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DISTURBED GASTRIC MOTILITY AND PANCREATIC HORMONE RELEASE IN DIABETES MELLITUS

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Background and aims: The influence of glucose metabolism and postprandial release of glucagon on gastric emptying in diabetes mellitus is still unclear. The aim of this study was to assess the relationship between glucose, insulin and glucagon and alterations of gastric motility in symptomatic diabetic subjects with delayed gastric emptying.

Methods: Scintigraphy for solids and liquids, ^{13}C -acetate breath test, electrogastrography and antral manometry were assessed in 20 symptomatic subjects with diabetes mellitus type II and in 20 healthy controls. Simultaneously, serum glucose, glucagon and insulin levels were determined during the functional studies.

Results: Postprandial increase in antral motility and myoelectrical activity were seen in controls, but were missing in the group with diabetes mellitus. Moreover, in the fasting state the dominant frequency instability coefficient observed in healthy individuals and in subjects with diabetes of short (<5 years) duration was significantly reduced in subjects with longer duration of diabetes while the postprandial increase in dominant frequency instability coefficient was missing in all diabetics. Following the standard test meal, serum glucose and plasma glucagon in the diabetics increased to a significantly higher degree when compared to controls.

Conclusions: Symptomatic subjects with delayed gastric emptying present abnormal patterns of gastric motor and electrical activity. Higher than normal postprandial plasma levels of glucagon may, at least in part, be responsible for disturbed gastric motility in non-insulin-dependent diabetic subjects.

Key words: *diabetic gastroparesis, hyperglycemia, glucagon, gastric motility*

INTRODUCTION

Gastric emptying is a complex process dependent on sufficient gastric muscle contractility, antro-pyloro-duodenal coordination and intact function of autonomic nerves. Additionally, a number of gut hormones may influence gastric motility pattern (1). Among diseases leading to delayed gastric emptying and gastroparesis, diabetes mellitus is the most frequent entity. The prevalence of diabetes is reported to be 4% and estimated to increase during the forthcoming decades. Depending on the definition and methods for assessment

of gastroparesis, its prevalence among diabetic subjects is estimated to about 50%, with figures ranging between 9,9 and 32%, and even up to 76%. (2-4). Previous studies have shown that hyperglycemia delays gastric emptying in both diabetic subjects and healthy individuals (6-8).

Scintigraphic test with radioisotopically labeled solid meal is the most widely accepted tool for diagnosis of gastroparesis. The use of liquid test meals may reveal an accelerated gastric emptying in asymptomatic subjects (5,9). Other methods, like antral or antro-pyloro-duodenal manometry (10-12), ^{13}C -octanoic acid breath test (13) and electrogastrography (EGG) (14) have been used for identification of disturbed gastric motility in subjects with diabetes mellitus, but their clinical relevance and diagnostic accuracy in diabetic gastroparesis have not been established yet.

In this study we assessed the relationship between blood glucose, glucagon and insulin levels and the results of the different function tests for gastric motor and electrical activity in symptomatic diabetic subjects with delayed gastric emptying and controls.

METHODS

Twenty subjects (12 males and 8 females) between 51 and 69 years of age, weighing 58-87 kg with diabetes mellitus type II entered the study. Known diabetes duration was between 4 and 13 years. Twenty healthy individuals of both sexes (11 males and 9 females) between 22 and 53 years of age and weighing 53-81 kg were enrolled into this study and served as controls. This study was approved by the appropriate Institutional Review Committee, and all subjects gave written informed consent to participate.

Patients

In all subjects who entered the study, delayed gastric emptying had been established previously (one to four weeks before) with the diagnosis being based upon scintigraphy for solid meal. All subjects had a varying degree of complaints like dyspepsia, regurgitation, nausea, vomiting, postprandial fullness or unexplained difficulties with serum glucose control. All subjects underwent endoscopy of the upper gastrointestinal (GI) tract, and none of them showed morphologic changes of the esophagus or the stomach. Biopsy specimens taken during the upper GI endoscopy did not show any pathologic changes of the mucosa. Furthermore, before inclusion into the study all subjects underwent ^{13}C urea breath test to exclude infection with *Helicobacter pylori*. Subjects with diabetic nephropathy with increased serum creatinine levels higher than 3 mg/dl were excluded from the study. Subjects who took any medication knowing to influence gastric motility were excluded from participation. All tests were performed in the early morning and oral hypoglycemic agents were not administered prior to examinations.

Healthy controls

The control group consisted of 20 healthy individuals. None of them had abdominal complaints or a history of gastric or esophageal disease. None of them was taking any medication knowing to influence gastric or esophageal motility.

Manometric techniques

Antral manometry was performed after an overnight fast using a low-compliance, water-perfused system. The Arndorfer catheter, with four side-holes oriented radially, 0,5 cm apart, and four more orifices located every 5 cm above the distal ones was placed in the stomach under fluoroscopic control, with the most upper channel located in the proximal part of the stomach, serving as a control position for the three lower channels located in the antrum at 5 cm intervals. The catheter was attached to force transducers and the recorded signals were amplified (Polygraph VIII, Synectics, Stockholm, Sweden) and stored for further analysis on the PC (80486-IBM compatible) equipped with specially designed software (Gastrosoft, Irving, Texas, USA). The study commenced 30 min after insertion of the tube to enable the subjects to accustom themselves to the presence of the tube. Observation of the fasting motility pattern enabled us to confirm the correct position of the catheter. After intubation subjects assumed a supine position and after 30 min of fasting period subjects ingested 500 ml standard semiliquid meal (Fresubin, Fresenius, Bad Homburg, Germany). Afterwards, the fed pattern was recorded for another 30 min. Data were calculated for fasting and fed period separately and the results were expressed as motility index (MI) of contractions.

Electrogastrography (EGG)

Simultaneously to manometric measurements of antral motility, gastric electrical activity was investigated by EGG. Three electrodes were positioned as follows: one was placed halfway between the umbilicus and xiphoid on the ventral midline, the second electrode was located 6 cm away on the left side, 1 cm below the lowest rib, and the third one (reference electrode) was placed such that it formed an equilateral triangle together with the remaining two electrodes. Fasting and fed recordings were performed for 30 minutes each, with a test meal of 500 ml as described above. Recordings were performed with a computerized PC polygraph system (Synectics, Stockholm, Sweden), data analysis was performed using specially designed software (Gastrosoft, Irving, Texas, USA). Results were expressed as dominant frequency, power content and frequency instability coefficient of gastric myoelectrical activity.

¹³C-acetate breath test

The standard meal used to evoke postprandial motor activity of the stomach was supplemented with ¹³C-acetate to measure the stomach emptying rate as described elsewhere (13). Before ingestion of food one reference sample was taken and the following fed samples were collected every 10 minutes for up to 180 minutes. The breath samples were analysed for isotopic enrichment with an isotope ratio mass spectrometer (Cediox analysator, EKAP 6670, Eppendorf, Hamburg, Germany) with an on-line gas chromatographic purification system. Results were expressed as the peak of ¹³C concentration in the breath air and shown as mean values \pm standard error of the mean (SEM).

Scintigraphic determination of the emptying rate of solids and liquids

Scintigraphic measurements of gastric emptying started immediately after ingestion of the solid (egg yolk) and liquid (200 ml Fresubin, Fresenius, Bad Homburg, Germany) test meal. Subjects maintained an upright position during the measurement. A dual-headed gamma camera (Philips, Eindhoven, Netherlands) with a medium energy collimator was interfaced with an on-line computer system that scanned the radioactivity every 60 sec for 180 min. Twenty percent energy windows were set with peaks at 140 keV for ^{99m}Tc. A region of interest corresponding to the stomach was outlined manually with a mouse on the computer display, to determine the gastric counts for each image. Corrections were made for background, scatter and radioactive decay. The calculated half-emptying times were taken to describe the emptying of solids and liquids. The measurements were performed at the Department of Nuclear Medicine, University of Münster.

Determination of glucose, insulin and glucagon

Serum glucose levels were determined before the start of the examinations and every 10 minutes during the test procedures. Thirty minutes before, 30 minutes and 90 minutes after the test meal for antral motility and EGG venous blood samples were taken for determination of insulin and glucagon. Radioimmunoassay for insulin and glucagon was performed using commercially available test kits (Amersham, Braunschweig, Germany) and performed as described previously (15).

Statistical analysis

Results are expressed as means \pm SEM. The significance of the difference between means was evaluated using analysis of variance followed by Duncañs test with a level of confidence at $P < 0.05$.

RESULTS

Antral manometry

In control subjects, the motility index (MI) after feeding rose from 3.91 ± 0.4 to 5.29 ± 0.35 ln ($\Sigma(\text{mmHg} \times \text{sec})/\text{min}$) (Fig. 1). The fasting MI of the diabetic subjects was 3.82 ± 0.34 and was not significantly different from that of the control. In diabetics the postprandial increase of antral motor activity was absent and MI even decreased to 3.61 ± 0.46 ln ($\Sigma(\text{mmHg} \times \text{sec})/\text{min}$) in subjects with diabetes history longer than five years.

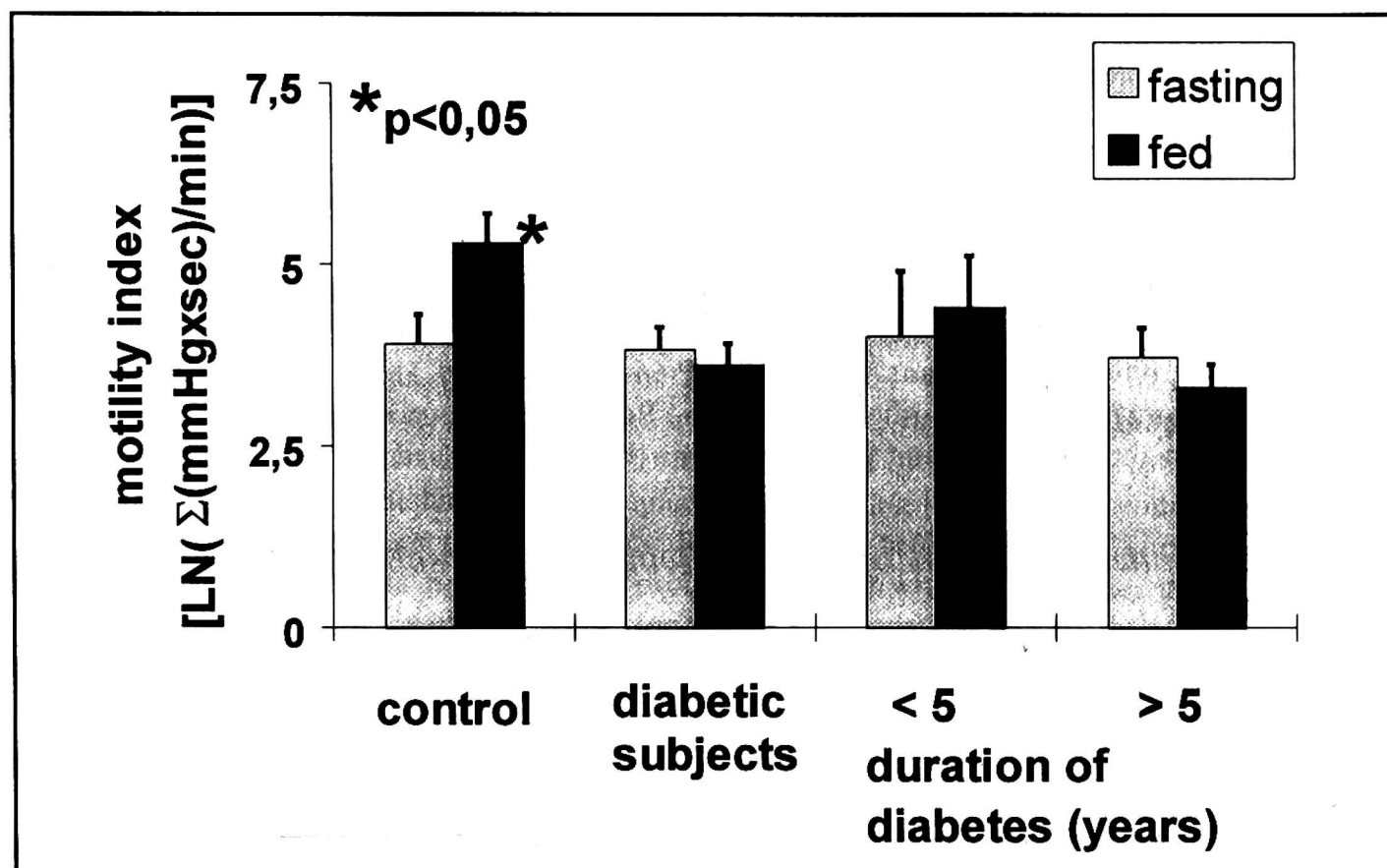


Fig. 1. Antral motor activity presented as motility index before and after feeding with standard meal. Mean values \pm SEM from 20 diabetic subjects and 20 healthy individuals (control). Asterisk indicates significant difference at $p < 0.05$.

Electrogastrography

In diabetic subjects, during the fasting period EGG recordings showed the basal rhythm with a leading frequency of 3 counts per minute (cpm) and no significant changes were observed during the postprandial period (Fig. 2a). The mean amplitude of electric oscillations remained unchanged (power content for all frequencies) after feeding when compared to the fasting period (fasting: 51740 ± 23340 vs. fed: 53084 ± 26209 $\mu\text{Volt}^2/30$ min) (Fig. 2b), whereas the power content of the control group increased from 62250 ± 12354 to 113405 ± 19566 $\mu\text{Volt}^2/30$ min.

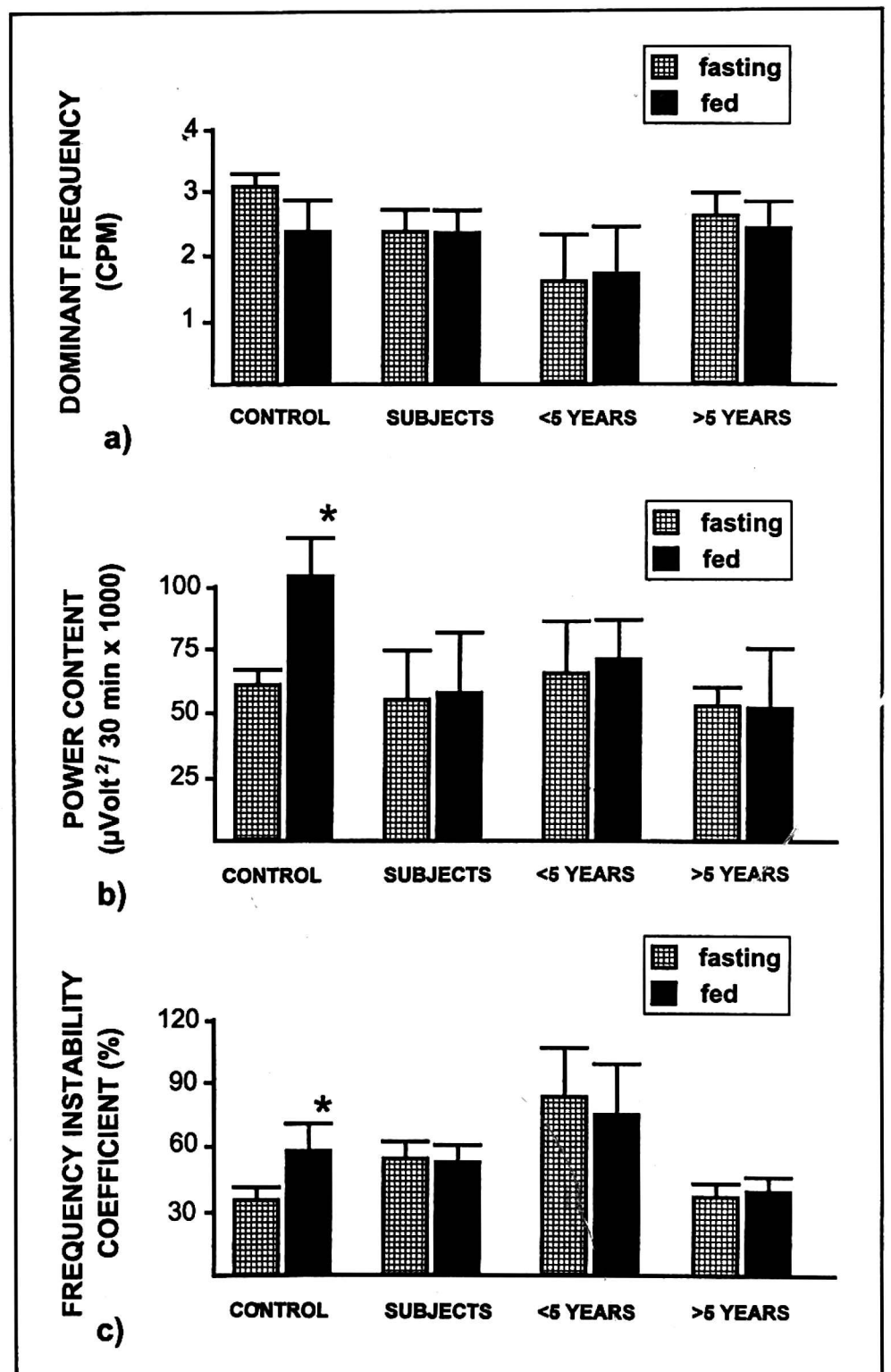


Fig. 2. Dominant frequency (a), power content (b) and frequency instability coefficient (c) of gastric myoelectrical activity determined by electrogastrography in tests during fasting and fed state. Mean values \pm SEM obtained from 20 diabetic subjects and 20 healthy individuals (control). Asterisk indicates significant difference at $p < 0.05$.

Dominant frequency instability coefficient (DFIC) as a reflection of the variation in the leading frequency did not show any difference when diabetics were compared to normal healthy individuals (fasting: $51.1 \pm 6.8\%$ in diabetics vs. $38.14 \pm 6.6\%$ in the control group, fed: $48.94 \pm 8.4\%$ in diabetics vs. $57.4 \pm 11.4\%$ in the control group) (Fig. 2b). While the control group showed a significant increase in DFIC after feeding, diabetics stayed at the same level as during the fasting period. This was demonstrable in subjects with shorter as well as longer duration of diabetes, however, fasting ($82.4 \pm 16.6\%$) and fed ($71.4 \pm 18.2\%$) values in subjects with shorter duration of diabetes mellitus were significantly higher than control values, whereas subjects with longer duration of diabetes had significantly reduced DFIC for both fasting ($39.1 \pm 5.2\%$) as well as fed ($40.3 \pm 4.9\%$) DFIC. Thus, subjects with longer history of diabetes showed a significantly reduced variation of gastric electrical activity under fasting and fed conditions.

¹³C-acetate breath test

Gastric emptying of liquids measured by means of ¹³C-acetate breath test was significantly delayed in diabetic subjects compared to healthy controls (Fig. 3). Healthy individuals showed a mean peak CO₂ excretion at 68.3 ± 12.4 min. whereas this value was significantly increased to 96.67 ± 5.1 min in diabetics. Subjects with diabetes mellitus having lasted longer than 5 years did not show any more pronounced delay of gastric emptying than those below 5 years (92 ± 12 min vs. 97 ± 7 min).

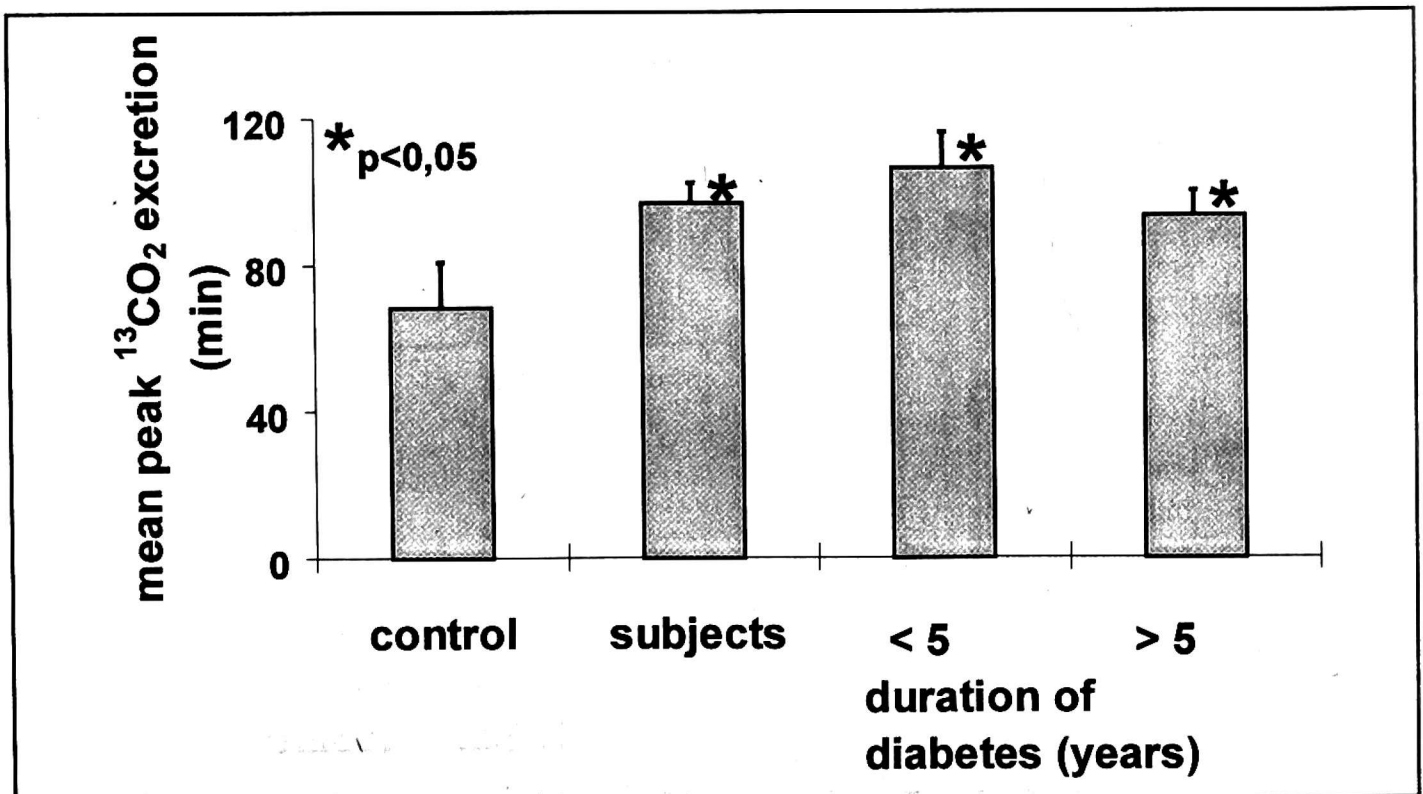


Fig. 3. Gastric emptying of semi-liquid test meal determined with ¹³C-acetate breath test. Mean values \pm SEM from 20 diabetic subjects and 20 healthy individuals (control). Asterisk indicates significant difference at $p < 0.05$.

Scintigraphy

In healthy individuals T_{50} of gastric emptying for liquids (Fig. 4b) was 52 ± 8 min and for solids it was 86 ± 13 min (Fig. 4a). In diabetic subjects T_{50} for liquids was not significantly different to the control group (67.6 ± 12.1 min), while gastric emptying for solids was delayed to 118 ± 14 min.

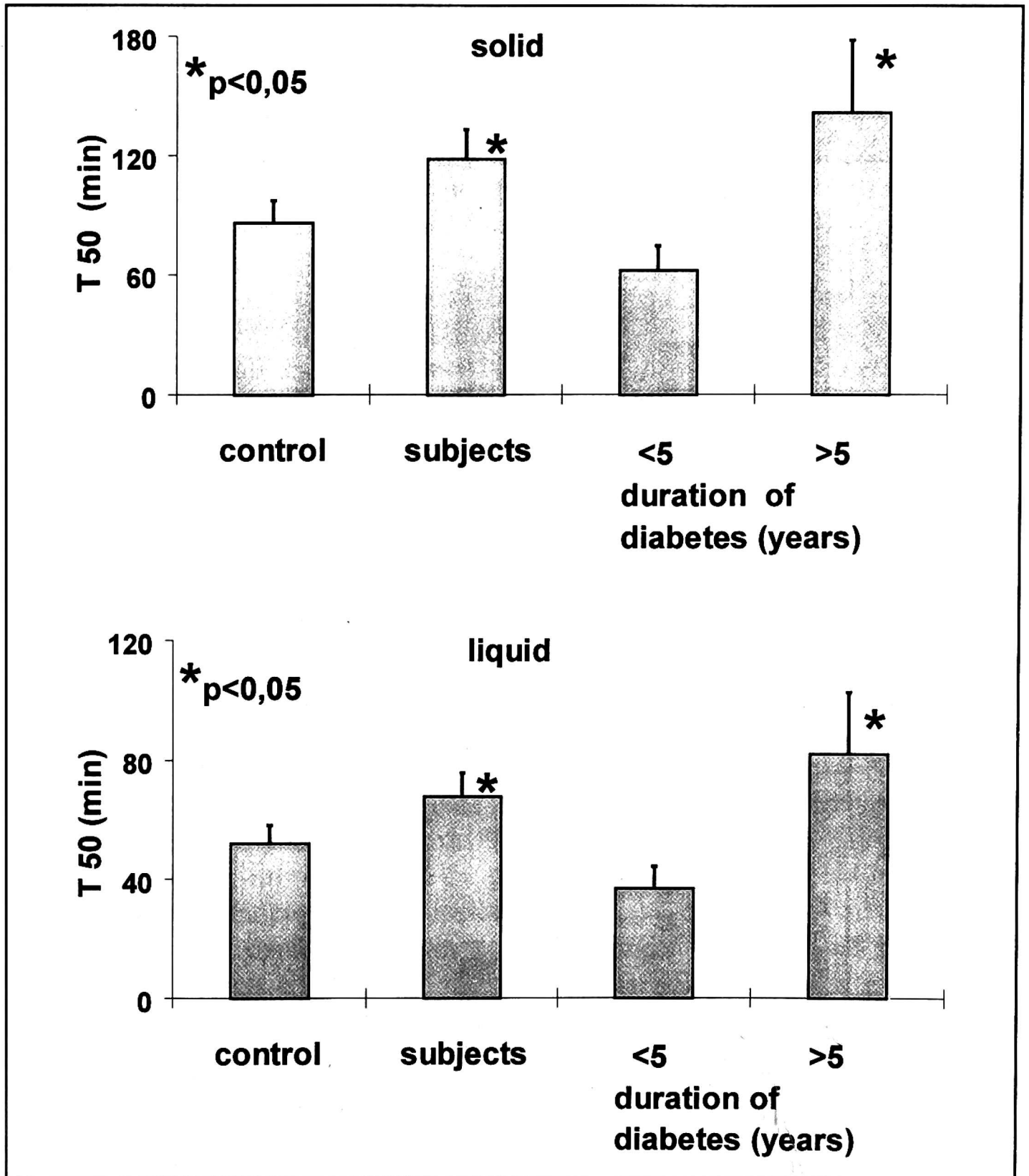


Fig. 4. Gastric emptying half-time of solids (upper panel) and liquids (lower panel) determined by scintigraphy. Mean values \pm SEM from 20 diabetic subjects and 20 healthy individuals (control). Asterisk indicates significant difference at $p < 0.05$.

Subjects with a duration of diabetes for less than five years showed a decrease of gastric emptying for liquids ($T_{50} = 36 \pm 8$) as well as solids ($T_{50} = 61.8 \pm 13.2$ min), whereas in the group of diabetics with a duration longer than 5 years both values were markedly increased in comparison to normal values (81.9 ± 20.1 min for liquids, 141.3 ± 31.1 min for solids).

Glucose, insulin and glucagon

In healthy individuals serum glucose rose from an initial value of 4.7 ± 0.2 mmol/l to 6.9 ± 0.3 mmol/l 30 min postprandially and to 5.9 ± 0.3 mmol/l 60 min

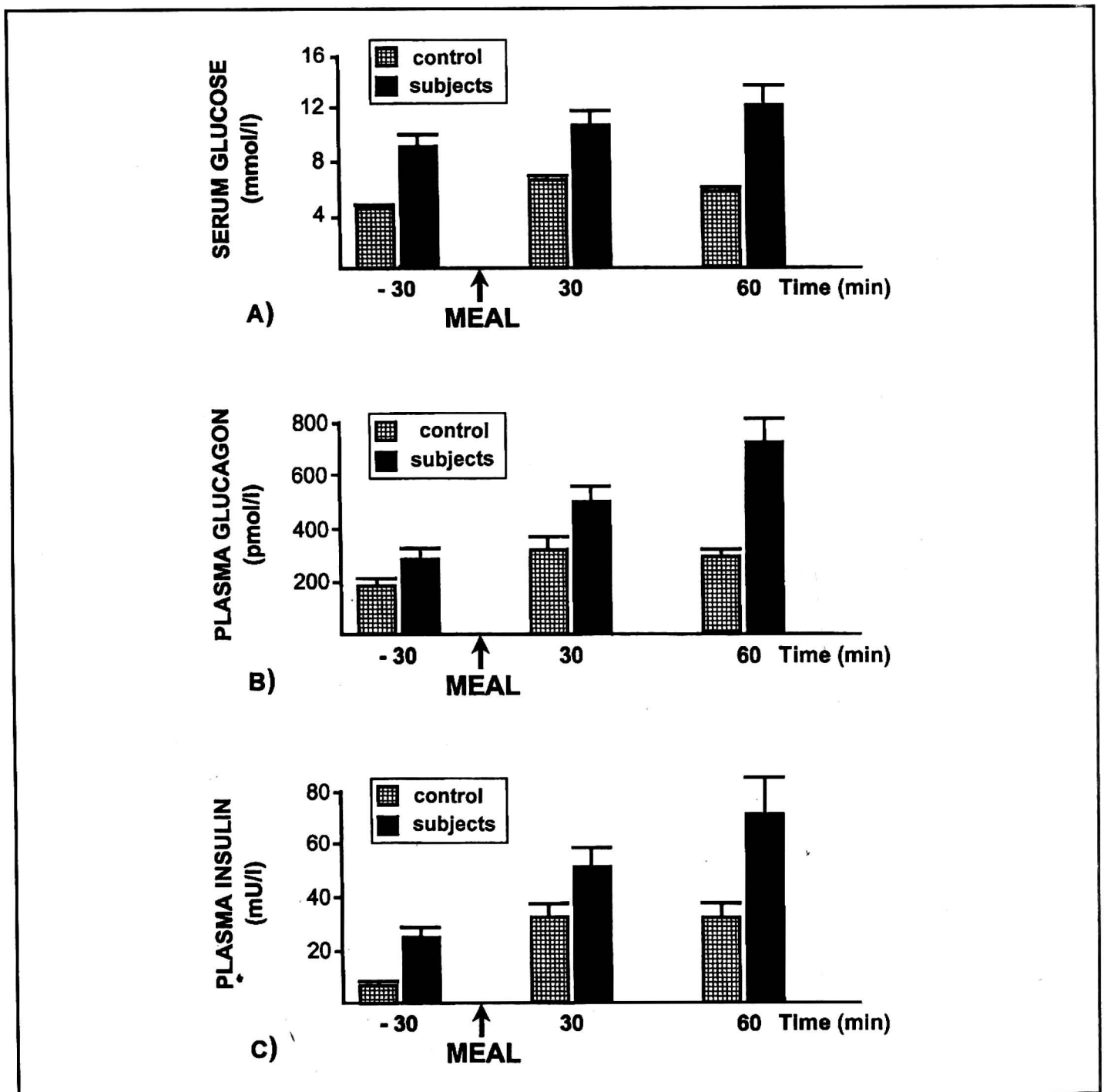


Fig. 5. Serum glucose (a), plasma glucagon (b) and plasma insulin (c) 30 minutes before and 30 as well as 60 minutes after test meal. Mean values \pm SEM from 20 diabetic subjects and 20 healthy individuals (control). Asterisk indicates significant difference at $p < 0.05$.

after the test meal. The subjects with diabetes mellitus showed an increase of serum glucose from 9.2 ± 0.9 mmol/l to 11.1 ± 1.0 mmol/l and further to 12.9 ± 1.4 mmol/l. Plasma glucagon levels in healthy individuals rose from initially 190.4 ± 24.4 pmol/l to 341 ± 57.9 pmol/l after 30 and 308.2 ± 20.6 pmol/l after 60 minutes. The basal plasma glucagon in diabetics was 246 ± 37.8 pmol/l and this was similar to that in healthy subjects, but following the test meal its plasma level increased to a significantly higher degree reaching values of 528.7 ± 67.1 pmol/l after 30 minutes and 754.6 ± 102.1 pmol/l after 60 minutes. In control subjects plasma insulin increased from initial values of 7.3 ± 2.1 mU/l to 34.3 ± 6.6 mU/l and 33.5 ± 7.1 mU/l after 30 and 60 min, respectively, whereas in diabetics it rose from initially 24.5 ± 5.3 mU/l to 51.7 ± 9.3 mU/l after 30 min and 69.8 ± 17.3 mU/l after 60 min.

DISCUSSION

All diabetic subjects who entered our study had significantly delayed gastric emptying for solids as measured by scintigraphy and for semisolid meal as determined by ^{13}C -acetate breath test. The postprandial increase in antral motility and gastric myoelectrical activity which could be observed in normal healthy controls was virtually missing in our subjects. There have been numerous reports on gastric emptying in diabetics (16—20), most of them pointing to the fact that delayed gastric emptying of solid meal is the most widely accepted tool for diagnosis of diabetic gastroparesis. In case of semisolid test meals there have been different reports: Novak *et al.* (9) reported both delayed and accelerated gastric emptying. In this study, however, he included subjects with diabetic nephropathy and a higher degree of renal failure, which itself might have an influence on gastric symptoms and gastric emptying. Other groups also reported an accelerated emptying of liquids in some subjects with diabetes mellitus, especially after only short duration of the disease (3, 5, 6, 21—23). Frank *et al.* (21) described an accelerated gastric emptying in non-neuropathic, non-insulin-dependent diabetes mellitus. Thus, the delayed gastric emptying of liquids that was demonstrable in our study might be explained by a higher number of subjects with autonomic dysfunction being examined in our study.

To the best of our knowledge, ^{13}C -acetate breath test with semisolid test meal has not yet been applied to determine gastric emptying in diabetes mellitus. ^{13}C -octanoate breath test with solid test meal which was first described by Ghos *et al.* (24) has been used by Ziegler *et al.* (25) as a non-isotopic technique for the measurement of gastric emptying in diabetes mellitus. The results correlated well with the scintigraphic results, the severity of the gastric symptoms and cardiovascular autonomic neuropathy and were not influenced by the blood glucose level (25).

There are only few data on the diagnostic value of electrogastrography for delayed gastric emptying. Koch *et al.* reported on alterations of the gastric pacemaker activity in patients with diabetes mellitus (26). Jebbink *et al.* (27) examined type I diabetic subjects with autonomic neuropathy under euglycemic conditions and found a decrease of postprandial/fasting power ratio in subjects who were symptomatic during the study. Performing glucose-clamp experiments, they described hyperglycemia-induced abnormalities (higher frequency of the normal pacemaker in the early postprandial state, a decrease of higher harmonics of the 3-cycle/min component and an increase of dysrhythmias) in subjects with diabetes mellitus type I (28). Furthermore, hyperglycemia was demonstrated to result in decreased antroduodenal motility (10), thus confirming our results regarding antroduodenal manometry. However, in our subjects dominant frequency and amplitude were not altered when compared to normal healthy individuals, whereas postprandial increase of amplitude and frequency instability coefficient (DFIC) were altered in our study. Pfaffenbach *et al.* (14) did not find any difference between the EGG recordings of diabetics when compared to normal healthy controls. Kühlbusch *et al.* (29) analyzed 9 patients with autonomic gastropathy with HIV infection and diabetes mellitus and also demonstrated a decreased frequency instability coefficient. However, the small number of patients and controls and the lack of data on the results of other tests of gastric emptying make interpretation of these data difficult. It is tempting to speculate that frequency instability of the stomach might be a parameter for evaluation of gastric autonomic neuropathy and this parameter can be substantiated by a non-invasive technique.

The major finding of this study is a significantly higher postprandial increase of plasma glucagon in subjects with diabetes mellitus compared to that in healthy controls. To our knowledge, the only alteration of gut peptides described in human diabetic gastroparesis is an elevation of plasma motilin which, however, is of uncertain significance (30). As expected, in diabetics, postprandial plasma glucose also rose to a significantly higher degree as compared to healthy controls. The influence of hyperglycemia on gastric motility has extensively been investigated and has led to controversial results. Most of the studies found a decrease in gastric emptying in normal healthy individuals and in type I diabetics (6—8). Samsom *et al.* (10) described a decrease in antral motility which was induced by hyperglycemia, which is in agreement with our results. Others found an accelerated gastric emptying for liquids without a correlation between blood glucose and gastric emptying half-time (9). The observation that subjects with type II diabetes without autonomic dysfunction had an accelerated gastric emptying for liquids despite massive hyperglycemia (21) does not support either the concept that hyperglycemia is the major cause of delayed gastric emptying. Gastric emptying of solids as measured with ^{13}C -octanoate breath test and scintigraphy did not

show any correlation to the glucose level (25). Whether reduced gastric motility and myoelectrical activity as observed by antral manometry and EGG do reflect autonomic neuropathy or are only due to postprandial hyperglycemia, is still a matter of discussion. To exclude the latter explanation it would be necessary to perform "glucose clamp experiments" with glucose levels maintained stable during measurements in diabetic subjects.

Glucagon might be another candidate responsible for altered gastric emptying in subjects with diabetes mellitus. In our study in diabetic subjects with gastrointestinal symptoms and delayed gastric emptying postprandial glucagon levels were significantly elevated. Recent data suggest that postprandial secretion of glucagon is deranged in subjects with diabetes mellitus (31, 32). Reports on the influence of glucagon on gastric motility have shown that it delays gastric emptying (33). Abell and Malagelada (34) also showed a glucagon-induced delay of gastric emptying and alterations in electrogastrography. Others described that mimicking plasma glucagon levels of diabetics by infusion of glucagon into healthy individuals did not lead to a decrease of gastric emptying of liquids or solids (35,36). Although the latter studies give evidence that glucagon levels found in diabetics are not able to delay gastric emptying in healthy subjects, they do not exclude the possibility, that glucagon will have this effect in diabetics and this might be due to an altered sensitivity of gastric motility to glucagon in those subjects. Furthermore, the increase in glucagon levels might be interpreted as a reactive increase due to hyperinsulinemia. However, the increase of glucagon exceeded by far the increase of insulin. Therefore, changes in insulin level are unlikely to be responsible for the decrease in gastric motility or the increase in plasma glucagon observed in our subjects.

This study indicates that symptomatic subjects with non-insulin-dependent diabetes mellitus and delayed gastric emptying for solids also have delayed gastric emptying for semisolid test meals, a lack of postprandial increase in gastric motility and myoelectrical activity and a higher postprandial increase in serum glucose and plasma glucagon levels. It is unclear, however, whether the observed states of hyperglucagonemia and hyperglycemia are the reason or the consequence of altered postprandial gastric motility.

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