A Community-Based, Controlled Study of the Epidemiology and Pathophysiology of Dyspepsia

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Background & Aims: Dyspepsia is common in clinical practice and in the community. The relationship of the symptoms to meals and the pathophysiology in community dyspeptic patients is unclear. The purpose of this study was to measure symptoms, demographic features, and gastric motor and sensory functions associated with dyspepsia in the community.

Methods: A Modified Bowel Disease Questionnaire was mailed to a random sample of Olmsted County, MN, residents. Dyspeptic patients and healthy controls identified among community respondents completed further questionnaires, Helicobacter pylori serology, gastric emptying by scintigraphy, gastric accommodation by 99mTc–single-photon emission computed tomography imaging, and postprandial symptoms and satiation by a nutrient drink test.

Results: A total of 34.1% of community respondents reported dyspepsia within the past year, frequent (at least 25% of the time in the past year) in 17.5%, and 18.4% reported meal-related dyspepsia. Dyspepsia was frequent and related to meals in 10.8% of respondents. Compared with nondyspeptic controls, community dyspepsia was associated with higher aggregate symptom scores and bloating after a fully satiating meal. Community dyspepsia also was associated with higher somatization scores (P = .001), reporting of other somatic symptoms (P = .07), and general severity score on the symptom checklist 90 (P = .01), but not with disordered motor or sensory function. Gastric volumes, gastric emptying, and maximum tolerated volumes were not significantly different between community controls and dyspeptic patients.

Conclusions: Meal-related dyspepsia is an important component of dyspepsia in the community. Community dyspeptic patients have higher symptom scores after a fully satiating meal, consistent with gastric hypersensitivity. This is associated with higher somatization scores rather than disorders of gastric emptying or volumes.

Functional dyspepsia is characterized by the presence of recurrent or chronic abdominal pain or discomfort without anatomic or biochemical abnormality. It is a common condition in clinical practice and in the community. By using a validated questionnaire, Talley et al. showed that up to 25% of the population complained of early satiety, nausea, upper abdominal pain, or discomfort; in other words, the symptoms of functional dyspepsia. Prior epidemiologic studies have not evaluated the relationship of these symptoms to meal ingestion.

Endoscopic evaluation usually is negative and an alternative diagnosis such as peptic ulceration or cancer rarely is encountered in patients presenting with dyspepsia (<10%). Consequently, it is thought that the majority of nonpresenters with dyspepsia in the community actually have functional dyspepsia.

The majority of people with dyspepsia do not seek health care. Those who seek care are not often referred to gastroenterologists and appear to have higher levels of psychologic distress and psychiatric disease. Therefore, clinic-based samples are not representative of people in the community with dyspepsia. To date, most published studies investigating the mechanisms of dyspepsia and associated disorders have been performed on a referral population.

Thus, despite the high prevalence of functional dyspepsia both in the community and in the clinic population, our understanding of the pathophysiology of the disorder is very limited. Consequently, treatment of dyspepsia in the primary care setting is empiric and limited in efficacy. An exception is seen in patients with concomitant gastroesophageal reflux disease who respond well to proton pump inhibitors, even though there is increasing evidence that some patients with functional heartburn or nonerosive esophageal disorder may not respond to such therapy.
A number of potential risk factors (gastritis, *Helicobacter pylori* infection, diet, stress, anxiety, depression, and abuse) for community dyspepsia have been evaluated, but few of these studies have been conclusive. The pathophysiology of community dyspepsia remains largely unknown. Validated, noninvasive methods to evaluate upper-gut motor and sensory functions make possible such studies in community dyspeptic patients.

Our hypothesis was that, in the community population, dyspepsia is associated with meal ingestion, and that this syndrome is associated with one of the pathophysiologic mechanisms described in people with dyspepsia in a tertiary referral population, or with high levels of somatization. The pathophysiologic mechanisms include: gastric hypersensitivity, decreased gastric accommodation, impaired gastric emptying, or a combination of these pathophysiologic disturbances.10–16

The aims of this population-based study were as follows: first, to assess gastrointestinal symptoms and their relationship to meal ingestion in a randomly selected cohort of residents of Olmsted County, MN; and, second, to determine whether symptoms related or unrelated to meals were associated with specific disturbances in gastric motor and sensory physiology or other risk factors, including somatization.

**Methods**

**Study Design**

This study was approved by the Mayo Clinic Institutional Review Board and was completed in 3 phases (Figure 1). HIPPA (Health Insurance Portability and Accountability Act of 1996) regulations were effective after the completion of this study. The first phase of the study involved developing and
mailing out the Modified Bowel Disease Questionnaire (MBDQ) to eligible participants. The second part of the study involved inviting those who met criteria for either dyspepsia or healthy controls and who met inclusion criteria for the General Clinical Research Center (GCRC) at the Mayo Clinic where they completed another MBDQ, a food frequency questionnaire (the Block 2000 Modification of the Block/NCI Health Habits and History Questionnaire), and a measure of psychological distress (symptom checklist 90 [SCL-90]). They also had blood drawn for *H. pylori* serology. Participant allocation to the healthy control or dyspepsia groups was based on the MBDQ responses and on an interview conducted by one physician (E.J.C.). Those who did not meet inclusion criteria were excluded from continuing on to the next phase of the study. Those meeting inclusion criteria then were invited to participate in the third phase of the study during which physiologic tests of gastric emptying, gastric volume measurements, and a satiation test were performed.

**Phase I: epidemiology.** Unique features of the Olmsted County, MN, medical environment and the data resources of the Rochester Epidemiology Project provided the opportunity to perform population-based research. The Section of Clinical Epidemiology at the Mayo Clinic has determined that more than 96% of Olmsted County residents have had medical encounter(s) at either the Mayo Clinic or Olmsted Medical Center over the course of 4 years. These resources provide what is essentially an enumeration of the population from which samples can be drawn. In the past, we used this environment to perform a series of population-based studies to which samples can be drawn. In the past, we used this environment to perform a series of population-based studies to gather information on gastrointestinal symptoms in the community. As a result, there is a cohort of over 6000 randomly selected Olmsted County, MN, residents for whom detailed symptom data have been collected in a cross-sectional manner over the past 15 years.

For this study, we drew an age- (5-year intervals) and sex- (equal number of men and women) stratified random sample of 1500 Olmsted County, MN, residents, aged 20–80 years in the year 2001, from the list of respondents to previous surveys. The sample was checked for authorization to use the medical record and willingness to be contacted for further research. Those subjects who declined involvement in research, had moved out of Olmsted County, or were deceased were excluded. No one was excluded on the basis of race. Only those residents of the county with a Mayo Clinic registration number were included. After all of these exclusions were applied to the sample of 1500 people, the sample size left was 1461 persons. Thus, only 2%–3% of the original sample were not eligible for inclusion in this study.

**Survey methods.** A new bowel disease symptom questionnaire was developed using previously validated symptom questions whenever possible. The Bowel Disease Questionnaire initially was developed at the Mayo Clinic in 1988 and consists of 71 separate items that were individually tested for reliability using a test-retest method and then were tested for concurrent validity by comparison with a physician interview. Additional questions were developed for further measurement of dyspepsia, gastroesophageal reflux, and familial aggregation in 1993. Because the symptom items were tested individually, subsequent questionnaires have used selected questions from these instruments. A new questionnaire, the MBDQ, was developed for this study by using some of the validated questions from previous surveys as well as new questions. The MBDQ contains all the symptom items required for identifying symptoms of dyspepsia and its subtypes, as well as symptoms of irritable bowel syndrome (IBS), gastroesophageal reflux, and other gastrointestinal symptoms. At the end of the survey, there was a somatic symptoms checklist (SSC). The SSC measures the frequency and severity of somatic complaints and other conditions.

Two versions of the MBDQ were used in the survey portion of the study. The long MBDQ developed for this study has 66 primary questions with an additional 38 questions in drop-down boxes. It is 14 pages long with questions organized into 15 sections: indigestion, upper-abdominal symptoms, nausea and vomiting, early satiety and bloating, heartburn, acid regurgitation, difficulty swallowing, chest pain, lower-abdominal pain and bowel habits, vital statistics, family history, insomnia, history of medical visits, medication history, and the SSC.

A shorter version of this survey was developed with 36 primary questions (identical to the long survey) and an additional 15 questions (identical to the long survey) in drop-down boxes. This survey instrument is 8 pages in length and the questions are organized into 10 sections. The sections on difficulty swallowing, chest pain, vital statistics, family history, and insomnia that were present in the longer survey were omitted.

The language of the questionnaires was set at a 6th-grade reading level. Feasibility testing was performed by 11 patients in the Mayo Clinic IBS class. These patients completed the questionnaire without any assistance. Minor changes were made according to comments and responses from these patients. Reliability testing of the survey was performed by using a test-retest method because a portion of the subjects completed the questionnaire first via the mail survey and several weeks later at the GCRC. On both occasions, the questionnaire was completed without assistance.

The long survey was mailed to a random sample of 484 of the 1461 subjects randomly selected to be included in this study. Each subject was mailed a cover letter and a questionnaire. The cover letter asked for their participation or return of the cover letter indicating refusal to participate. Nonresponders were sent a second mailing after 1 month. No further attempt to contact nonresponders after the second mailing was made, as required by the Mayo Clinic Institutional Review Board. The shortened questionnaire was mailed to 977 subjects.

**Definitions and scaling of symptom severity.** By using the responses from questionnaires, we identified people with frequent meal-unrelated or meal-related dyspepsia, as well as people without any other gastrointestinal symptoms (considered healthy controls in this study).
Dyspepsia. Dyspepsia was defined as having, in the past year, troublesome upper (above the belly button or navel) abdominal symptoms. The specific type of troublesome upper abdominal symptom was ascertained by asking participants to categorize the symptoms as pain, burning, feeling of upper belly or abdominal fullness, bloating, nausea, vomiting, feeling uncomfortably full soon (within 1 hour of starting to eat), or other (a category in which participants wrote in their specific complaint). Subjects were asked to identify only one symptom as their most troublesome, initially, and, later in the questionnaire, they were asked which symptoms (if any) accompanied their most troublesome symptom.

Dyspepsia related to meals required meeting the definition of dyspepsia along with symptoms often appearing with meals. The word often or frequent was defined as an occurrence at least 25% of the time in the past year. This was further described as meaning 1 day out of 4, or 1 week a month, or 3 months a year. Dyspepsia unrelated to meals was defined as dyspepsia with symptoms unassociated with meals. Pure dyspepsia was defined as any type of dyspepsia (ie, troublesome abdominal symptoms above the belly button in the past year) without heartburn, acid regurgitation, dysphagia, lower abdominal pain, altered bowel habits, or the need to take anything to have a bowel movement in the past year.

Body mass index. Weight and height recorded during the participants’ visit to the Mayo Clinic GCRC were used to calculate body mass index (BMI = kg/m²). Subjects then were categorized based on BMI as underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), class I obesity (30.0–34.9 kg/m²), class II obesity (35.0–39.9 kg/m²), or class III obesity (≥40 kg/m²).

Controls. Healthy controls were defined as those community participants without dyspepsia, heartburn, acid regurgitation, difficulty swallowing, or IBS symptoms on the questionnaire.

Phase II: physician interview and Helicobacter pylori testing. A review of the medical record for each of those individuals identified by the questionnaire as dyspeptic or healthy control was performed (E.J.C., D.A.S., D.M.G.) and those who did not meet criteria were excluded. Exclusion criteria were as follows: pregnancy or breastfeeding; history of abdominal surgery other than appendectomy or hysterectomy, caesarian section, or tubal ligation; history of eating disorder, psychiatric disease, or drug abuse; present or previous chronic gastrointestinal illness; presence of any systemic disease or use of medications that could affect gastrointestinal motility, affect appetite, or cause gastrointestinal side effects (ie, nonsteroidal anti-inflammatory drugs). Those individuals who met criteria were invited to the Mayo Clinic GCRC for a physician interview to complete questionnaires (MBDQ and SCL-90) and to have a blood sample drawn for H pylori status, as described earlier. If dyspepsia or absence of symptoms were confirmed, those people then were invited to participate in the third part of the study. Those people who did not meet criteria for physiologic testing (listed later) were not invited to participate.

Phase III: physiologic testing. Participants from the community who met criteria for dyspepsia or healthy controls, were between the ages of 18–80 years, and had a BMI no lower than 20 kg/m² were recruited for the physiologic testing phase of the study.

Exclusion criteria for healthy community controls and dyspeptics were the same as those listed earlier (phase II), as well as the occurrence of positive symptoms developing in the interim period between the physician interview in phase II and attendance for phase III studies on a validated abridged bowel disease questionnaire (for healthy controls only). In addition, the use of prescribed or over-the-counter medication within 7 days of the physiologic study was prohibited except for stable doses (>1 mo before and during study) of an oral contraceptive, estrogen/progesterone, or thyroxine replacement. Screening procedures (validated abridged bowel disease questionnaire and physical examination by one physician (E.J.C.)) were completed within 14 days before the first study day of physiologic testing.

All subjects underwent assessment of scintigraphic gastric emptying, gastric accommodation using the single-photon emission computed tomography technique, and assessment of postprandial symptoms using the satiety test. At least 24 hours lapsed between study days to allow for decay of test radioisotopes. Radiation exposure was within permissible limits for human volunteer studies and is documented in a previous publication from our laboratory. A pregnancy test was performed, if applicable, within 24 hours before studies.

Measurement of gastric emptying of solids. Gastric emptying of solids was measured using the scintigraphic method that has been validated and reported previously. Briefly, fasting participants presented to the GCRC and a radiolabeled meal was prepared by adding 0.75 mCi 99mTc-sulfur colloid to 2 raw eggs during the scrambling cooking process. The eggs were served on 1 slice of buttered bread along with a 240-mL glass of 1% milk (total calories: 296 kcal, 32% protein, 35% fat, 33% carbohydrate). Anterior and posterior γ camera images were obtained immediately after meal ingestion, every 15 minutes for the first 2 hours, and then every 30 minutes for the next 2 hours (for a total of 4 hours after the radiolabeled meal) to assess gastric emptying. Data were analyzed as in previous studies. The geometric mean of decay-corrected counts in anterior and posterior images of the stomach were used to estimate the proportion of 99mTc emptied at each time point (gastric emptying).

Measurement of fasting and postprandial gastric volume. As described in previous studies from our laboratory, tomographic images were acquired on a large field-of-view dual-headed γ camera system (SMV single-photon emission computed tomography system; SMV America, Twinsburg, OH) equipped with low-energy, high-resolution collimators. Volunteers were placed in a supine position on the imaging table with the detectors over the upper- and midabdomens to ensure imaging of the stomach and small bowel. Ten minutes after the intravenous injection of 10 mCi 99mTcO₄⁻, dynamic tomographic acquisition was performed using the multi-orbit mode of the system. In this mode,
the system performed 3 complete 360° orbits at approximately 15 minutes per orbit. For each orbit, images were acquired every 6° at 3 seconds per image. After completion of the acquisition, orbits were summed to improve counting statistics. These orbits then were reconstructed using filtered back-projection (Ramp-Butterworth filter, order 10, cut-off 0.45 Nyquist) to produce transaxial images of the stomach. Imaging was performed once during fasting and twice after ingestion of a 300-mL Ensure (Ross Products Division, Abbott Laboratories, Abbott Park, IL) drink through a straw. Stomach volume measurements were performed using the ANALYZE PC 2.5 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) software system, which has been used previously in volumetric imaging studies.30,31

Measurement of satiation, postprandial symptoms, and gastric emptying of liquid nutrient meal. A liquid nutrient meal (Ensure) was used to assess the maximum tolerated volume and postprandial symptoms. Satiation and postprandial symptoms were measured using previously described methods.33–36 The first glass of Ensure was radiolabeled with 0.05 mCi of 99mTc-DTPA. Participants then ingested unlabeled Ensure at a constant rate of 30 mL/min. Every 5 minutes, a 1-minute scan of the abdomen was obtained to assess gastric emptying of the Ensure. After the first hour, abdominal scans were obtained every 15 minutes until at least 50% of the meal was emptied from the stomach. The liquid gastric emptying measurements were based on the proportion of meal emptied from the stomach at 30 minutes when all participants had ingested the same volume of Ensure.

Participants scored their level of satiation using a graphic rating scale that combined verbal descriptors on a scale of 0 – 5 (0 = no symptoms; 1 = first sensation (threshold); 2 = mild; 3 = moderate; 4 = severe; 5 = maximum or unbearable). Ingestion of Ensure ended when a score of 5 was reached, providing the maximum tolerated volume of the nutrient drink. Thirty minutes after completing the test, participants scored their symptoms of bloating, fullness, nausea, and pain using a visual analog scale with 100-mm lines anchored with the words “unnoticeable” and “unbearable” at the left and right ends of the lines, respectively. The aggregate score is defined as the sum of the visual analog scale for each symptom (maximum score = 400).

Statistical Analysis

The primary end points for analysis were as follows: prevalence of dyspepsia and its subgroups in the community, prevalence of H pylori in the sample of dyspeptic patients and healthy controls, half-time for gastric emptying, percent of radio-labeled nutrient liquid meal (Ensure) emptied at 30 minutes, fasting and postprandial stomach volumes, maximum tolerated volume of Ensure, and aggregate postprandial symptom scores 30 minutes after ingestion of Ensure. Individual symptoms 30 minutes after nutrient drink ingestion were considered secondary end points. The proportion of patients with abnormal gastric emptying of solids and decreased change in gastric volume postmeal was computed for each group, relative to previously published data from healthy controls.30,37

Prevalence estimates (and 95% confidence intervals) were computed for dyspepsia and specific subgroups. The associations between symptom group (overall dyspepsia vs. controls and separately, controls vs. meal-related vs. meal-unrelated dyspepsia) and physiologic end points or somatic symptoms (SSC score and somatization scale on the SCL-90) were assessed using an analysis of covariance with BMI and sex as covariates. It is worth noting that none of the items in the SSC is related to the gastrointestinal tract. Moreover, in the SCL-90 somatization subscale, the only gastrointestinal item is “nausea or upset stomach.” There are 2 appetite-related questions: “poor appetite” and “overeating.” We did not eliminate this single gastrointestinal symptom or appetite-related questions from the somatization subscale because this could invalidate the psychometric properties established for this subscale.25

The nutrient drink symptom scores also were assessed using an analysis of covariance including BMI, sex, and SCL-90 somatization score as covariates.

In cases in which unadjusted P values are reported, this is clearly stated in the text, and the subsequent adjusted P values are provided as well.

Results

Study Flow, Responders, and Nonresponders

Response rate. The long survey was mailed to a random sample of 484 of the 1461 sample. There were 224 people who completed the survey, 66 people refused to participate, 176 did not respond to our mailings, and 18 people were excluded secondary to having moved out of Olmsted County. The overall response rate was 42%. The shortened survey was mailed to 977 people: 435 completed the questionnaire, 119 refused to participate, 319 did not respond, and 104 were excluded. The response rate for the short questionnaire was 49%. Thus, the overall response rate for both the long and short questionnaire was 46% (Figure 1).

Demographics of responders. Phase I respondents to the mailed questionnaire were 52% women, with a median age of 61 years (interquartile range, 50 – 71 y). There were no significant associations between gender distribution and participation (responders). For those whose race was disclosed, 97% were Caucasian, and 1% each were Asian, African American, or other. Of the people surveyed, 31% met the criteria for healthy controls (Table 1).

Phase II. A total of 92 people of 162 dyspeptic patients or controls identified by the mailed questionnaire and who met criteria came to the Mayo Clinic GCRC for the physician (E.J.C.) interview and other evaluations. Of these, 48 (52%) were women and 44 (48%) were men. Mean (± SE) age was 57 ± 1 years. All participants were Caucasian (Table 1).
Phase III. A total of 52 subjects agreed to participate in the physiologic studies. There were 24 (46%) women and 28 (55%) men. There were 17 healthy controls, 21 with dyspepsia unrelated to meal ingestion, and 14 with meal-related dyspepsia. All participants were Caucasian. The gender distribution in the control and dyspeptic groups was similar. However, there were more men (64%) than women (36%) in the meal-related dyspepsia group (Table 1).

Demographic and other characteristics of nonresponders. Figure 1 shows a summary of the study flow in the entire random sample, the questionnaire respondents or nonrespondents, those who visited or did not visit the GCRC for a physician interview, and the individuals who agreed to participate in physiologic studies, declined to participate, or were found to be ineligible. It is worth noting that response to the mailed survey was not associated with sex and, although younger subjects were less likely to return a completed survey ($P = .01$), the respondents were, on average, only 7 years older. The chart review and questionnaire assessment to identify subjects eligible for follow-up study in the GCRC resulted in a somewhat younger subset of the overall group of questionnaire respondents (hence, more representative of the overall sampled population). However, sex and SSC score were not associated with this selection process. In addition, age, sex, and SSC score were not associated with participation in the GCRC follow-up evaluation. Although age was associated with participation in the physiology studies ($P < .05$), the participants were, on average, only 7 years younger (mean [±SD] = 54 [±12]) than the nonparticipants (mean [±SD] = 61 [±14]). It is also worth noting that the age of the participants in the physiology study was closer to that of the overall sampled population.

Among the subjects (controls and dyspepsia patients) invited to participate in the physiology studies, other gastrointestinal symptoms (abdominal pain, IBS, abnormal bowel frequency, acid regurgitation, and heartburn) were evaluated for potential association with participation in the physiology studies. Of these symptoms, only heartburn was associated significantly with participation ($P < .05$), with 77% of those with heartburn agreeing to participate vs. 45% of those without.

Table 1. Demographics of Participants in All Phases of the Study

<table>
<thead>
<tr>
<th>Phases of study</th>
<th>Overall</th>
<th>Healthy controls</th>
<th>Dyspepsia</th>
<th>Meal-unrelated dyspepsia</th>
<th>Meal-related dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>n</td>
<td>Age, y</td>
<td>n (%) women</td>
<td>659</td>
<td>201</td>
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<tr>
<td></td>
<td></td>
<td>60 ± 1 (50–71)</td>
<td>345 (52)</td>
<td>59 ± 1 (48–72)</td>
<td>131 (58)</td>
</tr>
<tr>
<td>Phase II</td>
<td>n</td>
<td>Age, y</td>
<td>n (%) women</td>
<td>92</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57 ± 1 (46–70)</td>
<td>48 (52)</td>
<td>54 ± 2 (43–64)</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Phase III</td>
<td>n</td>
<td>Age, y</td>
<td>n (%) women</td>
<td>52</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54 ± 2 (44–62)</td>
<td>24 (46)</td>
<td>53 ± 2 (44–61)</td>
<td>15 (43)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase III</th>
<th>Overall</th>
<th>Female age, y</th>
<th>Male age, y</th>
<th>56 ± 3 (47–64)</th>
<th>54 ± 4 (44–62)</th>
<th>54 ± 6 (44–66)</th>
<th>54 ± 4 (44–62)</th>
<th>54 ± 6 (44–66)</th>
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<tbody>
<tr>
<td>Phase III</td>
<td>54 ± 2 (44–62)</td>
<td>56 ± 3 (47–64)</td>
<td>53 ± 2 (44–61)</td>
<td>54 ± 3 (48–59)</td>
<td>52 ± 3 (44–61)</td>
<td>52 ± 3 (44–61)</td>
<td>52 ± 3 (44–61)</td>
<td>52 ± 3 (44–61)</td>
</tr>
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</table>

| NOTE. Data for age are mean ± SEM (interquartile range); for women, data are number (%). |

Prevalence of Dyspepsia and Its Subgroups in a Community Sample

A total of 225 (34.2%) people in the community reported having dyspepsia, and this was frequent ($>25\%$...
of the time) in 17.5% of people. There were 121 (18.4%) people who reported having dyspepsia related to meals, and in 71 (10.8%) dyspepsia related to meals was frequent (Table 2).

Pure dyspepsia, unassociated with meals or other symptoms such as heartburn or bowel-related symptoms, was rare (n = 2, 0.3%). One patient had frequent dyspepsia and the other had meal-related dyspepsia.

Of the 225 patients who reported dyspepsia, 218 specified their one most troublesome symptom. The most prevalent troublesome upper abdominal symptoms were as follows: fullness in 50 (22.9%), burning in 40 (18.4%), bloating in 38 (17.4%), and pain in 36 (16.5%). Other symptoms were reported to be most troublesome in <10% of the community dyspeptic patients. These were uncomfortably full soon (≤1 h) after a meal in 9.2%, nausea in 6.9%, vomiting in 2.3%, and others (miscellaneous) in 6.4% (Table 2).

**Helicobacter pylori Status**

Of the 92 participants who came to the GCRC, there were 15 (16%) people who tested positive for *H pylori* and 2 had tests that were equivocal. Of those who tested positive, 6 were healthy controls and 9 had dyspepsia. Among the 52 participants who underwent physiologic testing, 1 of 17 controls, 4 of 21 meal-unrelated dyspeptics, and 2 of 14 meal-related dyspeptics were positive for *H. pylori*.

**Somatic Symptoms and SCL-90 Scores**

All 92 participants in phase II reported somatic symptom scores by questionnaire and completed the SCL-90. There were 3 participants whose results were considered invalid because they reported not having symptoms of any degree on the SCL-90. One of the subjects subsequently participated in the physiologic phase (phase III) of the study. For this subject, we imputed the SCL-90 score from the SSC score, based on a model using the somatic symptom scores to predict the SCL-90 score for all other participants. Somatization scores and the general severity subscore of the SCL-90 scores were higher in the meal-related dyspeptics as compared with healthy controls (Table 3).

**Somatic symptoms and somatization.** After adjusting for BMI and sex, average SSC scores (P = .07), and t scores for somatization (P = .001), the general severity index (P = .01) from the SCL-90 were associated significantly with symptom group, with higher values observed in the dyspepsia group vs. controls. These scores also were higher in patients with dyspepsia related to meals compared with patients with dyspepsia unrelated to meals.

Recomputing the (raw) SCL-90 somatization scale values without using the single gastrointestinal item (question 19) yielded an overall (N = 52) mean (±SE) value of 0.399 (±0.055); the (raw) SCL-90 somatization scale values including the lone gastrointestinal item had a mean (±SE) of 0.408 (±0.057), and the (Pearson) correlation between these 2 versions of the scale was 0.99. The correlation of the (raw) nongastrointestinal version with the t scale original version was 0.86 (a t scale for somatization for the nongastrointestinal version is not available because there are no norms for this nongastrointestinal version of the somatization scale). An analysis of covariance using the raw nongastrointestinal version of the somatization scale with BMI and sex as covariates (as in this report) indicated a significant association with subgroup status (P = .0035), the adjusted group means (±SEs) being 0.232 (±0.081) in controls, 0.374 (±0.069) in patients with meal-unrelated dyspepsia, and 0.681 (±0.090) in patients with meal-related dyspepsia.

**Physiologic Data**

**Body mass index.** There was a statistically significant association between BMI and symptom group (dyspepsia vs. control, P = .003). This association was most evident in the meal-related dyspepsia group that had the highest BMI, but may in part reflect the some-
what higher proportion of men in this subgroup compared with controls. The BMI of the group of patients with dyspepsia unrelated to a meal was only moderately greater than that of healthy controls (Table 3).

### Gastric emptying of solids and liquids. The $t_{lag}$ (data not shown) and half-time ($P = .2$) for gastric emptying of solids were not statistically associated with symptom groups. Similarly, there was no significant association between gastric emptying of liquids and symptom group ($P = .8$) (Table 4). The proportion of participants with abnormal gastric emptying of solids (<70 min or >150 min half-time) was 3 of 17 in the control group, 4 of 21 in the meal-unrelated dyspepsia group, and 2 of 14 in the meal-related dyspepsia group.

### Fasting and postprandial gastric volumes. All data acquired were used in these contrasts, except for data on one participant who was not fasting when she presented to the laboratory for testing. There was no statistically significant association between symptom group vs. overall dyspepsia. Sex was associated significantly ($P < .05$) with fasting gastric volumes, with women having a lower fasting volume (217.7 ± 15.2

### Table 3. BMI and Scores for Somatization, Somatic Symptom, and General Severity Index Subscore of SCL-90 for Participants in Phase III Physiologic Studies

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 17)</th>
<th>Dyspepsia (n = 35)</th>
<th>Meal-unrelated dyspepsia (n = 21)</th>
<th>Meal-related dyspepsia (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall BMI (kg/m²)</td>
<td>25.5 ± 0.7</td>
<td>29.2 ± 0.9</td>
<td>28.0 ± 1.0</td>
<td>31.0 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>(23.8–26.6)</td>
<td>(26.3–32.3)</td>
<td>(25.9–31.9)</td>
<td>(26.8–32.5)</td>
</tr>
<tr>
<td>Women</td>
<td>24.4 ± 0.9</td>
<td>27.5 ± 1.6</td>
<td>25.5 ± 1.2</td>
<td>31.5 ± 3.9</td>
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<tr>
<td></td>
<td>(23.1–24.9)</td>
<td>(24.2–30.1)</td>
<td>(23.4–28.2)</td>
<td>(26.5–30.3)</td>
</tr>
<tr>
<td>Men</td>
<td>26.8 ± 0.9</td>
<td>30.5 ± 0.8</td>
<td>30.3 ± 1.3</td>
<td>30.7 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>(24.8–28.6)</td>
<td>(26.8–32.8)</td>
<td>(26.4–33.2)</td>
<td>(29.8–32.5)</td>
</tr>
<tr>
<td>Somatic symptom score</td>
<td>1.3 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(1.1–1.4)</td>
<td>(1.3–1.8)</td>
<td>(1.3–1.7)</td>
<td>(1.5–2.0)</td>
</tr>
<tr>
<td>Somatization score*</td>
<td>44.8 ± 1.8</td>
<td>55.2 ± 1.4</td>
<td>52.3 ± 1.6</td>
<td>59.6 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>(39.0–49.0)</td>
<td>(49.0–61.0)</td>
<td>(49.0–59.0)</td>
<td>(55.0–65.0)</td>
</tr>
<tr>
<td>Women</td>
<td>44.6</td>
<td>54.5</td>
<td>52.1</td>
<td>59.4</td>
</tr>
<tr>
<td></td>
<td>(41.0–47.5)</td>
<td>(46.0–62.0)</td>
<td>(46.0–61.0)</td>
<td>(51.0–66.0)</td>
</tr>
<tr>
<td>Men</td>
<td>45.0</td>
<td>55.7</td>
<td>52.5</td>
<td>59.7</td>
</tr>
<tr>
<td></td>
<td>(37.0–51.0)</td>
<td>(49.0–59.5)</td>
<td>(49.0–57.0)</td>
<td>(57.0–62.0)</td>
</tr>
<tr>
<td>SCL-90 GSI subscore*</td>
<td>44.0 ± 2.3</td>
<td>51.5 ± 1.6</td>
<td>49.0 ± 2.1</td>
<td>55.4 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>(36.0–52.0)</td>
<td>(46.3–58.8)</td>
<td>(43.0–56.0)</td>
<td>(50.0–64.0)</td>
</tr>
<tr>
<td>Women</td>
<td>41.5</td>
<td>50.5</td>
<td>48.8</td>
<td>54.0</td>
</tr>
<tr>
<td></td>
<td>(35.0–48.5)</td>
<td>(39.0–58.0)</td>
<td>(38.0–56.0)</td>
<td>(50.0–63.0)</td>
</tr>
<tr>
<td>Men</td>
<td>46.5</td>
<td>52.3</td>
<td>49.1</td>
<td>56.2</td>
</tr>
<tr>
<td></td>
<td>(39.0–54.0)</td>
<td>(46.5–59.5)</td>
<td>(43.0–52.0)</td>
<td>(51.0–64.0)</td>
</tr>
</tbody>
</table>

NOTE. Data are shown as mean ± SEM (interquartile range).

*N = 16 (1 missing set of SCL-90 and somatic symptom scores) in healthy control group.

### Table 4. Gastric Motor Physiology and Maximum Tolerated Volume During Satiation Nutrient Drink Test

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 17)</th>
<th>Dyspepsia (n = 35)</th>
<th>Meal-unrelated dyspepsia (n = 21)</th>
<th>Meal-related dyspepsia (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t½ GE solids, min</td>
<td>118.2 ± 7.0</td>
<td>104.1 ± 5.5</td>
<td>109.0 ± 7.9</td>
<td>96.8 ± 6.9</td>
</tr>
<tr>
<td></td>
<td>(100.0–135.0)</td>
<td>(90.0–130.0)</td>
<td>(80.0–135.0)</td>
<td>(90.0–110.0)</td>
</tr>
<tr>
<td>% GE liquids at 30 min</td>
<td>19.9 ± 3.0</td>
<td>22.8 ± 2.1</td>
<td>24.2 ± 2.6</td>
<td>22.9 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>(13.7–26.5)</td>
<td>(14.1–30.7)</td>
<td>(15.0–31.7)</td>
<td>(13.0–26.0)</td>
</tr>
<tr>
<td>Fasting gastric volume</td>
<td>240.4 ± 21.3</td>
<td>247.5 ± 11.0</td>
<td>242.7 ± 14.9</td>
<td>254.7 ± 16.3</td>
</tr>
<tr>
<td>(mL)</td>
<td>(183.3–293.7)</td>
<td>(189.7–281.9)</td>
<td>(186.8–262.2)</td>
<td>(210.0–297.4)</td>
</tr>
<tr>
<td>Postprandial gastric volume (mL)</td>
<td>765.4 ± 44.3</td>
<td>784.3 ± 22.0</td>
<td>784.7 ± 29.6</td>
<td>783.7 ± 33.9</td>
</tr>
<tr>
<td></td>
<td>(643.8–825.5)</td>
<td>(708.6–832.2)</td>
<td>(688.3–920.6)</td>
<td>(688.3–920.6)</td>
</tr>
<tr>
<td>Change in gastric volume (mL)</td>
<td>525.0 ± 30.8</td>
<td>536.8 ± 18.6</td>
<td>542.0 ± 26.1</td>
<td>529.0 ± 26.3</td>
</tr>
<tr>
<td></td>
<td>(461.0–574.2)</td>
<td>(468.0–600.4)</td>
<td>(489.0–587.2)</td>
<td>(447.0–600.4)</td>
</tr>
<tr>
<td>Ratio of gastric volumes (mL)</td>
<td>3.3 ± 0.2</td>
<td>3.3 ± 0.1</td>
<td>3.4 ± 0.2</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>(2.8–3.8)</td>
<td>(2.7–3.9)</td>
<td>(2.8–4.3)</td>
<td>(2.7–3.6)</td>
</tr>
<tr>
<td>Maximum tolerated volume (mL)</td>
<td>1424.5 ± 90.4</td>
<td>1447.1 ± 75.6</td>
<td>1331.4 ± 95.6</td>
<td>1620.6 ± 111.4</td>
</tr>
<tr>
<td></td>
<td>(1259.0–1659.0)</td>
<td>(1185.0–1659.0)</td>
<td>(1065.0–1539.0)</td>
<td>(1302.0–1883.0)</td>
</tr>
</tbody>
</table>

NOTE. Data are shown as mean ± SEM (interquartile range). Note there are no significant differences in any of these physiologic measurements.

*One subject in the healthy control group was not included because of nonfasting state.
mL) than men (268.1 ± 13.6 mL). A slightly lower change in gastric volume (519.5 ± 25.5 mL) also was observed in women compared with men (532.9 ± 22.8 mL) but was not statistically significant. The proportion of participants with abnormal gastric volume change after the meal (<428 mL) was 3 of 17 in the control group, 4 of 21 in the meal-unrelated dyspepsia group, and 3 of 14 in the meal-related dyspepsia group.

**Maximum tolerated volume.** There was no statistically significant association between maximum tolerated volume and symptom group (healthy controls vs. overall dyspepsia group or separate subgroups), but maximum tolerated volume was associated with BMI (P = .045) and sex (P < .01). Men had a higher maximum tolerated volume than women (1596.2 ± 74.6 mL vs. 1295.8 ± 81.4 mL). Maximum tolerated volume was higher in the meal-related dyspepsia group, but this likely was owing to the higher BMI and proportion of men in this group.

**Postprandial symptom scores.** Univariate statistical analysis indicated a significant (P = .03) association between the aggregate postprandial symptom score and subject group (controls vs. overall dyspepsia), but this association was not significant after adjusting for BMI, sex, and t score for somatization (P = .07) (Table 5). However, bloating was associated significantly with dyspepsia vs. controls (P = .001), with higher scores in the overall dyspepsia group. This association remained significant after adjusting for BMI, sex, and t score for somatization (P = .0164). Subject group (overall dyspepsia, meal-related, and meal-unrelated vs. healthy controls) was associated marginally (P = .05) with the symptom of pain, even after adjustment for BMI, sex, and somatization score. Other symptoms (nausea, fullness) were not associated with subject group (dyspepsia vs. controls) in univariate analysis or after adjustment for covariates.

### Table 5. Postprandial Symptom Scores 30 Minutes After a Fully Satiating Meal

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 17)</th>
<th>Dyspepsia (n = 35)</th>
<th>Meal-unrelated dyspepsia (n = 21)</th>
<th>Meal-related dyspepsia (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregate symptom score</td>
<td>146.6 ± 22.1 (93.0–200.0)</td>
<td>198.3 ± 12.7 (145.0–265.0)</td>
<td>186.0 ± 16.8 (131.0–237.0)</td>
<td>216.8 ± 19.2 (164.0–268.0)</td>
</tr>
<tr>
<td>Nausea score</td>
<td>28.8 ± 7.4 (13.0–65.0)</td>
<td>36.1 ± 4.8 (48.0–85.0)</td>
<td>35.0 ± 5.8 (48.0–80.0)</td>
<td>37.7 ± 8.4 (56.0–85.0)</td>
</tr>
<tr>
<td>Bloating score</td>
<td>36.1 ± 6.9 (15.0–67.0)</td>
<td>65.7 ± 3.6a (48.0–85.0)</td>
<td>63.1 ± 4.8 (48.0–80.0)</td>
<td>69.6 ± 5.3 (56.0–85.0)</td>
</tr>
<tr>
<td>Fullness score</td>
<td>63.0 ± 5.4 (47.0–77.0)</td>
<td>69.8 ± 2.9 (4.0–82.0)</td>
<td>68.4 ± 4.0 (63.0–79.0)</td>
<td>72.0 ± 4.2 (54.0–83.0)</td>
</tr>
<tr>
<td>Pain score</td>
<td>18.8 ± 6.5 (0.0–20.0)</td>
<td>29.7 ± 4.0b (9.0–38.0)</td>
<td>24.5 ± 4.2 (9.0–35.0)</td>
<td>37.5 ± 7.4 (16.0–58.0)</td>
</tr>
</tbody>
</table>

NOTE. Data are shown as mean ± SE (interquartile range). Aggregate symptoms score was calculated 30 minutes postprandially. 

aP = .001 vs healthy controls. 

bP = .05.

Postprandial symptom scores and dyspepsia subgroups. There was no significant association of aggregate symptom score or nausea, fullness, or pain score with subject subgroups (controls vs. meal-related dyspepsia vs. meal-unrelated dyspepsia). However, considering the 3 subgroups (controls, meal-related, meal-unrelated) the overall association between bloating score and subgroup was P = .0004 (unadjusted for covariates), and P = .0578, adjusted for covariates. Thus, the pair-wise association of meal-related dyspepsia vs. controls (P = .0719) and meal-unrelated dyspepsia vs. controls (P = .0192), both adjusted for the covariates, reflects the adjusted subgroup means: 41.9 ± 6.7 in controls, 62.7 ± 5.2 in meal-unrelated dyspepsia, and 62.7 ± 7.5 in meal-related dyspepsia. These adjusted means are lower than the observed means (Table 5) because these subgroups had higher SCL-90 somatization scores and the model adjusts the means to the overall (groups) mean scores.

### Discussion

This study has combined epidemiologic and physiologic evaluations in a randomly selected community-based cohort of people with dyspepsia and healthy controls. There are several other strengths in this study relative to the prior literature. Potential study subjects were identified by drawing a random sample of county residents. Those with dyspepsia were identified by questionnaire response. This did not require presentation to a physician, or referral to a gastroenterologist or an academic medical center. The subjects in this study truly reflect people in the community who have symptoms. The controls were chosen from the same source population and were selected at random to receive a questionnaire. They did not report symptoms on the questionnaire and did not have significant illness identified on the medical (physician) interview.
The different versions of the survey instrument (MBDQ) were based on previously validated instruments, and findings in the questionnaires were verified by a direct interview conducted by one physician. Moreover, the study used a broad definition of dyspepsia, which included the troublesome upper-abdominal symptom in contrast to many previous studies that focused predominantly or exclusively on pain. To avoid observer bias, the technicians involved in data analysis were blinded to the status of the patient (healthy control vs. dyspepsia).

There are 3 important and novel observations in this study.

First, we have shown that community dyspepsia is associated, in about 60% of people who experience upper-abdominal symptoms, with a relationship to meal ingestion. From the wording of the question, the meal precipitated rather than relieved the upper-abdominal symptoms. Fully 10% of people in the community developed meal-related upper-abdominal symptoms (other than heartburn) frequently, that is, more than 25% of the time. This represents a significant symptom burden, and it shows the need to continue to develop understanding of the cause as well as the treatment of these symptoms.

Second, we have used validated noninvasive physiologic tests that can be applied in meaningful numbers that allow an appraisal of pathophysiology of dyspepsia in a community sample. We have shown that community dyspeptic patients have higher postprandial symptom scores after a provocative test in the form of a fully satiating meal. The maximum tolerated volumes of the caloric liquid nutrient drink in dyspeptic patients and healthy controls were similar, but the symptoms were greater in the dyspeptic patients. We acknowledge that hypervigilance also may play a role, resulting in greater subjective symptom reporting in the absence of a demonstrable sensory abnormality on the satiety test. In contrast, the motor functions of the stomach, that is, gastric emptying and fasting and postprandial volumes, were not significantly different between dyspepsia patients (combined or individual subgroups) compared with controls. This experience in community dyspeptic patients contrasts markedly from the observations in referred dyspeptic patients. In 2 large studies of referred patients, Tack et al \(^{13}\) and Bredenoord et al \(^{16}\), respectively, used invasive barostat or noninvasive single-photon emission computed tomography measurements to evaluate fasting and postprandial tone or volume, and were able to observe impaired gastric accommodation in ~40% of referred patients. Similarly, the literature suggested that 20%–40% of clinic-based dyspepsia patients have impaired gastric emptying of solids; overall, we observed no significant change in gastric emptying in community dyspeptic patients relative to controls.

Third, our study explored the associated risk factors for dyspepsia in this community cohort. As previously shown in this community, the prevalence of \(H\) \(_{\text{pylori}}\) infection is relatively low and there is no significant association between infection and either sensory or motor disorders in dyspepsia. \(^8\) In contrast, the higher aggregate and bloating scores after the fully satiating meal in the community dyspeptic patients were associated significantly with features of higher somatic scores or somatization. We acknowledge that self-selection for participation in the noninvasive physiologic studies may result in a greater tendency to have psychologic disturbances in the volunteer participants. It may be considered that the dyspepsia groups may have higher somatization scores by having physical symptoms that reflect gastrointestinal dysfunction. However, we noted that, in the SCL-90 subscales of interest, only one symptom is gastrointestinal related (nausea or upset stomach) and 2 others are appetite related (poor appetite and overeating). There are no gastrointestinal-related symptoms in the SSC in the MBDQ. Thus, somatic symptom scores and the SCL-90 are both heavily weighted by nongastrointestinal symptoms, and this suggests that the influence of somatization reflected not only gastrointestinal symptoms. Indeed, the general severity index subscores were higher in dyspepsia patients than in controls. We conclude that a tendency to present with somatization should be tested formally in dyspeptic patients presenting to clinics; psychologic factors are known to be important in determining whether patients will present to health care facilities.

The importance of psychologic disturbances and illness behavior in tertiary care patients with dyspepsia also was shown in a factor analysis of symptoms and associations by the Leuven group. \(^{10}\) Thus, in a tertiary care population, functional dyspepsia was shown to be a heterogeneous condition characterized by 4 major dimensions differentially associated with psychopathologic and pathophysiologic mechanisms. The cluster analysis identified one factor characterized by nausea, vomiting, early satiety, and weight loss, and a second factor characterized by postprandial fullness and bloating. Both factors were associated with delayed gastric emptying. It is intriguing that a third factor was characterized by pain symptoms and associated with gastric hypersensitivity and several psychosocial dimensions including medically unexplained symptoms and health-related quality-of-life dimensions. This factor appears most closely to mimic the presentation and physiologic findings of dyspeptic pa-
tients in our community study. In the study by Fischler et al., factor 4 was characterized by belching associated with hypersensitivity, but was unrelated to psychosocial factors.

These observations also have important implications for the management of dyspepsia in primary care or the community. The data suggest that behavioral or pharmacologic or alternative therapies that decrease gastric sensation or higher somatization scores should be used early in an empiric trial of therapy. However, it is important to point out that the mean somatization score for each group of dyspepsia was within 1 SD from the norm (t score, <60), suggesting that these are not psychologically abnormal scores, but that the difference observed may reflect different tendencies to report symptoms, which may determine dyspepsia vs. control (non-dyspepsia) group.

A weakness of this study is the response rate. The initial response to the questionnaire was less than 50%. We excluded from participation those questionnaire responders in whom an alternative explanation for dyspepsia (eg, nonsteroidal anti-inflammatory use) was identified on the physician interview. It is important to note that the vast majority of the prior epidemiologic studies in the literature did not use this exclusion criterion; our experience suggests that there is a significant burden of concomitant illness or medication intake that complicates such survey-based studies. Further, many questionnaire responders refused to present to be interviewed or to have tests, despite the noninvasive nature of the studies. Thus, the final set of study subjects is a small fraction of the entire group, and this can introduce bias.

We evaluated all the groups in the 3 phases of the study for differences in the psychologic distress as evidenced by the SSC scores that summarize the frequency and severity of symptoms (as bothersome). As shown in Figure 1, there were no clinically important differences in sex, age, or SSC scores between responders and non-responders in each phase of this 3-part study.

The responder rates recorded in this study reflect the challenge of attempting to perform medically sophisticated evaluations of people selected at random, as opposed to the more typical approach of patients who present to physicians with a desire to understand the cause and embark on treatment under the supervision of a physician, or the approach of healthy volunteers whose participation is truly altruistic.

A second challenge is the overlap among symptoms. Many of the subjects with dyspepsia also had symptoms of reflux or IBS and, thus, the number with pure dyspepsia was extremely small. Other studies previously have documented the overlap between gastroesophageal reflux disease and dyspepsia and the overlap of 80% between dyspepsia and IBS. This degree of overlap may indicate that the separation of functional gastrointestinal symptoms into symptom-based diagnoses of separate disorders is artificial and not easily achievable in a community sample. Some may argue that the absence of differences in the physiologic measurements between dyspepsia and controls may have been owing to a mixture of patients in our study. That may be true; however, our goal was to understand why approximately 20% of the population has symptoms of dyspepsia, rather than identifying the cause or pathophysiology of the subgroup, which has a prevalence of <1% in our community sample.

In summary, we have investigated community dyspeptic patients and identified the importance of meal-related symptoms and of the propensity to report higher post-meal and somatic symptoms. H pylori infection or gastric dysmotility seem to be less important in the Olmsted County community population. The higher somatization scores need to be addressed in people with dyspepsia in the community.

References


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