No Ghrelin Response to Oral Glucose in Diabetes Mellitus with Gastroparesis

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Abstract. To investigate the role of ghrelin, an endogenous ligand of the growth hormone secretagogue receptor, in diabetic gastroparesis, we evaluated the plasma ghrelin profile during the oral glucose tolerance test in 55 patients with diabetes (men/women: 36/19, mean ± SE of age: 55.1 ± 1.7 years) with or without gastroparesis (diagnosed by the $^{13}$C-acetate breath test). We also further examined cardiac autonomic neuropathy by assessing 24-hour variation of the R-R interval in randomly selected 32 patients with diabetes (men/women: 23/9, mean ± SE of age: 54.2 ± 2.5 years), and evaluated the influence of autonomic neuropathy on ghrelin. The fasting plasma ghrelin level was significantly lower in diabetes mellitus with gastroparesis than in healthy controls (7.9 ± 0.7 fmol/ml versus 16.6 ± 5.3 fmol/ml, p = 0.006). Patients with diabetes with gastroparesis showed no decrease of plasma ghrelin after glucose loading, unlike patients without gastroparesis or healthy controls. Diabetes mellitus with autonomic neuropathy, but not those without it, also showed no decrease of plasma ghrelin after glucose loading. Diabetic gastroparesis may be related to ghrelin-associated neurohormonal abnormalities, but the pathophysiological meaning of this abnormal ghrelin response needs further clarification.

Key words: Ghrelin, Diabetic gastroparesis, Cardiac autonomic neuropathy, $^{13}$C-acetate breath test, Coefficient of variation of the R-R interval

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GHRELIN is a 28-amino acid peptide with N-octanoylation at Ser3 that was originally identified as the endogenous ligand of the growth hormone secretagogue (GHS) receptor, and is primarily secreted by the stomach [1]. Although the GHS receptor is mainly expressed in the pituitary gland and the hypothalamus, it has also been demonstrated in a wide variety of peripheral organs/tissues, including the gastrointestinal tract, liver, pancreas, heart, lungs, kidneys, and adipose tissue, suggesting that ghrelin may have diverse physiologic roles [1–3]. Plasma ghrelin levels exhibit pronounced diurnal variation, show an increase with fasting as well as before meals and at night, and show a rapid decrease after food intake (particularly high-calorie or high-carbohydrate meals) [4]. The fasting plasma ghrelin level is negatively correlated with weight, and obese persons have lower fasting ghrelin levels than lean persons [5]. Thus, in addition to influencing growth hormone secretion, ghrelin seems to transfer information from the stomach to the brain and may play an important role in short-term regulation of the appetite and long-term regulation of the energy balance [6]. Although previous studies have demonstrated various hormones and other substances that can affect the plasma ghrelin level, such as leptin, insulin, glucose, somatostatin, and glucagon [7–11], the exact mechanism of ghrelin secretion remains unclear. Also, the physiological significance and mechanism underlying the suppression of ghrelin
secretion by food intake are unknown. Diabetic gastroparesis is a syndrome characterized by delayed emptying of the stomach in the absence of mechanical obstruction [12]. Symptoms attributable to gastroparesis, such as nausea, vomiting, abdominal discomfort, and postprandial fullness, are reported by 5 to 12% of patients with diabetes [13, 14]. Gastroparesis may interfere with food intake and can cause unexpected fluctuations of the plasma glucose level due to irregular intestinal glucose uptake and mistiming of the onset of action of antidiabetic drugs or insulin, thus leading to poor glycemic control and interfering with the quality of life [13]. Previous investigations have suggested a possible association between vagal dysfunction due to diabetic autonomic neuropathy and the pathogenesis of gastroparesis [12, 15]. Recent studies have indicated that plasma ghrelin levels may also be influenced by the vagal system [16, 17], and that administration of ghrelin enhances gastric emptying in patients with diabetic gastroparesis [18]. However, the direct interaction or connection between ghrelin and diabetic gastroparesis has not been fully investigated. Accordingly, the present study was performed to compare the plasma ghrelin profile during the 75 g-oral glucose tolerance test (OGTT) in patients with diabetes with or without gastroparesis (diagnosed by the \(^{13}\)C-acetate breath test [19]), as well as in healthy non-diabetic subjects. We also examined cardiac autonomic function by analysis of 24-hour variability of the R-R interval [20] in some of the patients with diabetes to evaluate the association between cardiac autonomic neuropathy and ghrelin regulation in diabetes.

Materials and Methods

Subjects

Fifty-five patients with type 2 diabetes (36 men and 19 women with a mean age of 55.1 ± 1.7 years: mean ± SE) who had been followed at the outpatient clinic of St. Marianna University Hospital since 2003 and seven healthy control subjects (5 men and 2 women with a mean age of 30.6 ± 1.2 years) who had no history of illness and were not taking medications were enrolled in this study. The diabetic patients had a fasting plasma glucose level <140 mg/dl on oral anti-diabetic agents and/or insulin therapy. They had no past or present history of gastric surgery, thyroid dysfunction, arrhythmia, or renal dysfunction (serum creatinine ≥ 1.5 mg/dl), and were not taking medications to suppress gastric acid secretion, anticholinergic agents, gastric motility activators, or anti-arrhythmic agents. Diabetic peripheral neuropathy was diagnosed when a subject had at least 2 of the following signs or symptoms: (1) neuropathic symptoms (pain, sensory loss, or dysesthesia in both feet), (2) absence or weakening of the Achilles tendon reflex, and (3) hypopallesthesia at both medial malleoli. Retinopathy was diagnosed by ophthalmologists using the Davis classification. Nephropathy was defined as a urinary albumin excretion rate ≥ 30 mg/24 hours.

The present study was approved by the Ethics Committee of St. Marianna University, and all subjects gave written informed consent to participation.

\(^{13}\)C-acetate breath test

After an overnight fast, expired air was collected in an aluminium bag (Shiseido Breath Test Bag®, Shiseido Fine Chemical Co., Tokyo, Japan) as the baseline sample before the intake of a liquid test meal. Then 100 mg of \(^{13}\)C-acetate (acetic-1-13 C sodium salt 99%, Sigma-Aldrich Co., St. Louis, MO, U.S.A.) was added to a 200-ml liquid test meal (200 kcal; Fibren YH®, Meiji Dairies Co., Tokyo, Japan), and stirred well. The calorie ratio of this test meal was 56% carbohydrate, 24% fat, and 20% protein. After ingestion of the test meal, expired air samples were collected every 10 min for the first 60 min, and then at 75, 90, 120, 150, and 180 min. Subjects were prohibited from drinking, eating, or smoking during the test. Breath samples were stored at room temperature in the dark until the \(^{13}\)CO\(_2/^{12}\)CO\(_2\) ratio of each sample was measured by automated stable isotope ratio mass spectrometry (ANCA-GSL®, SerCon Ltd., Cheshire, UK). The half gastric emptying time (\(T_{1/2}\)) and the lag phase (\(T_{lag}\)), which is the time of maximum gastric emptying according to Ghoos et al. [21], were calculated by using gastric emptying parameter software (Starmedical Inc., Tokyo, Japan). Delayed gastric emptying was defined as being present when \(T_{1/2}\) exceeded 1.79 hr and/or \(T_{lag}\) exceeded 1.08 hr [19]. Conversely, normal gastric emptying was defined as both \(T_{1/2}\) and \(T_{lag}\) being less than these values.
Measurement of biochemical parameters

Blood for the measurement of plasma ghrelin levels was taken from the subjects and transferred into tubes containing EDTA-2Na (1.25 mg/ml) and aprotinin (500 KIU/ml). Blood samples were immediately centrifuged at 3,000 rpm for 15 min at 4°C to obtain plasma, which was acidified with 1 nM HCl and stored at –80°C until assay. The acylated form of ghrelin was measured with an ELISA kit (Active Ghrelin ELISA Kit®, Mitsubishi Kagaku Iatron, Tokyo, Japan). The minimum detection limit of this assay system for acylated ghrelin was 2.5 fmol/ml, and its intra- and interassay coefficients of variation for acylated ghrelin were 3.8% and 3.9%, respectively. Samples were tested in duplicate. Plasma glucose, serum C-peptide (CPR), and serum creatinine levels were measured by the glucose oxidase method (Cicaliquid GLU®, Kanto Chemical Co., Tokyo, Japan), a C-peptide RIA kit® (Shionogi Co., Tokyo, Japan), and an enzymatic method (Pureauto S CRE-N®, Daiichi Pure Chemical Co., Tokyo, Japan), respectively.

Assessment of 24-hour heart rate variability

Thirty-two of the diabetic patients were randomly selected from the study population for 24-hour Holter electrocardiography with a digital Holter recorder (FM-800, Fukuda Denshi Co., Tokyo, Japan). Tapes were analyzed by using the Holter analysis system (SEM-280, Fukuda Denshi Co., Tokyo, Japan) and each QRS complex was labeled. After supraventricular and premature ventricular contractions were excluded automatically, the time series of the R-R intervals was computed, and the coefficient of variation over 24 hours (CV_{24h R-R}) was determined by the maximum entropy spectral analysis method (MemCalc®, GMS, Tokyo, Japan). It was previously reported that the coefficient of variation for 100 R-R intervals recorded at rest (CV_{100 R-R}) can be used as a marker of cardiac autonomic disturbance, with a value of less than 2% being abnormal [22]. In a preliminary study, we found a significant positive correlation between CV_{24h R-R} and CV_{100 R-R} in a combined group of healthy and diabetic subjects (n = 63, r = 0.554, p = 0.0001), and regression analysis showed that a CV_{24h R-R} of 15% was equivalent to a CV_{100 R-R} of 2%. Thus, we diagnosed the presence of cardiac autonomic neuropathy (CAN) when the CV_{24h R-R} was less than 15%. The frequency of sporadic supraventricular and premature ventricular contractions was less than 10 events per 24 hours in the subjects, which was in the normal range [23, 24].

Statistical analysis

Data are presented as the mean ± SE. Comparisons between the diabetic groups with or without gastroparesis were performed by using Student’s t-test or the \( \chi^2 \) test. The significance of changes of the plasma ghrelin level during the OGTT was evaluated by the paired Student’s t-test. Clinical parameters were compared among the three groups by one-way analysis of variance (ANOVA), followed by post hoc multiple comparison using Fisher’s protected least significant difference (Fisher’s PLSD) test. All analyses were performed with the StatView 5.0 statistical software package (Abacus Concepts, Berkeley, CA, USA), and p values of less than 0.05 were considered to indicate statistical significance.

Results

Clinical profile of the subjects

The diabetic patients were classified into a delayed gastric emptying group (group D, n = 36) and a normal gastric emptying group (group N, n = 19) based on the results of the \(^{13}\)C-acetate breath test. The \( T_{1/2} \) and \( T_{lag} \) values obtained in the \(^{13}\)C-acetate breath test for group D, group N, and the healthy controls are plotted in Fig. 1. The clinical characteristics of the subjects are displayed in Table 1. Although age, BMI, HbA1c, and \( T_{1/2} \) were all significantly higher in the diabetic patients than in the healthy control subjects, gender, serum creatinine, and \( T_{lag} \) did not differ between the two groups. Comparison between the two diabetic groups (group D and group N) showed that the prevalence of retinopathy and the \( T_{1/2} \) and \( T_{lag} \) values were significantly higher in group D, while \( CV_{24h R-R} \) was significantly smaller, but the other factors did not differ.

Plasma profiles of ghrelin and glucose

The fasting plasma ghrelin level before the OGTT was 7.9 ± 0.9 fmol/ml in group D, 10.5 ± 1.7 fmol/ml
in group N, and 16.6 ± 5.3 fmol/ml in the control group. The fasting ghrelin level of group D was significantly lower than that of the control group (p = 0.006), but there was no significant difference in the fasting ghrelin level between group D and group N (Table 1). Changes of the plasma glucose level and the % change of the plasma ghrelin level from baseline are shown in Fig. 2A and 2B, respectively. The plasma glucose level was always significantly higher in group N than in the control group, while group D had higher levels at baseline, 60 min, 90 min, 120 min, and 180 min. Plasma glucose levels were significantly lower in group D than in group N at baseline, 30 min, and 60 min. The plasma ghrelin level was significantly decreased from baseline at 60 min, 90 min, and 120 min in group N, as well as at 30 min and 60 min in the control group, but no reduction of plasma ghrelin was observed in group D. Although the plasma ghrelin level at 30 min was lower in Group D than in the control group (p = 0.051), there were no significant differences of the plasma ghrelin levels at 30 min, 60 min, 90 min, 120 min, and 120 min among the groups. Serum CPR levels were significantly lower in group D than group N at baseline, 30 min, 60 min, 90 min, and 120 min (data not shown).

Plasma ghrelin profile during oral glucose loading in diabetic patients with or without cardiac autonomic neuropathy

The diabetic patients were classified into the following two groups based on the \( CV_{24h\ R-R} \) value: a CAN (+) group (n = 15, \( CV_{24h\ R-R}<15\% \)) and a CAN (–) group (n = 17, \( CV_{24h\ R-R}\geq15\% \)). The characteristics of these two groups are shown in Table 2. The percentage of women, retinopathy and the \( T_{1/2} \) and \( T_{lag} \) values

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### Table 1. Clinical characteristics of the diabetic patients, delayed and normal gastric emptying groups, and controls.

<table>
<thead>
<tr>
<th></th>
<th>Group D (n = 36)</th>
<th>Group N (n = 19)</th>
<th>P value (Group D vs. Group N)</th>
<th>All diabetic patients (n = 55)</th>
<th>Controls (n = 7)</th>
<th>P value (Diabetics vs. Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female (n)</td>
<td>25/11</td>
<td>14/5</td>
<td>0.108</td>
<td>39/16</td>
<td>5/2</td>
<td>0.977</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.8 ± 2.1³</td>
<td>51.9 ± 3.0³</td>
<td>0.187</td>
<td>55.1 ± 1.7³</td>
<td>30.6 ± 1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.7 ± 0.8³</td>
<td>24.6 ± 0.8³</td>
<td>0.105</td>
<td>26.0 ± 0.6³</td>
<td>21.3 ± 0.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.75 ± 0.05</td>
<td>0.75 ± 0.06</td>
<td>0.885</td>
<td>0.74 ± 0.04</td>
<td>0.84 ± 0.06</td>
<td>0.369</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>9.1 ± 0.4</td>
<td>8.8 ± 0.4</td>
<td>0.615</td>
<td>9.0 ± 0.3³</td>
<td>4.8 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>14.5 ± 1.5</td>
<td>11.7 ± 2.1</td>
<td>0.191</td>
<td>13.3 ± 1.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Neuropathy: –/+ (n)</td>
<td>14/22</td>
<td>11/8</td>
<td>0.178</td>
<td>25/30</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Retinopathy: –/+ (n)</td>
<td>15/21¹</td>
<td>14/5</td>
<td>0.024</td>
<td>46/9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nephropathy: –/+ (n)</td>
<td>14/22</td>
<td>12/7</td>
<td>0.087</td>
<td>34/11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fasting ghrelin level (fmol/ml)</td>
<td>7.9 ± 0.9³</td>
<td>10.5 ± 1.7</td>
<td>0.232</td>
<td>8.8 ± 0.9³</td>
<td>16.6 ± 5.3</td>
<td>0.012</td>
</tr>
<tr>
<td>( T_{1/2} ) (hr)</td>
<td>2.02 ± 0.06³</td>
<td>1.50 ± 0.04</td>
<td>&lt;0.0001</td>
<td>1.84 ± 0.05³</td>
<td>1.50 ± 0.10</td>
<td>0.028</td>
</tr>
<tr>
<td>( T_{lag} ) (hr)</td>
<td>1.24 ± 0.04³</td>
<td>0.91 ± 0.03</td>
<td>&lt;0.0001</td>
<td>1.13 ± 0.04</td>
<td>0.96 ± 0.04</td>
<td>0.123</td>
</tr>
<tr>
<td>( CV_{24h\ R-R} ) (%)</td>
<td>14.6 ± 0.9³</td>
<td>18.8 ± 1.6³</td>
<td>0.026</td>
<td>15.7 ± 0.9³</td>
<td>24.6 ± 1.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are the mean ± SE unless otherwise indicated. Group D, diabetics with delayed gastric emptying; Group N, diabetics with normal gastric emptying; Controls, healthy controls; \( CV_{24h\ R-R} \), coefficient of variation of the R-R interval over 24 hours; \( T_{lag} \), lag phase in the \(^{13}\text{C}-\text{acetate breath test}; T_{1/2}, \text{half-emptying time in the } ^{13}\text{C}-\text{acetate breath test.}

² P < 0.05 vs. normal gastric emptying group.

³ P < 0.05 vs. healthy controls.
were significantly higher in the CAN (+) group than in the CAN (–) group, while CV$_{24h}$ was significantly lower. The prevalence of delayed gastric emptying did not differ between the two groups (Table 2). CV$_{24h}$ showed a significant negative correlation with T$_{lag}$ ($r = -0.35$, $p = 0.049$) and also with T$_{1/2}$ ($r = -0.41$, $p = \ldots$).
p = 0.018). Plasma glucose levels and the % change of plasma ghrelin from baseline during the OGTT are shown in Fig. 3A and 3B, respectively. Both plasma glucose (Fig. 3A) and serum CPR (data not shown) showed no differences of their profiles between the CAN (+) and CAN (–) groups. In contrast, plasma ghrelin levels showed a significant decrease from baseline at 90 min in the CAN (–) group, but no significant reduction was observed in the CAN (+) group. Although the plasma ghrelin level at 90 min was lower in the CAN (+) group than in the CAN (–) group (p = 0.059), there were no significant differences of plasma ghrelin between the two groups at any time during the OGTT.

**Discussion**

The present study demonstrated three main findings: 1) the fasting plasma ghrelin level was significantly lower in diabetic patients with delayed gastric emptying according to the $^{13}$C-acetate breath test (group D) than in the healthy control group; 2) there was no decrease of plasma ghrelin during the OGTT in group D, unlike the diabetic patients with normal gastric emptying (group N) or the control group; and 3) diabetic patients with a CV$_{24\text{h} \text{R-R}}$<15%, but not those with a CV$_{24\text{h} \text{R-R}}$$\geq$15%, also showed no decrease of plasma ghrelin during the OGTT.

Fasting plasma ghrelin levels are reported to display a negative correlation with weight, and obese subjects have lower ghrelin levels than lean subjects [5]. Consistent with such findings, BMI was significantly higher and the baseline plasma ghrelin level was significantly lower in our group D than in the control group. The baseline plasma ghrelin level of all subjects including the healthy controls showed a negative correlation with BMI and age (r = –0.31, p = 0.01 and r = –0.34, p = 0.01, respectively) (data not shown). However, a correlation between ghrelin and age was not demonstrated when only diabetic patients or only healthy controls were assessed (r = –0.24, p = 0.07 and r = –0.32, p = 0.51, respectively) (data not shown), although the correlation between ghrelin and BMI was still detected in diabetic patients (r = –0.24, p = 0.03). Fasting plasma ghrelin levels may be influenced by age. However, Akamizu et al. reported that the fasting plasma ghrelin level of healthy subjects showed no significant correlation with age [25]. Because only a small number of healthy subjects were enrolled in our study, further investigation of the relation between age and ghrelin is necessary.
Previous studies have revealed that the plasma ghrelin level decreases after the intake of a carbohydrate-rich meal or an oral glucose load [4], while a recent study showed that the increase of plasma glucose and the consequent rise of plasma insulin after intravenous infusion of glucose did not affect the plasma ghrelin level [26]. Thus, suppression of ghrelin by food or an oral glucose load may not be regulated by the plasma level of glucose and/or insulin, but rather by some direct or indirect information from the gastrointestinal tract. Very recently, Gaddipati et al. reported that sham feeding could increase the plasma ghrelin level in normal subjects, while such a response of ghrelin was not observed in patients with diabetic gastroparesis [27]. In contrast, Arosio et al. reported that circulating ghrelin concentrations decreased with sham feeding as they do with actual meal ingestion in humans [28]. The meal used in this study contained relatively more carbohydrates than the one used in the study by Gaddipati et al. This difference may affect the meal-induced changes in ghrelin levels. Vagotomy also leads to impairment of this ghrelin response during the fasting state [16, 29]. Furthermore, Pekic et al. reported no suppression of ghrelin levels during the OGTT in patients who had undergone vagotomy [30]. While there was no significant difference in the % change of plasma ghrelin between group D and group N in the present study, a significant decrease of ghrelin after glucose loading was not detected in group D, unlike group N. Because we intended to avoid the influence of renal dysfunction on the plasma ghrelin level, most of the subjects enrolled in the present study probably had mild autonomic neuropathy and this may partially explain the results. Taken together, these findings suggest that the lack of a decrease of ghrelin during the OGTT in our group D may have been partly be due to vagal dysfunction and may represent another aspect of diabetic autonomic neuropathy.

Autonomic neuropathy is a common complication of diabetes, and previous studies have shown that the gastric emptying rate is significantly correlated with cardiac autonomic neuropathy (CAN) in patients with type 1 diabetes [31]. Recently, Asakawa et al. reported that the CV\textsubscript{R,R} during deep breathing might be a good indicator of diabetic gastroparesis in type 2 diabetic patients [32]. Ewing et al. reported that heart rate variation computed from 24 hour Holter ECG records are more sensitive than simple bedside tests (i.e., Valsalva maneuver, orthostatic test and deep breathing) [33]. Since short-term CV\textsubscript{R,R} data may be influenced by various factors, we evaluated this parameter over 24 hours (CV\textsubscript{24h R,R}) by using Holter ECG recordings. We found that CV\textsubscript{24h R,R} was significantly lower in group D than in group N, and that it showed a significant negative correlation with both T\textsubscript{lag} and T\textsubscript{1/2}. In addition, the mean of CV\textsubscript{24h R,R} in healthy persons of 50 years old was 18.9 ± 3.8% (means ± SD) [34], which was approximately the same degree as that in group N. These results are consistent with those of previous studies. Since it is known that diabetic autonomic neuropathy can induce systemic autonomic dysfunction, it is reasonable to assume that cardiac and gastric autonomic neuropathy could develop simultaneously. CV\textsubscript{24h R,R} can be determined more easily compared with performing the \textsuperscript{13}C-acetate breath test, and patients with a low CV\textsubscript{24h R,R} may be suspected of having gastroparesis and an impaired ghrelin response to an oral glucose load or a high-carbohydrate meal.

As well as the indicators of autonomic neuropathy, there were other significant differences between groups D and N, diabetic and healthy subjects, and the CAN (+) and CAN (−) groups. We tried to find a factor that was independently associated with the blunted ghrelin response by multiple regression analysis, but we did not detect any independent factor related to the blunted response. As our study only included a small number of subjects, a larger population will need to be investigated to clarify the mechanism of the blunted ghrelin response.

Interestingly, ghrelin shows a structural resemblance to motilin, a gastrointestinal hormone that stimulates gastric motility, and the ghrelin receptor also displays structural similarity to the motilin receptor [35]. In addition, ghrelin infusion induces an increase of gastric contractility and emptying through vagal afferent pathways in the rat [36]. Therefore, the stomach may play an important role in the regulation of appetite and food intake via neurohormonal links. Lately Ueno et al. showed no significant postprandial decrease in total ghrelin levels at 30 and 60 min after meal was detected in diabetic patients with autonomic neuropathy which gave a definition of CV\textsubscript{R,R} [37]. However, the active form of ghrelin could be much more useful in determining its physiological and pathophysiological role than the total form. The present study demonstrated the lack of a decrease of active ghrelin during the OGTT in diabetic patients.
with gastroparesis and diabetic patients who had a low CV₂₄h R-R, which suggested that diabetic gastroparesis may be related to neurohormonal disturbances such as the abnormal ghrelin response that occurs secondary to vagal dysfunction. However, the pathophysiological meaning of this impaired ghrelin response to a glucose load remains unclear, and its role in gastric dysmotility and/or symptoms of diabetic gastroparesis should be further investigated.

In conclusion, a decrease of the plasma ghrelin level in response to an oral glucose load did not occur in diabetic patients with gastroparesis (according to the ¹³C-acetate breath test) or in diabetic patients with cardiac autonomic neuropathy (based on the CV₂₄h R-R).

References


