GASTRIC EMPTYING IS ACCELERATED IN OBESE TYPE 2 DIABETIC PATIENTS WITHOUT AUTONOMIC NEUROPATHY

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SUMMARY

Objective: To clarify the impact of type 2 diabetes mellitus on the gastric emptying rate.

Material and methods: Using a double-isotope scintigraphic technique, we assessed the gastric emptying of a standard liquid-solid meal in 13 obese type 2 diabetic patients without autonomic neuropathy (age: 47.4 ± 8.6 yr, body mass index: 33.9 ± 4.8 kg/m², glycaemia: 9.1 ± 2.6 mmol/l) and in 7 controls with similar sex ratio, age, BMI and body fat distribution.

Results: The half gastric emptying time for the liquid phase was not significantly different between diabetic patients and controls (respectively: 52.7 ± 14.5 min and 63.1 ± 15.2 min). However, the half gastric emptying time for the solid phase was significantly shortened in diabetic patients versus controls (respectively 88.8 ± 23.2 min in diabetic patients and 113.6 ± 26.9 min in controls; p < 0.04). Furthermore, a negative relationship was highlighted between the half gastric emptying time for the solid phase and basal glycaemia (r = – 0.65, p < 0.02) in diabetic patients. No significant relationship was found between gastric emptying parameters and cardiac autonomic nerve function, insulin or gastrin levels.

Conclusion: Solid gastric emptying is accelerated in obese type 2 diabetic patients without patent autonomic neuropathy when compared to obese non diabetic patients.

Key-words: type 2 diabetes, gastric emptying, scintigraphy, autonomic neuropathy, gastrin.

RÉSUMÉ - La vidange gastrique est accélérée chez les patients diabétiques de type 2 obèses sans neuropathie autonome.

Objectif : Clarifier l’impact du diabète de type 2 sur la vitesse de vidange gastrique.

Matériel et méthodes : En utilisant une technique scintigraphique de double marquage isotopique, nous avons mesuré la vidange gastrique des phases liquide et solide d’un repas standard, chez 13 patients obèses diabétiques de type 2 indemnes de neuropathie autonome (âge : 47,4 ± 8,6 ans, index de masse corporelle : 33,9 ± 4,8 kg/m², glycémie : 9,1 ± 2,6 mmol/l) et chez 7 sujets témoins (sex ratio, âge, IMC et tour de taille/tour de hanche comparables entre les 2 groupes).

Résultats : Le temps de demi-vidange gastrique de la phase liquide ne diffère pas significativement entre les patients diabétiques et les sujets témoins obèses (respectivement 52,7 ± 14,5 min et 63,1 ± 15,2 min). Cependant, le temps de demi-vidange gastrique de la phase solide est significativement réduit chez les patients diabétiques par rapport aux témoins (respectivement 88,8 ± 23,2 min et 113,6 ± 26,9 min; p < 0,04). De plus, une association négative est retrouvée chez les patients diabétiques entre le temps de demi-vidange gastrique de la phase solide et la glycémie de base (r = – 0,65, p < 0,02). Les paramètres d’évaluation de la vidange gastrique ne sont pas significativement associés aux taux plasmatiques d’insuline ou de gastrine, ni aux différentes mesures de l’activité du système nerveux autonome.

Conclusion : La vidange gastrique des solides est accélérée chez les sujets obèses diabétiques de type 2 sans atteinte du système nerveux autonome, comparativement à celle de sujets obèses non diabétiques.

Mots-clés : diabète de type 2, vidange gastrique, scintigraphie, neuropathie autonome, gastrine.

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Gastric emptying abnormalities are frequent in diabetes mellitus [1]. Delayed gastric emptying of solid and liquid meals has been reported in up to 50% of patients with type 1 diabetes mellitus [2, 3]. Visceral autonomic neuropathy is considered the main cause of these motility disorders [4, 5] although conflicting results have been reported [6]. More recently, it has been reported that glycaemia per se has a major impact on gastric emptying rate. Acute hyperglycaemia has been shown to slow gastric emptying in healthy subjects [7-11] and in type 1 diabetic patients [12, 13] whereas hypoglycaemia accelerates gastric emptying, this effect being mediated by parasympathetic stimulation [14, 15].

Unlike type 1 diabetes mellitus, few studies have assessed gastric emptying in type 2 diabetes mellitus [16-21]. Only two of them [19, 20] have been conducted with a double scintigraphic measurement of solids and liquids emptying using a standard meal [22]. They gave contradictory results possibly due to differences in the prevalence of autonomic neuropathy in diabetic patients and differences in the control population, especially concerning body mass index (BMI) and body fat distribution which could affect gastric emptying.

Our purpose was:

- to assess the gastric emptying of a standard meal in a type 2 diabetic obese population compared to a control population of similar sex ratio, age, BMI and body fat distribution index (waist-to-hip circumference ratio);
- to examine the relationships between gastric emptying and autonomic nerve function, blood glucose, insulin and gastric levels.

**Subjects and Methods**

**Subjects**

The study was performed in 13 obese patients (9 women, 4 men) with type 2 diabetes mellitus and 7 obese nondiabetic controls (5 women, 2 men), who were consecutively recruited from the department of diabetology and nutrition in our University hospital (outpatients consulting for diabetes mellitus or obesity). All the diabetic and control patients were non-smoking caucasian, ranging from 34 to 61 years of age. The exclusion criteria were:

- for the two groups: history of gastrointestinal pathology or of abdominal surgery, BMI < 30 kg/m², body weight variation upper than 1kg in the month preceding the test, significant change in daily food intake during the last two weeks (verified by a short questioning), ischemic cardiopathy, pulmonary disease;
- for the diabetic patients: history of ketosis, another antidiabetic medication than sulfonylurea or metformin, another treatment than angiotensin converting enzyme inhibitors in addition to oral antidiabetic treatment, dysautonomic symptoms determined by interview and review of medical records;
- for the control subjects: familial history of diabetes mellitus, defect in glucose tolerance to a 75-g oral glucose load accordingly to the WHO criteria [23], any medication.

All diabetic patients were treated by an oral antidiabetic medication (sulfonylurea in all and metformin in 10 patients). Retinal fundus photography showed that no patient had retinopathy. Three patients had microalbuminuria (but creatinine concentration was within the normal range), and three (two without microalbuminuria) had clinical signs of peripheral neuropathy (absence of ankle reflexes associated to an increase in the vibration perception threshold assessed by biothesiometry). All diabetic patients and controls were found to be free of any gastrointestinal symptoms using a standard questionnaire after inclusion [19]. None had infectious or inflammatory disease. C-reactive protein, erythrocyte sedimentation rate, and bacterial examination of the urines were normal or negative in all the patients. The study was approved by our local ethical committee and written informed consent was obtained from all patients and controls.

**Experimental Protocol**

Each subject attended the hospital at 8 AM after fasting overnight. Patients with type 2 diabetes omitted their morning medication. An intravenous catheter was inserted into an antecubital vein for blood sampling. Venous blood samples were drawn just before (~ 10 min) and at the end (0 min) of the meal administration, and then at 30 min intervals for 180 min. Blood samples were collected into tubes chilled on ice and centrifuged, and plasma was stored at -80°C until assayed. Latent autonomic neuropathy was systematically detected in diabetic patients by studying cardiovascular reflexes.

**Gastric emptying measurement**

Gastric emptying was evaluated with a double-isotope scintigraphic technique that allows simultaneous measurements of the emptying of solid and liquid meal components. The characteristics of scintigraphic measurements and the meal composition were

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>T_{sol}</td>
<td>half gastric emptying time for the solid phase</td>
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<tr>
<td>T_{liq}</td>
<td>half gastric emptying time for the liquid phase</td>
</tr>
<tr>
<td>T_{50sol}</td>
<td>half gastric emptying time</td>
</tr>
<tr>
<td>T_{50liq}</td>
<td>for the liquid phase</td>
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<tr>
<td>T_{50sol}</td>
<td>for the solid phase</td>
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those previously described by Jian et al. [24]. The meal was composed of 70 g coarsely ground beef, 40 g bread, 10 g butter, 10 g sugar, one egg white (30 g), 200 ml skimmed milk, followed by 150 ml water. The overall energy intake was 440 kcal (26% protein, 38% carbohydrate, 36% fat). The solid-phase marker was 99mTc–Technetium colloid (30MBq 99mTc) mixed with the egg white before cooking, and the liquid-phase marker was 111Indium diethylenetriaminepentacetic acid (5.5MBq 111In-DTPA) added to the water. The stability and specificity of the labeling had been previously checked [25, 26]. The entire meal was ingested within 10 min. Immediately after the meal (time 0), consecutive 1-min gamma camera images were obtained every 30 min for 180 min while the patient was standing. Between standing image acquisitions, the subjects were allowed to sit in a chair at a 90° angle.

Gastric emptying data were acquired from geometric means of anterior and posterior counts which were calculated for each image. Data were stored on disks and processed by a digital computer (SMV, France): an area of interest corresponding to the stomach was outlined, and the radioactivity in this area was counted on each image. All counts were corrected for physical decay of the markers. They were expressed as a fraction of total meal against time, and all biochemical data were analysed using a simple least square method implemented on an Excel worksheet.

Assays
Glucose concentration was measured by an enzymatic assay with glucose oxidase (Boehringer Mannheim, Meylan, France). HbAlc was measured by a solid phase immunoradiometric analyzer (Bio-Rad, Ivry-sur-Seine, France). HbA1c was measured by a high-pressure liquid chromatography on a Diamat analyzer (Bio-Rad, Ivry-sur-Seine, France). Insulin was measured by a solid phase immunoradiometric assay calibrated on WHO 66/304 (Insulin-IRMA, Medgenix, Belgium). Gastrin was measured by a radioimmunoassay (GASK-PR, Cis Biointernational, Gif sur Yvette, France).

Assessment of autonomic function
Autonomic nerve function was assessed by standard cardiovascular reflex tests. Parasympathetic function was evaluated according to the variation of the R-R interval in the electrocardiogram during deep breathing and the immediate response of the heart rate upon standing (30: 15 ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. The following indexes were measured: the ratio of the R-R interval measured during expiration (E) and inspiration (I) of six deep breaths (E: I ratio) (normal, ≥ 1.21; borderline, 1.11-1.20; abnormal, ≤ 1.10); the ratio of the R-R interval of the 30th beat to the 15th after standing (30: 15 ratio) (normal, ≥ 1.04; borderline, 1.01-1.03; abnormal, ≤ 1.00); and a drop in systolic blood pressure after standing (normal, ≤ 10 mmHg; borderline, 11-29 mmHg; abnormal, ≥ 30 mmHg). The results of these tests were scored as 0, normal; 1, borderline; 2, abnormal, according to the criteria defined by Ewing and Clarke [27]. A total score higher than 3 indicated the presence of an autonomic nerve disorder.

Statistical analysis
Data were expressed as mean ± SD. Groups were compared using the Mann-Whitney U test (unpaired data). Gastric emptying, metabolic and hormonal responses in the type 2 diabetes and control groups were compared using repeated measures analysis of variance (ANOVA).

Relationships between gastric emptying parameters and all biochemical data were analysed using a simple regression analysis. A p value less than 0.05 was considered significant. All statistics were done with a computer program software (Statview® SE, V1.03; Abacus Concepts, Berkeley, CA).

Results

Comparison of study groups
There was no difference in sex ratio, age, BMI and waist-to-hip circumference ratio between groups (Table I). Fasting plasma glucose concentrations were higher in the diabetic subjects (p < 0.001) whose values ranged from 6.6 to 13.8 mmol/l.

Evaluation of gastric emptying
All subjects tolerated the meal well and none experienced nausea or gastrointestinal symptoms. The mean half-emptying time for the liquid phase (T50liq) was 52.7 ± 15.2 min in diabetic and 63.1 ± 15.2 min in control subjects (difference not significant) (Fig. 1). The mean half-emptying time for the solid phase (T50sol) was 88.8 ± 25.2 min in diabetic and 113.6 ± 26.9 min in control subjects, showing a shorter gastric emptying time in diabetic patients (p < 0.04). The β coefficient of diabetic patients was not significantly different from that of controls (2.0 ± 0.3 vs 2.5 ± 0.7) and β was not correlated with the T50sol value. The mean remaining activity time curves of the liquid and solid phases in the two groups are presented in Figure 2.
Relationships between gastric emptying and other parameters

Age, sex and duration of diabetes mellitus

Gastric liquid and solid emptying rates as assessed by T_{50} were not significantly related to age, sex and duration of known diabetes mellitus.

Autonomic function

Among diabetic patients, none had evidence of an autonomic nerve disorder (Ewing’s global score was always ≤ 3). There was no significant relationship between absolute values, individual or global scores of autonomic nervous tests and solid or liquid gastric emptying parameters.

Glycaemic control and plasma insulin levels

Blood glucose concentrations were higher in the diabetic than the control subjects both before and after the meal ingestion (p < 0.001) (Fig. 3). The magnitude of the rise in blood glucose from baseline was greater in the diabetic subjects at all time points (Fig. 3). The peak blood glucose occurred later in the diabetic patients (60 min versus 30 min in control subjects). There was a significant negative relationship between T_{50}sol and basal glycaemia (r = −0.65, p < 0.02) in diabetic patients (Fig. 4). A similar relationship was observed between HbA1c and T_{50}sol although at a non significant level (r = −0.45; p < 0.12). The increment of glycaemia in the first 30 or 60 min after the meal and the area under the glucose concentration curve for the first 120 min or the entire period of analysis, were not significantly associated to gastric emptying data in diabetic patients. Plasma insulin levels were similar in the two groups before the test. After the ingestion of the meal, significant differences between the two groups were detected at 90 and 120 min (p < 0.03) (Fig. 3) without significant difference in the area under the insulin concentration curve for the entire period of analysis. Insulin concentrations were not associated with any of the studied gastric emptying parameters.

Gastrin concentration

Plasma gastrin levels were not significantly different between the two groups before the test meal or at any time of the gastric emptying analysis (Fig. 5). No relationship between gastrin levels and gastric emptying parameters could be detected.

TABLE I. Comparison of studied subjects.

<table>
<thead>
<tr>
<th></th>
<th>type 2 diabetes (n = 13)</th>
<th>control (n = 7)</th>
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<tbody>
<tr>
<td>number of women/men</td>
<td>9/4</td>
<td>5/2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.4 ± 8.6</td>
<td>44.0 ± 4.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>90.1 ± 11.8</td>
<td>94.8 ± 13.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.9 ± 4.8</td>
<td>34.6 ± 3.4</td>
</tr>
<tr>
<td>W/H</td>
<td>1.00 ± 0.09</td>
<td>0.93 ± 0.14</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>9.1 ± 2.6</td>
<td>4.8 ± 0.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 ± 1.1</td>
<td>5.5 ± 0.3</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>6.5 ± 8.5</td>
<td>–</td>
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</table>

Results are presented as mean ± SD; W/H: Waist-to-Hip circumference ratio, * p < 0.001; p = degree of significance (a value less than 0.05 was considered significant).
The control of gastric emptying is complex and involves a number of factors – neurologic, metabolic, hormonal – whose relative contributions in gastric motility abnormalities in diabetic patients are unclear. The present study was performed in a homogeneous population of 13 type 2 diabetic obese patients. No one had subclinical cardiac autonomic dysfunction, precluding the confusing effect of autonomic neuropathy on gastric motility. In addition, given the potential interference of BMI and body fat mass distribution with gastric emptying, the diabetic population was compared to a control one with similar characteristics for age, sex ratio, BMI and waist-to-hip circumference ratio. Using a dual scintigraphic technique, our study shows a significant acceleration of the solid gastric emptying rate of a standard meal in diabetic obese patients compared with obese controls. The same tendency was detected when studying the liquid gastric emptying rate although the difference was not significant between the two groups.

Our results are in apparent contradiction with two previous studies in type 2 diabetic patients using the same scintigraphic technique [19, 20]. In the first study, Horowitz et al. [19] found delayed gastric emptying for liquids and for solids in 20 diabetic patients. This result may be explained by the high rate of autonomic neuropathy in their diabetic population (40%). All diabetic patients in our study had normal autonomic function. In addition, Horowitz et al. recruited normal weighed controls. Ponderal excess and upper body fat mass distribution per se may have contributed to the delay in gastric emptying in diabetic patients.

**FIG. 2.** Mean remaining activity time curves of the solid and liquid phases of the meal in 13 type 2 diabetic patients and 7 controls.

**FIG. 3.** Mean (± SEM) plasma glucose and insulin concentrations following ingestion of the meal in 13 type 2 diabetic patients and 7 controls. * = p < 0.001 and † = p < 0.03 between the two groups.
patients. Indeed, several studies have reported an association between gastric emptying rate and obesity [28-30]. Furthermore, intraabdominal fat accumulation potentially interferes with gastric emptying by changing gastric position [31, 32]. In the second study, Frank et al. [20] reported that gastric emptying for the liquid component of a mixed solid/liquid meal was faster in 10 patients with longstanding type 2 diabetes (mean duration 4.2 yr) without autonomic neuropathy than in controls with a similar mean BMI (about 28 kg/m²). Gastric emptying of solids was also faster but the difference with controls was not significant. It is of interest that patients in this study were positioned at an angle of 45° with the horizontal during scintigraphic analysis. Such a position could delay gastric emptying especially for solids, with a potentially different kinetic in diabetic versus control subjects [31].

Our results are in agreement with those of Schwartz et al. [18], who found a more rapid gastric emptying of a solid pancake meal in type 2 diabetic patients versus controls with a similar mean BMI (30 kg/m²). The same group using an oral glucose load reported also an accelerated gastric emptying in type 2 diabetic patients [17]. However, these results were not confirmed by Jones et al. [16] who found no significant difference.

Apart from an acceleration in gastric emptying rate in type 2 diabetes mellitus, we found for the first time a significant negative relationship between basal glycaemia (ranging from 6.6 to 13.8 mmol/l) and the half gastric emptying rate for the solid phase. This observation contrasts with previous studies which have shown that acute hyperglycaemia may substantially decrease gastric motility and gastric emptying in normal subjects [9, 11, 13, 15] and diabetic patients [8, 12, 13, 19]. In type 1 diabetic patients, gastric emptying is, indeed, slower during hyperglycaemia compared to euglycaemia [12] and accelerated during hypoglycaemia [14]. However, the magnitude of the decrease in gastric emptying rates associated with acute hyperglycaemia is possibly less in diabetic patients when compared with normal subjects [13], and our results are in agreement with those of Schwartz et al. [18] whose 8 type 2 diabetic patients had a higher basal glycaemia than our patients (respectively 11 mmol/l vs 9.1 mmol/l). Other studies on the liquid gastric emptying of an oral glucose load, did not report a slower gastric emptying rate in type 2 diabetic patients vs control subjects [16, 17]. More recently, no significant changes in the first 50-min gastric emptying rates of a semisolid standard meal could be detected after one week of better metabolic control in type 2 diabetic subjects [33]. Therefore, the gastric emptying response to hyperglycaemia may be different between type 1 and type 2 diabetes mellitus and between acute and chronic situations.

Fasting insulinemia which partly depend on body fat mass distribution was found similar between diabetic and control subjects in the present study as in Schwartz’s study [18]. These data suggest that insulinemia per se cannot explain the differences detected in gastric emptying rates. Furthermore, the moderate slowing effect of hyperinsulinaemia on gastric motility previously reported in normal subjects [34, 35] has not been confirmed in patients with uncomplicated type 1 and type 2 diabetes [36]. We also measured blood gastrin concentrations because acute hyperglycaemia was reported to reduce gastrin secretion in healthy subjects [37], and abnormalities in gastrin

Fig. 4. Relationship between the half gastric emptying time for the solid phase (T₅₀ sol) and basal glycaemia in 13 type 2 diabetic patients (r = –0.65, p < 0.02).

Fig. 5. Mean (± SEM) plasma gastrin concentrations following ingestion of the meal in 13 type 2 diabetic patients and 7 controls.
secretion could modulate gastric emptying directly or by inducing alterations in gastric acid secretion [38]. The mean fasting gastrin level was similar between our diabetic patients and controls, and we did not find significant differences in blood gastrin levels after the meal ingestion.

In summary, our study shows an accelerated rate of solid gastric emptying in obese type 2 diabetic patients without patent autonomic neuropathy. Hormonal and/or neurologic factors involved in gastric emptying changes induced by hyperglycaemia could be modulated by the time exposure to hyperglycaemia in type 2 diabetes mellitus. This is a particularly relevant matter since a rapid gastric emptying could contribute to a lower metabolic control in type 2 diabetic patients. It would then be of some interest to pharmacologically lower gastric emptying in obese type 2 diabetic patients.

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REFERENCES

13 Schwarz E, Palmer M, Aman J, Horowitz M, Stridsberg M, Berne C. Physiological hyperglycemia slows gastric emptying in normal sub-
jects and patients with insulin-dependent diabetes mellitus. Gastroen-
14 Schwarz E, Palmer M, Aman J, Lindkvist B, Beckman KW. Hy-

