100 mg, and atom% excess (APE) is 99 atom%. The time taken to reach the maximum concentration (T_{max}, min) was directly decided by the $^{13}CO_2$ excretion rate. The cumulative %dose was used as a marker of the total amount of $^{13}CO_2$ derived from acetate oxidation until that time.

Gastric emptying was determined using Ghoos' method.[7] The gastric half-emptying time ($T_{1/2}$) is the time when half of the substrate is metabolized.

Venous blood samples were obtained before ingestion and at 30, 60, 90, and 120 min after ingestion. The plasma glucose and serum insulin levels were measured. The homeostasis model assessment insulin resistance (HOMA-R) was calculated using the following formula:

HOMA-R = fasting insulin (μU/mL) × fasting glucose (mg/dL) / 405

The insulinogenic index (II) was calculated as the ratio of change in insulin and glucose responses from baseline to 30 min, reflecting an early response of insulin secretion.

Statistical analysis

Results are reported as mean ± standard deviation, un-

Table 1 Demographic variables of subjects who underwent the 75-g glucose tolerance test

	Mean	SD	Range
Age (years)	60.4	10.1	30-84
Height (cm)	157.5	10	134-187
Weight (kg)	59.7	10.3	39-103
HbA1c (%)	6.7	1.6	4.5-11.2
Fasting glucose (mg/dL)	144.7	52.2	79-398
Fasting insulin (μU/mL)	5.3	4.6	1-31

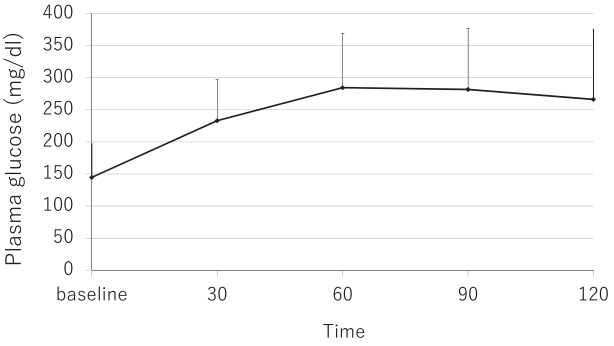

Fig. 1 Change in plasma glucose levels before and after the 75-g oral glucose tolerance test in all subjects.

less otherwise indicated. Correlation analyses were performed to assess the relationships among HOMA-R, IRI/BG, and cumulative insulin levels and measured values of $^{13}CO_2$ at 30, 60, 90, and 120 min, $T_{1/2}$, and T_{max}. All statistical analyses were performed using JMP ver. 13 (SAS Inc., Cary, NC).

Results

Demographic variables are summarized in Table 1. There were 42 women and 40 men, with a mean age of 60.4 years (30-84 years), a mean height of 157.5 cm (134-187 cm), and a mean weight of 59.7 kg (39-103 kg). Glycosylated hemoglobin levels were 6.7% ± 1.6% (4.5%-11.2%). Fasting plasma glucose and insulin levels were 144.7 ± 52.2 mg/dL (79-398 mg/dL) and 5.3 ± 4.6 μU/mL (1-31 μU/mL), respectively.

Both the plasma glucose and serum insulin levels rapidly increased and peaked at 60 min after the glucose load (Fig. 1, 2). The $^{13}CO_2$ concentrations increased from the beginning, and peak enrichment values were reached after 50 min. Cumulative $^{13}CO_2$ exhalation reached 10% at 60 min and 25% at 120 min after the oral administration of 100 mg of sodium ^{13}C-acetate.

The relationship between blood glucose, serum insulin,

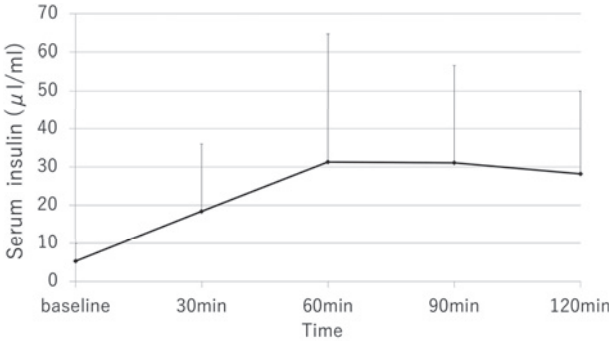

Fig. 2 Serum insulin response to the 75-g oral glucose tolerance test in all subjects.

and $^{13}CO_2$ excretion at each point in time is shown in Table 2, 3. There was a direct correlation between serum insulin at 30 min and $^{13}CO_2$ excretion at 30, 60, and 90 min. Serum insulin and $^{13}CO_2$ excretion at 60 min was also directly correlated (Table 2). There was no relationship between $^{13}CO_2$ excretion and serum insulin at 90 min or later. Cumulative $^{13}CO_2$ exhalation was directly correlated with serum insulin at all time points, except at 120 min (Table 2). Cumulative $^{13}CO_2$ exhalation at 120 min was not correlated with insulin levels at any time point.

Contrary to the relationship between serum insulin and $^{13}CO_2$ excretion, an inverse correlation was found between plasma glucose and $^{13}CO_2$ excretion, as shown in Table 3. However, such a relationship was not found at the same time. This indicated that a higher plasma glucose level at a late phase was directly correlated with lower $^{13}CO_2$ excretion at an early phase, suggesting that patients with hyperglycemia at a late phase have delayed gastric emptying. As shown in Table 3, the plasma glucose level at all time points, except at 30 min, was inversely correlated with cumulative $^{13}CO_2$ exhalation at 90 and 120 min. Only at 30 min, there was a direct correlation. From these results, postprandial hyperglycemia at an early phase may depend on gastric emptying times, whereas that at a late phase may be influenced by glucose metabolism, mainly glucose oxidation.

Both the sum of serum insulin at each time point and II, reported as a useful parameter of insulin response to a glucose load, had an inverse correlation with T_{max}, but a direct correlation with $^{13}CO_2$ excretion at 30 min and cumulative $^{13}CO_2$ exhalation at all time points (Table 4). A change in correlation coefficient between $^{13}CO_2$ excretion (%dose/h) at each time point and II is demonstrated in Fig. 3. These values all decreased with time. Although the change in

Table 2 Correlation coefficients between serum insulin levels and $^{13}CO_2$ excretion or cumulative $^{13}CO_2$ excretion at 30, 60, 90, and 120 min

	Serum insulin (μU/mL)			
	30 min	60 min	90 min	120 min
$^{13}CO_2$ excretion (%dose/h)				
30 min	*0.4763	0.1841	− 0.0169	− 0.0990
60 min	*0.4967	*0.2438	− 0.0159	− 0.1032
90 min	*0.3287	0.1887	0.0162	− 0.0463
120 min	− 0.0530	0.0094	0.0525	0.0975
Cumulative $^{13}CO_2$ excretion (%dose)				
30 min	*0.6179	*0.5512	*0.4792	*0.4009
60 min	*0.4690	*0.4846	*0.4279	*0.3537
90 min	*0.3524	*0.3454	*0.3149	*0.2667
120 min	− 0.1069	− 0.0759	− 0.0492	− 0.0261

*$p < 0.05$.

Table 3 Correlation coefficients between plasma glucose levels and $^{13}CO_2$ excretion or cumulative $^{13}CO_2$ excretion at 30, 60, 90, and 120 min

	Plasma glucose (mg/dL)			
	30 min	60 min	90 min	120 min
$^{13}CO_2$ excretion (%dose/h)				
30 min	0.1136	− 0.1580	* − 0.2360	* − 0.2578
60 min	− 0.0240	− 0.2020	* − 0.2395	* − 0.2311
90 min	− 0.2040	* − 0.2697	− 0.1961	− 0.1588
120 min	* − 0.2966	* − 0.2941	− 0.1558	− 0.0751
Cumulative $^{13}CO_2$ excretion (%dose)				
30 min	*0.2333	0.1286	0.0481	− 0.0148
60 min	0.0101	− 0.0553	− 0.1133	− 0.1503
90 min	− 0.1627	* − 0.2253	* − 0.2536	* − 0.2576
120 min	* − 0.2624	* − 0.3147	* − 0.3245	* − 0.3030

*$p < 0.05$.

correlation coefficient between $^{13}CO_2$ excretion (%dose/h) at each time point and the sum of serum insulin showed the same trend, the value reached the highest at 20 min and decreased gradually to a negative value by 100 min or later (Fig. 4).

The HOMA-R, which is widely used as a parameter of insulin resistance, was not correlated with $^{13}CO_2$ excretion at all time points, except at 90 min (Table 4).

Discussion

The 75-g OGTT is widely used to diagnose diabetes mellitus and to estimate impaired glucose metabolism. From the results of the 75-g OGTT, various parameters, such as insulin response to a glucose load and insulin resistance, are set and studied to estimate glucose metabolism as precisely and carefully as possible. II is a parameter of rapid insulin response to a glucose load calculated by the ratio of incremental serum insulin to incremental plasma glucose at 30 min.[8,9] The HOMA-R is frequently used as a simple parameter of insulin resistance because type 2 diabetes mellitus is mainly characterized by a delayed insulin response and insulin resistance. Although delayed gastric emptying in diabetic patients has been recognized as a complication of progressive autonomic neuropathy, viewed from another angle, it could be an adaptive response to correct postprandial hyperglycemia. Consider-

Table 4 Correlation between the parameter of the 75-g OGTT and the ^{13}C-acetate breath test

	Sum of insulin	HOMA-R	II
T_{max}	* − 0.2442	− 0.1697	* − 0.2347
$T_{1/2}$	− 0.1617	− 0.1162	0.0027
$^{13}CO_2$ excretion (%dose/h)			
30 min	*0.3761	− 0.0289	*0.3381
60 min	0.1885	− 0.1449	0.1955
90 min	0.0001	* − 0.2274	0.1259
120 min	− 0.0560	− 0.1985	0.0956
Cumulative $^{13}CO_2$ excretion (%dose)			
30 min	*0.3873	0.0476	*0.5345
60 min	*0.3847	− 0.0129	*0.4779
90 min	*0.3443	− 0.0605	*0.4413
120 min	*0.2894	− 0.1017	*0.4096

II: insulinogenic index.
*$p < 0.05$.

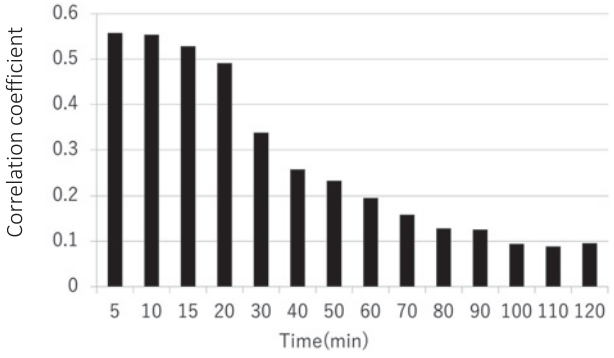

Fig. 3 Changes in the correlation coefficient between $^{13}CO_2$ excretion (%dose/h) at each time point and the insulinogenic index.

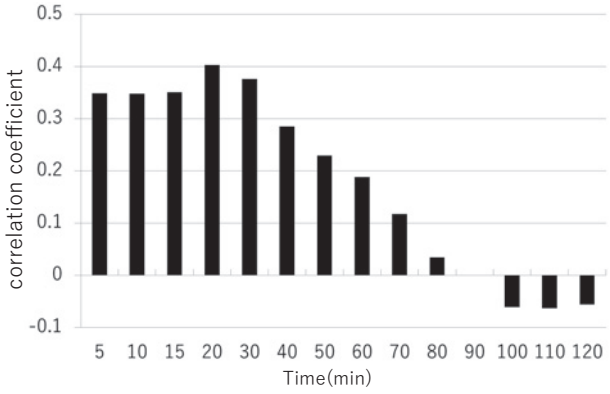

Fig. 4 Changes in the correlation coefficient between $^{13}CO_2$ excretion (%dose/h) at each time point and the total amount of serum insulin for 120 min.

ing that type 2 diabetes progresses from an early asymptomatic stage with insulin resistance to mild postprandial hyperglycemia and then to true diabetes that requires pharmacological treatment, it is likely that various adaptations to postprandial hyperglycemia begin at the initial stage. Furthermore, patients with delayed gastric emptying are sometimes asymptomatic, resulting in a wide variation in the prevalence of delayed gastric emptying.[10–12] This variation could be linked to the substantial variability of the 75-g OGTT because gastric emptying is considered a major determinant of postprandial glucose levels.[13, 14] From that point of view, this study was conducted to evaluate the influence of gastric emptying on the outcome of the 75-g OGTT. Unlike insulin secretion, plasma glucose at 90 and 120 min had a statistically significant inverse correlation with $^{13}CO_2$ excretion at 30 and 60 min (Table 3), indicating that slower gastric emptying induces higher glycemia at a late phase. Additionally, there was an inverse association between $^{13}CO_2$ excretion at 120 min and plasma glucose at 30 and 60 min. It is quite reasonable that delayed gastric emptying could reduce postprandial hyperglycemia because increased $^{13}CO_2$ excretion at 120 min reflects decreased gastric emptying

Relationship between $^{13}CO_2$ excretion and blood sample values of the 75-g OGTT at each time point

In this study, a direct correlation was found between serum insulin at 30 min and $^{13}CO_2$ excretion at 30, 60, and 90

min, whereas an inverse correlation was found between plasma glucose and $^{13}CO_2$ excretion at 120 min. Serum insulin and $^{13}CO_2$ excretion at 60 min was also directly correlated, but there was an inverse correlation between plasma glucose at 60 min and $^{13}CO_2$ excretion at 90 and 120 min. Plasma glucose at 90 and 120 min had a closer inverse correlation with $^{13}CO_2$ excretion at 30 and 60 min than with $^{13}CO_2$ excretion at 90 and 120 min. There was no correlation between $^{13}CO_2$ excretion and serum insulin at 90 and 120 min. $^{13}CO_2$ excretion measures the rate of the entire process, including gastric emptying, acetate oxidation, and excretion in the breath. When the rate of acetate oxidation and CO_2 excretion in the breath is constant during the 75-g OGTT procedure, it is likely that $^{13}CO_2$ excretion levels reflect gastric emptying rates at each time point. Given that glucose is usually emptied from the stomach at a linear rate between 1 and 4 kcal/min,[15] the early rise in plasma glucose is directly related to gastric emptying and is probably expressed as a $^{13}CO_2$ excretion value at 30 min. However, a significantly close relationship was not found between $^{13}CO_2$ excretion and serum glucose but was found between $^{13}CO_2$ excretion and serum insulin levels at 30 min.

It is reasonable that plasma glucose at 30 min reflects the early glycemic response regulated by insulin secretion, hepatic insulin sensitivity, and hepatic and peripheral glucose disposal, whereas serum insulin reflects only the secretion of insulin from pancreatic β-cells. As shown in Table 2, the correlation coefficient between serum insulin levels at 30 min and $^{13}CO_2$ excretion values was greater at earlier time points. Similarly, there was a significantly close relationship between serum insulin levels and cumulative $^{13}CO_2$ excretion at all time points, except at 120 min. This indicates that the rate of gastric emptying is not a critical determinant of postprandial glycemia but of insulin secretion. This is because various factors influence postprandial glycemia, such as insulin resistance, glucose absorption, and incretin hormone release.

Relationship between $^{13}CO_2$ excretion and parameters of insulin secretion

II, a parameter of rapid insulin response, has a close association with $^{13}CO_2$ excretion at 30 min and with cumulative $^{13}CO_2$ excretion at each time point (Table 4). As shown in Fig. 4, the correlation coefficient between $^{13}CO_2$ excretion and II was the highest at 5 min and gradually decreased over time. There was an inverse correlation between II and T_{max}, indicating that the higher value of II reflects the lower value of T_{max}, which results from rapid gastric emptying. These suggest that a rapid insulin response strongly depends on the gastric emptying rate at an early phase. As the prevalence of delayed gastric emptying ranges from 28% to 65%,[10–12, 16] it is important to evaluate the gastric emptying rate in individuals to accurately regulate postprandial glycemia. Hypoglycemia is possible when delayed gastric emptying is underestimated.

Relationship between $^{13}CO_2$ excretion and parameters of insulin resistance

Insulin resistance was assessed using the HOMA-R and calculated as "fasting plasma glucose × fasting serum insulin / 405." As shown in Table 4, the HOMA-R had a weak inverse relationship with $^{13}CO_2$ excretion only at 90 min. There was no association between the HOMA-R and cumulative $^{13}CO_2$ excretion, T_{max}, or $T_{1/2}$. These results suggest that gastric emptying does not influence insulin resistance but does influence an early insulin response.

The factors influencing postprandial plasma glucose are numerous and include meal composition, rate of gastric emptying, small intestinal function (glucose absorption, incretin hormone release), secretion of insulin and glucagon, insulin resistance, and pre-prandial glucose concentrations. The importance of postprandial hyperglycemia has recently been emphasized, because it precedes fasting hyperglycemia as a precursor of diabetes and has been identified as an independent risk factor for cardiovascular disease.[17, 18] Given that the relationship between cardiovascular autonomic neuropathy and gastric emptying is not well established,[19] the evaluation of gastric emptying in individuals is necessary to prevent cardiovascular diseases as well as hypoglycemia when taking medication for diabetes. Because diabetic patients with delayed gastric emptying do not always complain of abdominal symptoms, it makes the management of gastric motility disorders difficult in clinical practice. When a patient has unstable postprandial glycemia, gastric emptying can be estimated using some modalities.

We previously conducted a longitudinal study using an animal model of diabetes and reported that the utilization of glucose is suppressed in the early stages of prediabetes.[20] This suggests that intestinal function can adapt to postprandial glycemia at the early phase before the development of diabetes. Gastric emptying is a major determinant of the glycemic and incretin responses to carbohydrate in healthy individuals and patients with type 2 diabetes. Glucagon-like peptide-1 (GLP-1) is an incretin hormone

secreted from the gut that stimulates insulin secretion, inhibits inappropriately elevated glucagon levels, and delays gastric emptying.[21–24] In patients with type 2 diabetes, preloading with protein stimulates GIP and GLP-1 and markedly reduces postprandial glycemic excursions.[25] In addition, the relationship of glycemia and GLP-1 secretion with small intestinal glucose delivery is nonlinear in healthy individuals and in patients with type 2 diabetes, possibly inducing a greater response to macronutrient load, given a small change in the gastric emptying rates. We previously demonstrated a high prevalence of maldigestion and malabsorption even in the 75-g OGTT.[26] Unabsorbed nutrients should stimulate incretin secretion from the gut and influence the late insulin response. Thus, both the early and late insulin responses are affected by gastric emptying, although the early insulin response is more closely associated. These are supported by results where the cumulative $^{13}CO_2$ excretion values were closely associated with serum insulin at all time points, except at 120 min.

As a potential limitation of the present study, we did not measure plasma GIP or GLP-1 levels, which regulate insulin secretion and gastric emptying. Furthermore, gastric emptying was evaluated using an indirect method, the ^{13}C-acetate breath test. The $^{13}CO_2$ levels in exhaled air are a result of a long, complex process including gastric emptying, absorption from the intestine, acetate oxidation in the liver, and the rate of $^{13}CO_2$ excretion in the lungs. Finally, the HOMA-R was used for assessing β-cell function and insulin resistance, although prospective data regarding its relationship to the risk of diabetes in ethnically diverse populations are limited.

In conclusion, gastric emptying is an important determinant of not only rapid but also late insulin response. This should be deeply engraved in our minds for the management of diabetic patients, especially in patients with unstable plasma glucose control.

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Conflicts of interest: None declared.

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