Delayed Postprandial Gastric Emptying and Impaired Gallbladder Contraction Together With Elevated Cholecystokinin and Peptide YY Serum Levels Sustain Satiety and Inhibit Hunger in Healthy Elderly Persons

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Background. Altered gastric and cholecystic motility are risk factors for malnutrition in elderly persons, mainly through impaired satiety-appetite rhythm. Contrasting data have been published about this topic. The aim of this study was to evaluate, in healthy elderly participant, postprandial gastric and cholecystic emptying in relation to serum CCK (cholecystokinin) and PYY (peptide YY), as well as satiety and hunger sensations.

Methods. We studied 10 community-dwelling elderly persons, (77 ± 3 years old) and 9 younger adult persons (32 ± 8 years old). Using ultrasonography, we measured gastric antrum area and cholecystic volume in fasting condition and after an 800-kcal mixed meal. Time for gastric and cholecystic emptying, and percentage of cholecystic emptying were calculated. Satiety and hunger were evaluated every 30 minutes using visual analogue scales. CCK and PYY serum levels were assayed 30 minutes before and at times 0, 30, 60, 120, and 240 minutes after the meal.

Results. Elderly participants showed a longer gastric emptying time compared to younger participants (448 ± 104 vs 306 ± 57 minutes, \( p < .002 \)). Postprandial cholecystic emptying was significantly reduced in the older group (maximum contraction, 69% vs 84%; \( p < .05 \)). After the meal, CCK and PYY levels showed higher, persistent elevation in elderly participants. In this group, postprandial satiety lasted significantly longer than in younger participants, and hunger was suppressed throughout the postprandial period. Antral area directly correlated with satiety and inversely with hunger. Gallbladder volume inversely correlated to satiety.

Conclusions. This study showed, in a group of healthy elderly people, delayed gastric emptying associated to reduced cholecystic contractility together with higher CCK and PYY serum levels. These modifications facilitated long-lasting satiety and hunger suppression after a meal. This condition may lead to caloric restriction and finally to malnutrition at older ages.

Protein-energy malnutrition is a frequent condition in elderly persons, associated with a reduction in the adaptive response to physiological and pathological conditions of aging (1). The pathogenesis of malnutrition is likely to be multifactorial. A low calorie intake represents one of the main risk factors for malnutrition. This condition has been referred to as “anorexia of aging” (2). Many factors are involved with the pathogenesis of anorexia in elderly persons, but alterations in gastrointestinal motility may play a pivotal role in unbalancing satiety-appetite. In particular, delayed gastric emptying may cause prolonged postprandial satiety (3–7). An altered cholecystic contractility has also been postulated in elderly persons (8); however, ultrasound studies failed to demonstrate age-related contractility abnormalities and the relationship with satiety received poor attention (8–11). Cholecystokinin (CCK) and Peptide YY (PYY) are enteric peptides involved in gastrointestinal motility in response to eating, which provide a potent anorexigenic signal. They mediate a slowing of gastric emptying induced by the presence of nutrients in the small intestine (12,13). Abnormally high levels of fasting and postprandial CCK have been described in elderly persons, and its role in the so called anorexia of aging seems to be well defined (2). PYY inhibits Neuropeptide Y (NPY)-mediated appetite stimulus (14). Nevertheless, data on the relation between PYY and appetite in vivo are still very limited. Only one study conducted in elderly persons measured PYY fasting and meal-stimulated serum levels, but the authors could not find any difference between older and younger persons (12). The aim of our study was to determine gastric emptying and cholecystic contractility in relation to CCK and PYY postprandial levels, satiety, and hunger sensations in elderly compared to young adult participants after a balanced solid-liquid meal.

Participants and Methods
Study evaluations were conducted on 10 healthy, non-smoking, community-dwelling elderly persons, (five men, five women), with ages ranging from 72 to 82 years (mean age 77 ± 3 years) and body mass index (BMI) from 23.5 to 29.3 kg/m², and in 9 young adult controls, (five men, four women) with ages ranging from 25 to 53 years (mean age 32 ± 8 years) and BMI from 22.7 to 28.1 kg/m².
Table 1. Gastric Motility Parameters

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<th>Parameter</th>
<th>Elderly (N = 10)</th>
<th>Young (N = 9)</th>
<th>p</th>
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<tr>
<td>Fasting antral area, cm²</td>
<td>416 ± 182</td>
<td>364 ± 77</td>
<td>.84</td>
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<tr>
<td>Maximal postprandial area, cm²</td>
<td>878 ± 315</td>
<td>1143 ± 363</td>
<td>.06</td>
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<tr>
<td>Emptying time, min</td>
<td>448 ± 104</td>
<td>306 ± 57</td>
<td>.002</td>
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Exclusion criteria were: any abdominal surgical procedure, cholelithiasis, diabetes, neurological diseases, pregnancy, chronic gastrointestinal peptic or inflammatory diseases, malignancies, and any acute ongoing disease. Also excluded were persons with known cardiac, renal, or respiratory function impairment and persons with a BMI lower than 18.5 or greater than 30 kg/m². We also excluded people taking drugs that may interfere with gastrointestinal motility and visceral sensitivity. The study was approved by the ethical committee of the University of Verona, and each participant gave written informed consent.

Experimental Design
After overnight fasting, young and elderly participants were evaluated in basal condition; they were then asked to take the standard meal in about 20 minutes. The end of the meal was considered time 0, and evaluations were repeated every 30 minutes for 4 more hours.

The meal consisted of 60 grams of “macaroni alla bolognese” with 70 grams of meat sauce, 50 grams of ham, 50 grams of soft fatty cheese, one roll, and 250 ml of water. Total energy was 800 kcal (15% proteins, 45% fat, 40% carbohydrates).

Gastric emptying.—Real-time ultrasonography was performed by using a 3.5-MHz linear probe (Ansaldo AU560; Ansaldo, Italy) to measure gastric antrum diameters before the meal, immediately after it (time 0), and every 30 minutes up to 240 minutes after the end of the meal. The mean of three readings was calculated at each time during interdigestive relaxation. The antral section was calculated, accepting an elliptical shape, by measuring the two major diameters on a sagittal plane crossing the aorta at the epigastrium level. Antral area was obtained using the formula: (first diameter) × (second diameter) × π/4 (15). Antral area values were plotted against time to draw an emptying curve following the initial filling time; the regression line for antral emptying was calculated and total emptying time identified by the point where the tendency line crossed the basal value. A previous study showed a good correlation between emptying time obtained by ultrasonography and scintigraphy with a mean difference of only 4.5 minutes (16). A 9.1% variation coefficient of emptying time was calculated by repeating the test twice on nine controls.

Gallbladder motility.—Gallbladder volume was measured by ultrasonography immediately after gastric evaluation. With the participant in supine position and holding his or her breath for a few seconds during measurement, longitudinal, transverse, and oblique scans at the right hypochondrium were used to identify the longest (longitudinal) diameter of the gallbladder (D1). By rotating the probe perpendicularly to the length, the anteroposterior (D2) and the transverse (D3) diameter were measured. Then the ellipsoid method, originally described by Dodds and colleagues (17) was used by applying the formula: volume (cm³) = D1 × D2 × D3 × π/6 (15).

Mean fasting volume was measured, then a curve of postprandial absolute and percent volume reduction was plotted against time. Maximal percent volume reduction and time of maximal reduction were calculated as well.

Satiety and hunger evaluation.—Visual analogue scales were used to measure subjective satiety and hunger. Satiety was defined as the sensation of fullness after eating so that one does not eat for a certain time. Hunger was defined as the subjective driving force for the search, choice, and ingestion of food (18). Participants were instructed to make a single vertical mark on a horizontal 10 cm bar indicating assessment of their current feelings between “not hungry at all” to “really hungry” and from “empty” to “full” (19). Baseline evaluations were collected 30 minutes before the meal, at the end of the meal, and 60, 120, 180, and 240 minutes after the meal.

Peptides.—Blood samples were collected 30 minutes before, immediately after, and 60, 120, 180, and 240 minutes after the meal. After centrifugation, serum samples were stored at −80°C. Enzyme-linked immunosorbent assay kits were used for CCK-octapeptide 26-33 and PYY 3-36 serum measurement (Phoenix Pharmaceuticals, Belmont, CA). Both tests have intra-assay variations <5% and interassay variations <14%.

Statistical Analysis
Statistical analysis was performed by using SPSS for Windows release 11.5 (Chicago, IL). Results are shown as mean ± standard deviation. Variable differences between young controls and elderly participants were evaluated by Student t test and with analysis of variance for repeated measures. The Pearson correlation coefficient was used to test associations between variables.

Results
Table 1 shows mean values of fasting and maximal antral area as well as emptying time. Older participants had a significant delay in gastric emptying compared to younger adults (p < .002). Figure 1 shows mean antral area plotted against time, before and after the meal. Analysis of variance for repeated measures was not statistically different between the two groups, but the curve slope of the antral area was different, determining a significantly longer emptying time in elderly persons.

Table 2 shows mean gallbladder fasting volume, time, and percentage of maximal volume reduction. Older participants showed, on average, significantly lower maximal postprandial gallbladder contraction (p < .05). Figure 2 shows mean cholecystic postprandial volumes, expressed as percentage of fasting volume. In both groups, gallbladder showed an average 40% volume reduction immediately after...
the meal, but later on, the emptying curve was significantly slower in the elderly group (p < .02).

Figure 3 presents mean values of fasting and postprandial satiety and hunger scores. Fasting satiety and hunger sensation were similar in the two groups. Immediately after the meal, the curves differed both for satiety (p < .05) and hunger (p < .01). In the younger participants, 2 hours after the meal, satiety score crossed hunger sensation; after 4 hours, scores were comparable to fasting values. On the contrary, in the elderly counterparts, 4 hours after the meal, satiety sensation still had higher score than hunger.

Basal serum CCK was higher in the elderly group (21.6 ± 16 vs 12.6 ± 5.5 pmol/L, p < .05). After the meal, the CCK curve showed a higher and sustained rise in older participants, whereas in the younger, CCK showed a modest and rapid elevation (Figure 4, p < .05).

PYY serum values were similar in the two groups under fasting conditions and up to 2 hours after eating, but later, the elderly participants’ PYY levels were significantly higher (Figure 5, p < .01).

The relationships between satiety and hunger sensation scores, ultrasound, and laboratory variables were evaluated by calculating correlations at every measurement point for each participant. Table 3 shows that satiety scores were significantly associated with the antral area in young controls (R = 0.55, p < .001) but not in the elderly group, and were inversely correlated to gallbladder volume only in the elderly group (R = −0.311, p < .03). Hunger only correlated to the antral area and only in young controls (R = −0.580, p < .001). CCK values did not correlate with antral area, gallbladder volume, or satiety and hunger sensation. PYY inversely correlated to gallbladder volumes in all the participants (R = −0.252, p < .025) and in the elderly group (R = −0.562, p < .001), but not in young controls (data not shown in tables). No association was found between PYY, antral area, satiety, and hunger scores.

**DISCUSSION**

Our study shows longer gastric emptying time and minor postprandial cholecystic contraction in healthy elderly participants compared with younger controls. In the elderly group, postprandial satiety lasted significantly longer, and hunger was suppressed throughout the postprandial period. Greater and more persistent elevation of serum CCK and PYY concentrations were observed in the elderly group as well. Satiety was directly and hunger inversely correlated with gastric emptying time. Gallbladder volume was inversely correlated with satiety.

Previous studies on gastric emptying in elderly persons showed contradictory results. Scintigraphic evaluation demonstrated slower emptying of both solid and liquid meal components (3,6,7), or only of liquid in another observation (4). Ultrasound studies, using liquid meals, showed more rapid emptying (5) or no difference (10) between older and younger persons.

Different methods and different composition of the study meal may explain contradictory results. One study, conducted by ultrasound evaluation after a mixed meal,

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<th>Elderly (N = 10)</th>
<th>Young (N = 9)</th>
<th>p</th>
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<tbody>
<tr>
<td>Fasting volume, cm³</td>
<td>11.1 ± 4.5</td>
<td>15.9 ± 7.8</td>
<td>.11</td>
</tr>
<tr>
<td>Time of maximal volume reduction, min</td>
<td>189 ± 55</td>
<td>157 ± 25</td>
<td>.24</td>
</tr>
<tr>
<td>Maximal postprandial volume reduction, %</td>
<td>68.5 ± 18.5</td>
<td>83.7 ± 8.4</td>
<td>.05</td>
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Figure 2. Mean ± standard error of the mean fasting and postprandial percent gallbladder volume in elderly (broken line) and young (solid line) participants. Analysis of variance for repeated measures difference between groups p < .02.
showed age-related longer gastric emptying time (11), in accordance with our results.

Ultrasoundography can only evaluate antral emptying, and cannot study fundus filling and emptying or distinguish between liquid and solid components of food. Nevertheless, complete gastric emptying time, extrapolated by ultrasound antral area dynamics, proved to be reliable when compared with “gold-standard” scintigraphy (16). Furthermore, in physiologic conditions, neurohormonal response to a meal (which regulates food intake and digestion) mainly acts on antral motility, according to antral filling and nutrient delivery from the antrum to the small intestine (12,13). A reduced fundus compliance has been suggested in elderly persons but, again, this may reduce food intake because of distention of the antrum due to earlier delivery of food (2).

A slower gastric emptying in elderly persons may be the consequence of reduced digestive ability of the stomach (20). Chronic gastritis or medications may cause hypochloridria that slows gastric emptying (21). Hypochloridria cannot be ruled out in our sample. However, in one other study conducted in healthy elderly persons, their acid output was not different from that in younger controls (22). Slower gastric emptying could also be the consequence of an “ideal brake” effect, caused by a neurohormonal response to the presence of nutrients in the small intestine over its digestive and absorptive ability (13,23). Finally, a primitive age-related decline of gastric motility may be involved, but its role cannot be confirmed from the present model, and few data are present in the literature (2).

Our findings of impaired cholecystic contraction in elderly persons seem to be in line with the higher prevalence of cholelithiasis at more advanced ages (8,10). A resistance to high levels of CCK has been hypothesized (9), and in aged animal models a reduction of CCK receptors on the gallbladder has been demonstrated (10). Nevertheless, previous ultrasound studies failed to demonstrate any cholecystic contractility abnormality in elderly persons (8–10). In our experiment, the administration of a meal rich in calories and lipids, requiring submaximal digestive response, probably unmasked the difference between younger and older participants. Gastric and cholecystic emptying are coordinated after ingestion of a meal, and the gallbladder starts to refill only when the stomach is almost empty (24). In our study, we demonstrate slower gastric emptying coinciding with reduced gallbladder contraction. Gastric emptying leads to gallbladder contraction by delivering nutrients into the small intestine where CCK is produced (24). Only one other study simultaneously evaluated gastric and cholecystic emptying by ultrasonography in elderly persons (10). However, Wedmann and colleagues did not find any gastric or cholecystic motor abnormality after a lighter liquid meal. Eating inhibited hunger and sustained satiety for a longer period of time in elderly persons. In our study, satiety remained high in the elderly group even at the end of the observation, when only a small quantity of food was in the antrum. This suggests a possible sensory abnormality. Similarly, the ingestion of a small snack reduced the quantity of the subsequent meal in elderly persons in one other study (25).

In our sample, the correlation between satiety and antral area was not significant in the elderly group. This may be attributable to wider variability in visceral sensitivity. Furthermore, it has been recently suggested that elderly persons may be less accurate in recording their satiety sensation (26).

CCK was elevated in the elderly participants under fasting condition, as previously described (12). Moreover, postprandial CCK and PYY showed a higher and more prolonged elevation in the elderly group. CCK and PYY were not significantly correlated to satiety and gastric motility parameters; however, at the end of observation,
when the antrum contained small volumes of food, the elderly group still had high circulating CCK and PYY levels corresponding to high satiety and low hunger. Previous study on postprandial PYY did not find any difference between young and older persons, probably because a shorter period of observation was used (12).

The findings observed in elderly participants of an inverse correlation between gallbladder postprandial volumes and PYY levels as well as between gallbladder volumes and satiety scores are intriguing but they have no clear explanation. Multifactorial mechanisms may influence in elderly persons not only motility, but also digestive alterations, so specific research in these fields is needed. Abnormally high postprandial hormone levels may inhibit the search for a second meal, thus leading to longer fasting intervals resulting in a risk of malnutrition in elderly persons (2).

This study has some limits. First, our sample of healthy elderly persons does not reflect the general population, as our elderly participants represented successful aging, free of chronic diseases and medications. It is reasonable to believe that chronic illness, medications, and malnutrition would only worsen abnormalities shown in healthy persons (2).

In this study, we used a meal which may be higher in calories and lipids than is the average meal of many elderly persons. Results need to be confirmed after a more balanced meal (i.e., lower in energy and fat load). As already mentioned, visual analogue scales may be less reliable in elderly persons than in younger adults (26), so satiety and hunger scores should be validated against more direct and objective markers of energy intake control.

Finally, the enzyme-linked immunosorbent assay used for CCK assay in this study cross-reacts with gastrin, so part of the high levels of CCK may be attributable to gastrin. Nevertheless, high gastrin levels are unlikely in this sample, and results are in line with previous observations conducted by radioimmunoassay (12,27).

Conclusion

This study showed, in a group of elderly men and women, delayed gastric emptying associated to reduced cholecystic contractility, as well as sustained increased CCK and PYY serum levels. These modifications facilitated long-lasting satiety and hunger suppression after a meal. This condition may lead to caloric restriction and finally to malnutrition.

References


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