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Laura A. Wilson: Study design, statistical analysis, manuscript preparation

Henry P. Parkman: Study design, subject recruitment, data collection, contribution to manuscript preparation

Linda Nguyen: Study design, subject recruitment, data collection, contribution to manuscript preparation

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BLOATING IN GASTROPARESIS: SEVERITY, IMPACT, AND ASSOCIATED FACTORS

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Abstract

Objectives—Bloating is commonly reported in gastroparesis, but its prevalence, impact, and associated factors have not been investigated. We aimed to quantify the prevalence of bloating in gastroparesis and relate its severity to clinical factors and quality of life.

Methods—Survey, examination, and scintigraphy data were compared in 335 gastroparesis patients from 6 centers of the NIDDK Gastroparesis Clinical Research Consortium. Bloating severity was stratified using Gastroparesis Cardinal Symptom Index (GCSI) bloating subscale scores.

Results—Bloating of at least mild severity (GCSI ≥ 2) was reported by 76% of patients. Bloating severity related to female gender ($P < 0.0001$) and overweight status ($P = 0.04$) on regression analysis and correlated with intensity of nausea, postprandial fullness, visible distention, abdominal pain, and altered bowel function (all $P < 0.05$). Disease etiology, smoking status, and gastric emptying did not relate to bloating subset (all $P > 0.05$). Disease-specific quality of life and general measures of well being were progressively impaired with increasing bloating severity (all $P < 0.001$). Among medications, probiotic ($P = 0.03$) and norepinephrine reuptake inhibitor antidepressant ($P = 0.045$) use related to bloating severity; antiemetic use trended higher with worsening bloating ($P = 0.06$).

Conclusions—Bloating is prevalent in gastroparesis and is severe in many individuals. Bloating severity relates to female gender, body weight, and intensity of other gastroparesis symptoms. The symptom impairs quality of life but is not influenced by gastric emptying rates. Antiemetics, probiotics, and norepinephrine reuptake inhibitor antidepressants may affect reports of bloating. These findings provide insight into this underappreciated symptom of gastroparesis.

INTRODUCTION

Manifestations of gastroparesis are varied. Symptoms other than nausea and vomiting may be prominent. The validated Gastroparesis Cardinal Symptom Index (GCSI) quantifies nine symptoms in 3 subscales—nausea and vomiting, postprandial fullness, and bloating (1). Case series characterizing specific symptoms in gastroparesis often relate bloating to gastric function or response to prokinetic therapy (2). Furthermore, greater degrees of bloating and distention in patients with gastroparesis have been associated with poorer responses to therapy (3).

Characteristics of bloating in functional bowel disorders have been extensively investigated. Prominent bloating in irritable bowel syndrome (IBS) and functional dyspepsia contributes to disease severity and impairs quality of life (4, 5). Pathogenic factors for bloating in these disorders include luminal sensorimotor dysfunction and altered abdominal somatic musculature activity (6, 7, 8, 9, 10). Smoking also may contribute to bloating in IBS (11). Agents stimulating transit, modulating visceral sensation, or altering gut flora treat bloating in the functional disorders (12, 13, 14, 15). The prevalence of bloating in gastroparesis and the relation of bloating severity to demographic factors, severity of other symptoms, quality of life, gastric and extragastric factors involved in its pathogenesis, and medication use are unexplored.

Demographic information, clinical features, disease-specific severity and quality of life scores, examination findings, and gastric scintigraphy results from patients with gastroparesis from US academic centers were analyzed to address four aims: (i) quantify the prevalence of bloating and relate bloating severity to demographic factors to test the hypotheses that intensity of bloating is dependent on patient gender and age, (ii) to test the hypotheses that bloating severity correlates with investigator-rated disease severity, intensity of other manifestations of gastroparesis measured by validated symptom surveys (GCSI and Patient Assessment of Upper Gastrointestinal Disorders Symptoms Severity Index [PAGI-QOL]), and quality of life measured by both an upper gut sensorimotor disorder specific survey (Patient Assessment of Upper Gastrointestinal Disorders Quality of Life [PAGI-QOL]) and a more general measure of functional health and well being (Short Form-36 [SF-36]), (iii) define gastric and extragastric factors potentially pathogenic of bloating to test the hypotheses that bloating severity relates to delayed gastric emptying, lower gut factors, obesity, and smoking, and (iv) relate medication use to bloating severity to test the hypothesis that pharmaceutical factors are associated with this symptom (1, 16, 17). Through these investigations, we hoped to gain insight into bloating in gastroparesis to provide a foundation for future investigations into the pathogenesis and management of this underappreciated symptom.

MATERIALS AND METHODS

Patient Population

Three hundred thirty-five gastroparesis patients were recruited by six centers of the NIDDK Gastroparesis Clinical Research Consortium into a Gastroparesis Registry from January 2007 through November 2009 (ClinicalTrials.gov Identifier: NCT00398801). Patients ≥ 18 years old with symptoms of gastroparesis for ≥ 12 weeks (not necessarily contiguous) and with delayed gastric emptying ($>60\%$ retention at 2 hours and/or $>10\%$ at 4 hours) on 4 hour gastric scintigraphy after a low fat meal within 6 months of enrollment were included (18). Most patients were referred for specialized care of gastroparesis from providers in the community to expert clinicians at the study centers. Other patients were sent from other physicians within the study centers to the principal investigators at those sites. In most instances, referrals were made seeking second opinions. In some centers, referrals were initiated to gain access to specialized services such as prescription programs for domperidone, endoscopic pyloric botulinum toxin injection, or surgical implantation of gastric stimulator devices. Some patients initiated their own referrals after accessing websites describing the Gastroparesis Registry. Exclusion criteria included other conditions potentially explanatory of symptoms (e.g. obstruction, inflammatory bowel disease, eosinophilic gastroenteritis, neurologic disease, acute liver or kidney disease); and prior fundoplication, gastric resection or pyloroplasty.

Institutional Review Board approval was obtained at Clinical Centers and the Data Coordinating Center. Patients provided written informed consent.

Data Acquisition and Analysis

Data Collection—On enrollment, questionnaires quantifying symptoms of gastroparesis (including bloating) were administered to subjects. During face-to-face interviews, the Principal Investigator or Study Coordinator completed the Baseline Medical History questionnaire which queried symptoms, disease profiles, associated conditions, and therapies. Physical examination findings, laboratory profiles, and findings of upper endoscopy (within the prior 12 months) and gastric scintigraphy (within the prior 6 months) were recorded. Patient-reported bloating severity was quantified by extracting the Gastroparesis Cardinal Symptom Index (GCSI) from the Patient Assessment of Upper Gastrointestinal Disorders Symptoms Severity Index (PAGI-SYM) questionnaire (16). The GCSI enumerates 9 symptoms from 0 (no symptoms) to 5 (most severe)(1). Mean GCSI bloating subscale scores were calculated by averaging the scores for bloating (feeling like you need to loosen your clothes) and stomach or belly visibly larger. For the comparisons of this investigation, patients were stratified by GCSI bloating subscale score into those with the lowest (score 0 to 1.9), intermediate (2 to 3.9), and highest (≥ 4) bloating severity.

Relation of Bloating Severity to Clinical Variables—Demographic variables were gleaned from the Registration and Baseline Medical History forms and included age on Registry enrollment, gender, ethnicity, race, duration of gastroparesis symptoms, and gastroparesis etiology. One hundred sixteen individuals were deemed to have gastroparesis because of diabetes, while 219 patients had gastroparesis of an idiopathic nature based on no prior gastric surgery, no diabetes history, a normal hemoglobin A1c, and no other known etiologies. Patients with conditions other than diabetic or idiopathic gastroparesis were too few in number to undergo meaningful analysis and were excluded.

Gastroparesis severity and quality of life were quantified using several surveys. Investigator-rated severity was queried on Baseline Medical History forms. Grade 1 gastroparesis was defined by easily controlled symptoms with maintenance of weight on a regular diet. Grade 2 gastroparesis was defined by moderate symptoms partly controlled by daily medications, but with maintenance of nutrition with dietary modification. Grade 3 gastroparesis was defined if symptoms were medication-refractory, if frequent physician and emergency department visits or hospitalizations were reported, and/or if oral nutrition was impossible. This stratification has been proposed by an expert panel (19). Nausea and vomiting and postprandial fullness subscale scores were calculated from the GCSI survey. Disease-specific quality of life was assessed by the Patient Assessment of Upper Gastrointestinal Disorders Quality of Life (PAGI-QOL) survey, which scores 30 factors from 0 (none of the time) to 5 (all of the time)(17). Overall PAGI-QOL scores are calculated by taking means of all subscores after reversing item scores; thus a mean PAGI-QOL score of 0 represents poor quality of life while 5 reflects the best life quality. Four physical (physical functioning, role-physical, bodily pain, general health) and four mental (vitality, social functioning, role-emotional, mental health) subscores from Short Form-36 (SF-36) surveys were calculated as additional quality of life measures. These SF-36 subscores were combined to form composite Physical Component and Mental Component scores.

Gastric and extragastric factors with potential pathogenic relevance were quantified by selected survey, physical examination, and gastric functional data. Percentages of patients with self-reported visible distention on the Baseline Medical History form were noted. Upper and lower abdominal pain, constipation, and diarrhea scores from the PAGI-SYM were scored from 0 (no symptoms) to 5 (most severe)(16). Body mass index (BMI), overweight status ($\text{BMI} \geq 25 \text{ kg/m}^2$), waist circumference, hip circumference, and the waist to hip circumference ratio were calculated to assess increased girth from luminal gas retention, altered somatic muscle activity, or obesity. Current and past smoking was queried

on the Baseline Medical History form. Scintigraphic gastric retention at 1, 2, and 4 hours was quantified.

Medication use at the time of Registry enrollment was determined from the Baseline Medical History form. Use of prokinetics (metoclopramide, erythromycin, domperidone, clarithromycin, azithromycin, pyloric botulinum toxin), antiemetics (prochlorperazine, promethazine, trimethobenzamide, meclizine, ondansetron, granisetron, dolasetron, aprepitant), opiates, probiotics (patients were not queried about probiotics until April 2008; 155 patients are missing this item), neuropathic pain modulators (gabapentin, pregabalin, topiramate), and antidepressants was queried. Antidepressant use was further stratified into those individuals taking a single norepinephrine reuptake inhibitor antidepressant (amitriptyline, nortriptyline, desipramine, imipramine, bupropion, venlafaxine, duloxetine) versus a single agent acting via other mechanisms (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, mirtazapine, trazodone). Data from 12 patients on more than one antidepressant were not included in the analysis of norepinephrine reuptake inhibitors.

Statistical Analysis—Differences in baseline characteristics were compared for those with GCSI bloating subscale scores of 0 to 1.9 versus 2 to 3.9 versus ≥ 4 . P values were derived from chi square tests for categorical variables, Fisher's exact test for categorical variables with small expected numbers, or analysis of variance for continuous variables. All data are reported as mean or percent followed by 95% confidence intervals. For categorical variables, the exact binomial 95% confidence intervals are presented. Nominal, two-sided P values were used and were considered to be statistically significant if $P < 0.05$; no adjustments for multiple comparisons were made. Backwards stepwise ordinal logistic regression analysis was used after testing that the assumption of a rank outcome was met to identify significant predictors of bloating severity from among candidate predictors at enrollment: Hispanic ethnicity, duration of symptoms, etiology (diabetic, idiopathic), investigator-rated severity (Grades 1, 2, and 3), GCSI nausea/vomiting and postprandial fullness scores, PAGI-QOL score, SF-36 physical and mental components, visible distention, individual PAGI-SYM scores, overweight status, waist to hip circumference ratio, smoking status (current, previous, never), gastric retention (1, 2, and 4 hours), and medication classes (prokinetics, antiemetics, opiates, neuropathic pain modulators, antidepressants). The model was forced to include terms for age at enrollment, gender, and race. P values for elimination from the model were < 0.05 . The ordinal model estimated the relative cumulative odds of a higher bloating severity subset relative to a lower bloating severity subset for each candidate predictor. All analyses were performed using SAS statistical software (version 9.1, SAS Institute, Cary, NC) and Stata (Release 10.0, Stata Corporation, College Station, TX)(20, 21).

RESULTS

Relation of Bloating Severity to Demographic Variables

Demographic data from 335 patients were stratified according to bloating severity as measured by the GCSI (Table 1). Eighty patients reported GCSI bloating subscale scores from 0 to 1.9, while 116 recorded scores of 2 to 3.9 and 139 individuals noted bloating subscale scores ≥ 4 . Female gender showed significant relation to bloating severity scores ($P < 0.0001$). On pairwise comparisons, female predominance was greater in those with GCSI bloating subscale scores 2 to 3.9 versus 0 to 1.9 ($P = 0.02$) and with scores ≥ 4 versus 2 to 3.9 ($P = 0.02$). There were no differences in age at enrollment ($P = 0.72$), or ethnic ($P = 0.37$) or racial ($P = 0.89$) composition between groups. Percentages of patients reporting short (0 to 1.5 years), medium (1.6 to 4.9 years), or long (≥ 5 years) duration of symptoms were similar in the different bloating severity subsets ($P = 0.59$). Diabetics comprised approximately one

third of patients; there were no differences in disease etiology between bloating severity groups ($P=0.49$). Relative distributions of type 1 and type 2 diabetics in the subject groups were similar ($P=0.61$).

Relation of Bloating Severity to Gastroparesis Severity and Quality of Life

Bloating was related to investigator- and patient-rated gastroparesis severity. Among all subjects, investigators rated gastroparesis as grade 1 in 12.3%, grade 2 in 53.8%, and grade 3 in 33.9% (Table 2). Investigator-rated severity showed significant differences between bloating severity subsets ($P=0.001$). On pairwise comparisons, those with bloating subscale scores ≥ 4 had lower percentages of grade 1 severity patients versus those with scores 0 to 1.9 ($P=0.02$) and 2 to 3.9 ($P=0.003$). Patient-reported nausea and vomiting GCSI subscale scores averaged in the mild to moderate range for each bloating subset. Mean nausea and vomiting scores were higher in those with increased bloating severity ($P=0.02$). Postprandial fullness GCSI subscale scores also showed a relation to bloating severity, being higher in those with greater bloating subscale scores ($P<0.0001$). On pairwise comparisons, patients with bloating subscale scores ≥ 4 had significantly greater nausea and postprandial fullness scores than those with scores 2 to 3.9 and with scores 0 to 1.9 (all $P<0.05$).

Bloating was related to two quality of life measures (Table 2). Combining PAGI-QOL scores in all subjects (2.5 ± 1.1) indicated moderately impaired quality of life. Mean PAGI-QOL scores showed inverse correlation with bloating severity, being lowest in those with the highest GCSI bloating subscale scores ($P<0.0001$). On pairwise comparisons, patients with bloating subscale scores ≥ 4 had worse PAGI-QOL scores than those with bloating scores of 2 to 3.9 ($P<0.0001$) and those with bloating scores 2 to 3.9 had lower PAGI-QOL scores than patients with bloating scores of 0 to 1.9 ($P=0.001$). Both the physical and mental component scores of the SF-36 survey showed inverse relation to bloating severity, being lower in patients with high bloating subscale scores ($P<0.001$). On pairwise comparisons for both SF-36 comparisons, patients with bloating subscale scores ≥ 4 had worse scores than those with bloating subscale scores of 2 to 3.9 and those with scores of 0 to 1.9 (both $P<0.05$).

Relation of Bloating Severity to Potential Pathogenic Factors

Potential pathogenic factors were compared between bloating subsets (Table 3). Reports of visible distention showed strong correlation with bloating severity; distention was not noted by those with the lowest bloating scores but was universally reported by those with the highest bloating subscale scores ($P<0.0001$). On pairwise comparisons, patients with bloating subscale scores ≥ 4 more often reported distention than those with bloating scores of 2 to 3.9 ($P<0.0001$) and those with bloating scores of 2 to 3.9 more frequently noted distention than patients with bloating scores of 0 to 1.9 ($P<0.0001$). Upper ($P<0.0001$) and lower ($P<0.0001$) abdominal pain, constipation ($P<0.0001$), and diarrhea ($P=0.002$) scores on the PAGI-SYM survey showed significant positive correlation with bloating severity. On pairwise comparisons, patients with bloating subscale scores ≥ 4 had higher upper and lower abdominal pain, constipation, and diarrhea scores than those with bloating scores of 2 to 3.9 and 0 to 1.9 (all $P\geq 0.05$). Patients with bloating scores 2 to 3.9 had higher constipation scores than those with bloating scores of 0 to 1.9 ($P=0.05$). There were no differences in BMI ($P=0.15$), percentages of patients who are overweight ($P=0.18$), waist circumference ($P=0.39$), hip circumference ($P=0.33$), and ratios of waist to hip circumference ($P=0.62$) between bloating severity groups. Proportions who never smoked, smoked only in the past, and were current smokers were similar in the three groups ($P=0.37$). Pooling all subjects, 4 hour gastric retention averaged 33% indicating delayed emptying that was moderately severe. There were no differences in retention at 1 ($P=0.57$), 2 ($P=0.79$), or 4 ($P=0.47$) hours between bloating severity subsets.

Relation of Bloating Severity to Medication Use

Bloating was related to medication use in the three groups (Table 4). There was a trend to differences in antiemetic use between bloating severity groups ($P=0.06$). On pairwise comparisons, patients with bloating subscale scores of 0 to 1.9 had less antiemetic use than those with bloating scores of 2 to 3.9 ($P=0.05$) and ≥ 4 ($P=0.03$). Probiotics showed a positive association with bloating severity ($P=0.03$). On pairwise comparisons, patients with bloating subscale scores ≥ 4 showed greater probiotic use than those with bloating scores of 2 to 3.9 ($P=0.03$). When all antidepressant classes were considered together, there were no differences in use in the three bloating severity subsets ($P=0.11$). However, there were significant differences in bloating subset distribution between different antidepressant classes ($P=0.045$). On pairwise comparisons, the percentage of patients on norepinephrine reuptake inhibiting agents was significantly higher and the percentage on drugs acting via other pathways was significantly lower in the patients with bloating subscale scores of 0 to 1.9 versus those with scores of 2 to 3.9 ($P=0.02$). There were no differences in prokinetic medication ($P=0.72$), opiate drug ($P=0.24$), and neuropathic pain modulator use ($P=0.30$) between bloating severity subsets.

Ordinal Logistic Regression Analysis to Identify Predictors of Bloating Severity

Backwards stepwise ordinal logistic regression analysis identified factors predictive of bloating severity subset measured by the GCSI bloating subscale (Table 5). Female gender related to increasing bloating severity ($OR=3.12$, $P<0.0001$). Among other symptoms, lower abdominal pain severity ($OR=1.38$, $P<0.0001$) and constipation severity ($OR=1.17$, $P=0.02$) on the PAGI-SYM related to increasing bloating subscale scores. PAGI-QOL scores related inversely to bloating severity ($OR=0.40$, $P<0.0001$). Higher SF-36 mental component scores predicted greater bloating scores ($OR=1.02$, $P=0.009$). Finally, the likelihood of being overweight predicted bloating severity ($OR=1.62$, $P=0.04$).

DISCUSSION

Most studies focus on nausea and vomiting as the main symptoms of gastroparesis (19). However from single center series, it is apparent that gastroparesis can present with other symptoms. Bloating is prominent in IBS and functional dyspepsia, (4, 5, 7). Information on demographic profiles of bloating in these conditions, its impact on disease severity and quality of life, its pathogenesis, and its response to therapy is available (7, 8, 9, 10, 11, 12, 13, 14, 15). Little is known about features of bloating in gastroparesis. The present investigation accessed a multicenter registry to investigate characteristics of bloating in gastroparesis. Strengths of these analyses are the number of patients, rigorous inclusion and exclusion criteria, standardized scintigraphy methods, well-validated surveys administered, and careful statistical methods used. As a consequence, this study provides the most detailed evaluation of this symptom in gastroparesis.

Bloating of at least mild severity was reported by a majority of gastroparesis patients (76%), similar to reports in IBS and greater than the 20% reported in general populations (4, 5, 7). Bloating is the third most common reason for seeking health care in IBS, and has been reported as the most common gastrointestinal symptom in diabetes (4, 22). In this investigation, patients were stratified into three bloating severity subgroups based on GCSI bloating subscale scores. This permitted identification of factors associated with severity of this symptom in gastroparesis. Bloating severity showed strong female predominance, similar to reports in IBS (4, 5). Distribution of bloating severity was similar in diabetic and idiopathic gastroparesis. Studies suggest the neuropathology underlying diabetic and idiopathic gastroparesis is different (23). Our findings suggest bloating is not influenced by such differential neuronal impairment.

In the present study, bloating severity was related to symptom severity and quality of life. Investigator-rated gastroparesis severity showed significant differences between bloating subgroups. Most prominently, ratings of grade 1 severity were lowest in those in the highest bloating severity subset indicating that more intense bloating is associated with more severe gastroparesis. Likewise, severity of other symptoms of gastroparesis including nausea and vomiting and postprandial fullness measured using GCSI surveys increased with worsening bloating severity. These observations are similar to studies in IBS that report bloating is bothersome in a majority of IBS patients and is predictive of IBS severity (24). Disease-specific quality of life on the PAGI-QOL showed progressive impairment with increasing bloating severity on both univariate and ordinal logistic regression analysis. Additionally, bloating severity related to reductions in both the physical and mental components of the SF-36 survey on univariate analysis. Curiously on the multivariate analysis, the mental component of the SF-36 showed a slight but significant increase in quality of life with increasing bloating severity possibly secondary to undetermined interactions between SF-36 scores and other variables. By comparison, bloating relates to impaired quality of life on SF-36 testing in functional bowel disease and correlates with impaired energy/fatigue levels and physical functioning in IBS (4, 11).

Examination and survey findings were compared to discriminate possible pathogenic factors of bloating in different gastroparesis subsets. In IBS, distinctions between perceived bloating and visible distention have been made. Distention is absent in diarrhea-predominant IBS; bloating with distention in constipation-predominant IBS relates to prolonged small intestinal and colonic transit (7, 24). Bloaters without distention exhibit reduced thresholds for rectal perception, suggesting heightened visceral sensation (9, 10). Altered abdominal somatic muscle activity also promotes distention. Patients with dysmotility syndromes exhibit increased abdominal volumes with anterior abdominal wall protrusion and upward diaphragmatic displacement (8). In the present study, visible distention correlated strongly with bloating severity. Distention was not reported by any patient with the lowest degrees of bloating and was noted universally in those with the highest symptom scores. Despite these reports, no differences in waist or hip circumferences could be discerned between bloating subgroups. On PAGI-SYM scoring, bloating severity also strongly related to a range of distal gut symptoms in both diabetic and idiopathic patients including lower abdominal pain, constipation, and diarrhea on univariate analysis and lower abdominal pain and constipation on ordinal logistic regression analysis. These observations raise the possibility of associated generalized dysmotility involving extragastric regions underlying the pathogenesis of bloating. Reports of bloating also may be influenced by non-gaseous factors. As preliminary data suggests gastroparesis patients often are overweight, we hypothesized that bloating severity relates to body weight factors (25). Although bloating did not correlate with BMI on univariate analysis, overweight status predicted bloating severity on ordinal logistic regression analysis. In functional bowel patients, bloating is associated with smoking possibly due to aerophagia or inhibitory motor effects of tobacco (11). Smoking did not relate to bloating severity in gastroparesis patients in this study.

Gastric retention at different times postprandially was similar in the bloating severity subsets, indicating this symptom is not influenced by degrees of emptying delay. Other studies relating delayed gastric emptying to bloating in gastroparesis, functional dyspepsia, and diabetes provide conflicting results (26, 27). In one recent single center study, bloating scores were greater in patients with delayed versus normal gastric emptying (28). Conversely, rapid emptying has been observed in fat intolerant patients with bloating (29). Additional factors related to bloating in functional dyspepsia and diabetes include enhanced phasic fundic contractions, impaired fundic relaxation, altered intragastric distribution, and increased antral diameter (6, 22, 30). Future investigations will determine if these regional dysfunctions contribute to bloating in gastroparesis.

Medication use was analyzed in the present study to improve understanding of drug classes relating to bloating in gastroparesis. This issue is significant as a recent report has related unfavorable responses to therapy of gastroparesis to increases in bloating and visible distention (3). Trials quantifying benefits of prokinetics on bloating in gastroparesis have shown improvements, exacerbation, or no effect (2, 19). Serotonin 5-HT₄ agonists and acetylcholinesterase inhibitors decrease bloating and distention in other functional disorders (5). Prokinetic use in the current study was similar in the bloating severity subsets, indicating possible lack of efficacy for this symptom. There was a trend to higher antiemetic use in relation to bloating severity. On pairwise comparisons, the difference in antiemetic use was statistically significantly higher in those with the most severe versus the least severe bloating, consistent with the observation that nausea and vomiting severity parallels bloating in gastroparesis. Opiate use was no different in different subgroups, suggesting narcotics were not pathogenic of bloating. Likewise, neuropathic pain modulators were taken similarly in the three bloating severity subsets. Such pain modulating agents are reported to blunt visceral sensation in IBS, but appear not to influence bloating in gastroparesis (31). Probiotic use was higher in those with the most severe bloating. However, the numbers of patients on probiotics in this investigation were small regardless of bloating severity. Thus, the utility of probiotic supplementation in gastroparesis warrants further study. In comparison, probiotics decrease gaseous symptoms in IBS likely because they target colonic rather than gastric microbiota (13). Gastroparesis also is associated with bacterial overgrowth (32). This study did not query antibiotic use; further investigation of benefits of antibiotics for bloating in gastroparesis is warranted.

Antidepressants showed intriguing associations with bloating severity in this study. When antidepressants were subcategorized, norepinephrine reuptake inhibitor use was greatest in those with the lowest bloating subscale scores while use of agents without norepinephrine reuptake inhibition was greater in those with higher degrees of bloating severity. It cannot be determined from our data whether norepinephrine reuptake inhibitors improve bloating or if other classes (such as selective serotonin reuptake inhibitors) worsen this symptom in gastroparesis. Furthermore, our data do not permit determination of the reason for use of such agents; it is uncertain if antidepressants in different classes were prescribed for psychiatric disease or gastrointestinal symptomatology. Norepinephrine reuptake inhibitors blunt afferent function in functional bowel disorders; their inhibition of perception of bloating in gastroparesis is unproved. Other therapies of gastroparesis such as gastric electrical stimulation may reduce symptoms by inhibiting afferent transmission (33). However, selective serotonin reuptake inhibitors show limited antinociceptive activity although citalopram and fluoxetine reportedly reduce bloating in IBS (15). Our findings suggest that prospective studies be performed to test if norepinephrine reuptake inhibitors are beneficial in patients with severe bloating.

Although this study associated clinical factors with bloating in gastroparesis, there are limitations to these findings. Data were analyzed on enrollment only. Longitudinal follow-up could provide additional data regarding medication benefits in reducing bloating. Secondly in the non-diabetic patients, there is overlap of symptom profiles in those with idiopathic gastroparesis versus functional dyspepsia. Current clinical definitions provided by consensus documents do not permit confident discrimination of the two disorders on symptoms alone (34). Furthermore, many functional dyspeptics exhibit delayed gastric emptying and could thus be considered to have idiopathic gastroparesis (35). Some expert panels have suggested distinguishing the two disorders on the basis of symptom predominance (pain for functional dyspepsia, nausea and vomiting for idiopathic gastroparesis)(19). However in a preliminary report, pain predominance was reported in a fifth of patients with gastroparesis both with diabetes and with idiopathic disease (36). These observations suggest that idiopathic gastroparesis and functional dyspepsia are related

disorders with heterogeneous defects in sensory, motor, or central nervous system function. Although invasive testing of gastric afferent and motor function has characterized a range of abnormalities in functional dyspepsia, such testing has been less intensively employed to study idiopathic gastroparesis.

In conclusion, bloating is prevalent in gastroparesis and is severe in many affected patients. Bloating severity in gastroparesis relates strongly to female gender and to, a lesser degree, body weight. Patients with more severe gastroparesis also report increased intensity of other gastroparesis symptoms as well as higher levels of symptoms relatable to the lower gut, suggestive of possible associated extragastric dysmotility. Increasing bloating severity correlates with impaired disease-specific quality of life and general measures of physical and mental health and well being. Bloating does not relate to gastric retention or tobacco use. Antiemetic and probiotic use relates to bloating severity subclass. Antidepressant use may affect reports of bloating severity, with reductions in those on norepinephrine reuptake inhibitors and increases in other classes. These findings provide insight into this underappreciated symptom of gastroparesis and provide the foundation for future investigations into its pathogenesis and management.

STUDY HIGHLIGHTS

1. What is current knowledge?

- Symptoms other than nausea and vomiting are commonly reported by patients with gastroparesis and may be prominent.
- Bloating is prevalent in functional bowel disorders and has significant impact on disease severity and quality of life in these conditions.
- The prevalence of bloating in gastroparesis and the relation of its severity to demographic factors, severity of other symptoms, quality of life, gastric and extragastric factors involved in its pathogenesis, and medication use are unexplored.

2. What is new here?

- Bloating is prevalent in gastroparesis and is severe in many patients.
- Bloating severity relates to female gender and body weight and correlates with intensity of other symptoms including nausea, postprandial fullness, visible distention, abdominal pain, and altered bowel function.
- Increasing bloating severity in gastroparesis leads to significant impairments in disease-specific quality of life and general measures of health and well being.
- Antiemetic medications, probiotics, and norepinephrine reuptake inhibitor antidepressants may affect reports of bloating.
- These findings provide insight into this underappreciated symptom of gastroparesis.

REFERENCES

- 1). Revicki DA, Rentz AM, Dubois D, et al. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Aliment Pharmacol Ther.* 2003; 18:141–150. [PubMed: 12848636]
- 2). Arts J, Van Gool S, Caenepeel P, et al. Influence of intrapyloric botulinum toxin injection on gastric emptying and meal-related symptoms in gastroparesis patients. *Aliment Pharmacol Ther.* 2006; 24:661–667. [PubMed: 16907899]

- 3). Anaparthi R, Pehlivanov N, Grady J, et al. Gastroparesis and gastroparesis-like syndrome: response to therapy and its predictors. *Dig Dis Sci*. 2009; 54:1003–1010. [PubMed: 19277867]
- 4). Ringel Y, Williams RE, Kalilani L, et al. Prevalence, characteristics, and impact of bloating symptoms in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2009; 7:68–72. [PubMed: 19124113]
- 5). Jiang X, Locke GR, Choung RS, et al. Prevalence and risk factors for abdominal bloating and visible distention: a population-based study. *Gut*. 2008; 57:756–763. [PubMed: 18477677]
- 6). Troncon LE, Bennett RJ, Ahluwalia NK, et al. Abnormal intragastric distribution of food during gastric emptying in functional dyspepsia patients. *Gut*. 1994; 35:327–332. [PubMed: 8150341]
- 7). Agrawal A, Houghton LA, Reilly B, et al. Bloating and distention in irritable bowel syndrome: the role of gastrointestinal transit. *Am J Gastroenterol*. 2009; 104:1998–2004. [PubMed: 19491831]
- 8). Accarino A, Perez F, Azpiroz F, et al. Abdominal distention results from caudo-ventral redistribution of contents. *Gastroenterology*. 2009; 136:1544–1551. [PubMed: 19208364]
- 9). Camilleri M, McKinzie S, Busciglio I, et al. Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2008; 6:772–781. [PubMed: 18456567]
- 10). Agrawal A, Houghton LA, Lea R, et al. Bloating and distention in irritable bowel syndrome: the role of visceral sensation. *Gastroenterology*. 2008; 134:1882–1889. [PubMed: 18455167]
- 11). Tuteja AK, Talley NJ, Joos SK, et al. Abdominal bloating in employed adults: prevalence, risk factors, and association with other bowel disorders. *Am J Gastroenterol*. 2008; 103:1241–1248. [PubMed: 18422817]
- 12). Arts J, Caenepeel P, Verbeke K, et al. Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut*. 2005; 54:455–460. [PubMed: 15753526]
- 13). Brenner DM, Moeller MJ, Chey WD, et al. The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Am J Gastroenterol*. 2009; 104:1033–1049. [PubMed: 19277023]
- 14). Accarino A, Perez F, Azpiroz F, et al. Intestinal gas and bloating: effect of prokinetic stimulation. *Am J Gastroenterol*. 2008; 103:2036–2042. [PubMed: 18802999]
- 15). Tack J, Broekaert D, Fischler B, et al. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. *Gut*. 2006; 55:1095–1103. [PubMed: 16401691]
- 16). Revicki DA, Rentz AM, Tack J, et al. Responsiveness and interpretation of a symptom severity index specific to upper gastrointestinal disorders. *Clin Gastroenterol Hepatol*. 2004; 2:769–777. [PubMed: 15354277]
- 17). De la Loge C, Trudeau E, Marquis P, et al. Cross-cultural development and validation of a patient self-administered questionnaire to assess quality of life in upper gastrointestinal disorders: the PAGI-QOL. *Qual Life Res*. 2004; 13:1751–1762. [PubMed: 15651545]
- 18). Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol*. 2000; 95:1456–1462. [PubMed: 10894578]
- 19). Abell TL, Bernstein RK, Cutts T, et al. Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil*. 2006; 18:263–283. [PubMed: 16553582]
- 20). SAS software, version 9.1 of the SAS system for Windows. SAS Institute, Inc.; Cary, NC: 2002.
- 21). Stata statistical software: release 10. StataCorp.; College Station, TX: 2007.
- 22). Undeland KA, Hausken T, Svebak S, et al. Wide gastric antrum and low vagal tone in patients with diabetes mellitus type 1 compared to patients with functional dyspepsia and healthy individuals. *Dig Dis Sci*. 1996; 41:9–16. [PubMed: 8565773]
- 23). Gaddipati KV, Simonian HP, Kresge KM, et al. Abnormal ghrelin and pancreatic polypeptide responses in gastroparesis. *Dig Dis Sci*. 2006; 51:1339–1346. [PubMed: 16868831]
- 24). Salvioi B, Serra J, Azpiroz F, et al. Origin of gas retention and symptoms in patients with bloating. *Gastroenterology*. 2005; 128:574–579. [PubMed: 15765392]

- 25). Parkman HP, Yates K, Koch K, et al. Dietary intake and nutritional deficiencies in patients with gastroparesis (abstract). *Am J Gastroenterol*. 2009; 103:S55.
- 26). Stanghellini V, Tosetti C, Horowitz M, et al. Predictors of gastroparesis in out-patients with secondary and idiopathic upper gastrointestinal symptoms. *Dig Liver Dis*. 2003; 35:389–396. [PubMed: 12868674]
- 27). Jones KL, Russo A, Stevens JE, et al. Predictors of delayed gastric emptying in diabetes. *Diab Care*. 2001; 24:1264–1269.
- 28). Khayyam U, Sachdeva P, Gomez, et al. Assessment of symptoms during gastric emptying scintigraphy to correlate symptoms to delayed gastric emptying. *Neurogastroenterol Motil*. 2010; 22:539–545. [PubMed: 20082665]
- 29). Lin HC, Van Citters GW, Zhao XT, et al. Fat intolerance depends on rapid gastric emptying. *Dig Dis Sci*. 1999; 44:330–335. [PubMed: 10063919]
- 30). Samsom M, Roelofs JM, Akkermans LM, et al. Proximal gastric motor activity in response to a liquid meal in type 1 diabetes mellitus with autonomic neuropathy. *Dig Dis Sci*. 1998; 43:491–496. [PubMed: 9539642]
- 31). Houghton LA, Fell C, Whorwell PJ, et al. Effect of a second-generation α_2 delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. *Gut*. 2007; 56:1218–1225. [PubMed: 17446306]
- 32). Reddymasu SC, McCallum RW. Small intestinal bacterial overgrowth in gastroparesis: are there any predictors? *J Clin Gastroenterol*. 2010; 44:e8–13. [PubMed: 20027008]
- 33). Qin C, Chen JD, Zhang J, et al. Modulatory effects and afferent pathways of gastric electrical stimulation on rat thoracic spinal neurons receiving input from the stomach. *Neurosci Res*. 2007; 57:29–39. [PubMed: 17046091]
- 34). Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. *Gastroenterology*. 2006; 130:1466–1479. [PubMed: 16678560]
- 35). Sarnelli G, Caenepeel P, Geypens B, et al. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol*. 2003; 98:783–788. [PubMed: 12738456]
- 36). Hasler WL, Wilson L, Parkman HP, et al. Importance of abdominal pain as a symptom in gastroparesis: relation to clinical factors, disease severity, quality of life, gastric retention, and medication use (abstract). *Gastroenterology*. 2010; 138:M2023.

Table 1
RELATION OF GCSI BLOATING SUBSCALE SCORE TO DEMOGRAPHIC VARIABLES

FACTOR	GCSI BLOATING SUBSCALE SCORE 0-1.9 (N=80)			GCSI BLOATING SUBSCALE SCORE 2-3.9 (N=116)			GCSI BLOATING SUBSCALE SCORE ≥4 (N=139)			OVERALL P VALUE	PAIRWISE COMPARISONS		
	N	Mean or %	95% CI	N	Mean or %	95% CI	N	Mean or %	95% CI		P VALUE 0-1.9 vs. 2-3.9	P VALUE 0-1.9 vs. ≥4	P VALUE 2-3.9 vs. ≥4
Age at enrollment (yrs), mean	80	42.5	38.9 – 46.1	116	42.0	39.5 – 44.4	139	43.3	41.3 – 45.4	0.72			
Female gender	54	67.5%	56.1 – 77.6	95	81.9%	73.7 – 88.4	128	92.1%	86.3 – 96.0	<0.0001	0.02	<0.0001	0.02
Hispanic/Latino ethnicity	1	1.3%	0.03 – 6.8	6	5.2%	1.9 – 10.9	6	4.3%	1.6 – 9.2	0.37			
Race	66	83.5%	73.8 – 91.1	98	86.0%	78.6 – 91.9	121	88.3%	82.0 – 93.3	0.89			
	10	12.7%	6.2 – 21.8	12	10.5%	5.5 – 17.4	12	8.8%	4.5 – 14.6				
	3	3.8%	1.8 – 10.6	4	3.5%	0.9 – 8.6	4	2.9%	0.8 – 7.2				
Duration of symptoms	27	33.8%	23.6 – 45.2	27	23.3%	15.9 – 32.0	41	29.5%	22.1 – 37.8	0.59			
	30	37.5%	26.9 – 49.0	48	41.4%	32.3 – 50.9	53	38.1%	30.0 – 46.7				
	23	28.8%	19.2 – 40.0	41	35.3%	26.7 – 44.8	45	32.4%	24.7 – 40.8				
Etiology	30	37.5%	26.9 – 49.0	43	37.1%	28.3 – 46.5	43	30.9%	23.4 – 40.8	0.49			
	50	62.5%	51.0 – 73.1	73	62.9%	53.5 – 71.7	96	69.1%	60.7 – 76.6				
Diabetic subtype	19	63.3%	52.2 – 74.2	24	55.8%	46.5 – 65.2	22	51.2%	43.2 – 60.3	0.61			
	11	36.7%	25.8 – 47.8	19	44.2%	34.8 – 53.5	21	48.8%	40.4 – 57.5				

Data are means or percents and 95% confidence intervals. P values are from chi-square tests or Fisher's exact test for categorical variables and ANOVA for continuous variables.

Table 2
RELATION OF GCSI BLOATING SUBSCALE SCORE TO GASTROPARESIS SEVERITY AND QUALITY OF LIFE

FACTOR	GCSI BLOATING SUBSCALE SCORE 0-1.9 (N=80)			GCSI BLOATING SUBSCALE SCORE 2-3.9 (N=116)			GCSI BLOATING SUBSCALE SCORE ≥4 (N=139)			OVERALL P VALUE	PAIRWISE COMPARISONS		
	N	Mean or %	95% CI	N	Mean or %	95% CI	N	Mean or %	95% CI		P VALUE 0-1.9 vs. 2-3.9	P VALUE 0-1.9 vs. ≥4	P VALUE 2-3.9 vs. ≥4
Investigator-rated severity	Grade 1	16	20.3%	15	13.0%	7.4 – 20.4	10	7.2%	3.5 – 12.8	0.001	0.06	0.02	0.003
	Grade 2	41	51.9%	49	42.6%	33.1 – 51.8	89	64.0%	55.5 – 72.0				
	Grade 3	22	27.9%	51	44.4%	35.6 – 54.3	40	28.8%	21.4 – 37.1				
GCSI score	Nausea and vomiting subscale	80	2.2	116	2.5	2.2 – 2.7	139	2.8	2.5 – 3.0	0.02	0.22	0.006	0.09
	Postprandial fullness subscale	79	2.7	115	3.1	2.9 – 3.2	139	4.0	3.8 – 4.1	<0.0001	0.06	<0.0001	<0.0001
PAGI-QOL score	80	3.1	2.9 – 3.4	116	2.6	2.5 – 2.8	138	1.9	1.8 – 2.1	<0.0001	0.001	<0.0001	<0.0001
SF-36	Physical component	80	35.7	116	34.5	33.3 – 35.7	139	31.6	30.6 – 32.6	<0.0001	0.24	<0.0001	0.0003
	Mental component	80	35.6	116	34.6	33.5 – 35.6	139	32.5	31.7 – 33.4	0.0003	0.24	0.0001	0.003

Data are means or percents and 95% confidence intervals. P values are from chi-square tests or Fisher's exact test for categorical variables and ANOVA for continuous variables.

Table 3
RELATION OF GCSI BLOATING SUBSCALE SCORE TO POTENTIAL PATHOGENIC FACTORS

FACTOR	GCSI BLOATING SUBSCALE SCORE 0-1.9 (N=80)			GCSI BLOATING SUBSCALE SCORE 2-3.9 (N=116)			GCSI BLOATING SUBSCALE SCORE ≥4 (N=139)			OVERALL P VALUE	PAIRWISE COMPARISONS		
	N	Mean or %	95% CI	N	Mean or %	95% CI	N	Mean or %	95% CI		P VALUE 0-1.9 vs. 2-3.9	P VALUE 0-1.9 vs. ≥4	P VALUE 2-3.9 vs. ≥4
Visible distention	0	0%	0.0 – 3.7	64	55.2%	45.7 – 64.4	139	100%	97.9 – 100	<0.0001	<0.0001	<0.0001	<0.0001
PAGI-SYM score	80	2.4	1.9 – 2.8	116	2.8	2.5 – 3.1	139	3.6	3.4 – 3.9	<0.0001	0.10	<0.0001	<0.0001
	80	1.4	1.0 – 1.7	116	1.8	1.5 – 2.1	139	2.8	2.5 – 3.0	<0.0001	0.06	<0.0001	<0.0001
	80	1.7	1.3 – 2.0	115	2.1	1.8 – 2.4	139	2.9	2.6 – 3.2	<0.0001	0.05	<0.0001	0.0005
Constipation	80	1.4	1.1 – 1.8	116	1.9	1.6 – 2.1	139	2.3	2.0 – 2.6	0.002	0.07	0.001	0.05
Diarrhea	80	25.6	24.2 – 27.1	116	27.1	25.6 – 28.7	139	27.7	26.5 – 28.9	0.15			
Body mass index (kg/m ²)	37	46.3%	35.0 – 57.8	58	50.0%	40.6 – 59.4	81	58.3%	49.6 – 66.6	0.18			
Overweight (BMI≥25 kg/m ²)	80	87.4	83.7 – 91.0	116	89.9	85.8 – 94.0	139	91.0	88.1 – 94.0	0.39			
Waist circumference (cm)	80	100.7	97.5 – 103.9	116	101.8	98.5 – 105.2	138	103.9	101.4 – 106.5	0.33			
Hip circumference (cm)	80	0.86	0.85 – 0.88	116	0.88	0.86 – 0.90	138	0.87	0.86 – 0.89	0.62			
Waist to hip ratio	52	65.0%	53.5 – 75.3	69	59.5%	50.0 – 68.5	94	67.6%	59.2 – 75.3	0.37			
Never	17	21.3%	12.9 – 31.8	29	25.0%	17.4 – 33.9	21	15.1%	9.6 – 22.2				
Previous	11	13.8%	7.1 – 23.3	18	15.5%	9.5 – 23.4	24	17.3%	11.4 – 24.6				
Current	79	80.2	76.7 – 83.7	115	82.3	80.0 – 84.7	139	81.7	79.4 – 84.0	0.57			
Smoking history													
Gastric retention (%)													

FACTOR	GCSI BLOATING SUBSCALE SCORE 0-1.9 (N=80)				GCSI BLOATING SUBSCALE SCORE 2-3.9 (N=116)				GCSI BLOATING SUBSCALE SCORE ≥4 (N=139)			PAIRWISE COMPARISONS		
	N	Mean or %	95% CI		N	Mean or %	95% CI		N	Mean or %	95% CI	OVERALL P VALUE	P VALUE 0-1.9 vs. 2-3.9	P VALUE 0-1.9 vs ≥4
2 hours	80	64.1	59.7 – 68.5		116	64.1	60.7 – 67.6		139	65.5	62.6 – 68.5	0.79		
	79	34.7	28.6 – 40.8		116	33.4	29.5 – 37.4		139	30.9	27.3 – 34.6	0.47		

Data are means or percents and 95% confidence intervals. P values are from chi-square tests or Fisher's exact test for categorical variables and ANOVA for continuous variables.

Table 4

RELATION OF GCSI BLOATING SUBSCALE SCORE TO MEDICATION USE

		GCSI BLOATING SUBSCALE SCORE 0-1.9 (N=80)			GCSI BLOATING SUBSCALE SCORE 2-3.9 (N=116)			GCSI BLOATING SUBSCALE SCORE ≥4 (N=139)			OVERALL P VALUE	PAIRWISE COMPARISONS		
		N	%	95% CI	N	%	95% CI	N	%	95% CI		P VALUE 0-1.9 vs. 2-3.9	P VALUE 0-1.9 vs ≥4	P VALUE 2-3.9 vs. ≥4
MEDICATION CLASS	Prokinetic	46	57.5%	45.9 – 68.5	60	51.7%	42.3 – 61.1	74	53.2%	44.6 – 61.7	0.72			
	Antiemetic	41	51.3%	39.8 – 62.6	76	65.5%	56.1 – 74.1	92	66.2%	57.7 – 74.0	0.06	0.05	0.03	0.91
	Opiate	28	35.0%	24.7 – 46.5	52	44.8%	35.6 – 54.3	64	46.4%	37.5 – 54.7	0.24			
	Probiotic	1	2.0%	0.3 – 8.7	1	1.3%	0.2 – 6.1	8	9.8%	5.6 – 16.3	0.03	1.0	0.15	0.03
	Neuropathic pain modulator	14	17.5%	9.9 – 27.6	19	16.4%	10.2 – 24.4	33	23.7%	16.9 – 31.7	0.30			
	Antidepressant	22	27.5%	18.1 – 38.6	44	37.9%	29.1 – 47.4	58	41.7%	33.4 – 50.4	0.11			
Anti- depressant class	NERI	18	90.0%	81.2 – 95.6	26	60.5%	50.8 – 69.3	37	75.5%	67.5 – 82.4	0.045	0.02	0.32	0.18
	Non-NERI	2	10.0%	4.4 – 18.8	17	39.5%	30.7 – 49.2	12	24.5%	17.6 – 32.5				

Data are percents and 95% confidence intervals. P-values from chi-square tests or Fisher's exact test.

NERI=Norepinephrine reuptake inhibitor

Table 5

PREDICTORS OF HIGHER GCSI BLOATING SUBSCALE SCORE FROM ORDINAL LOGISTIC REGRESSION ANALYSIS

FACTOR	ODDS RATIO	95% CONFIDENCE INTERVAL	P VALUE
Female gender	3.12	1.70 – 5.73	<0.0001
Lower abdominal pain severity from PAGI-SYM	1.38	1.18 – 1.61	<0.0001
Constipation severity from PAGI-SYM	1.17	1.03 – 1.34	0.02
PAGI-QOL Score	0.40	0.29 – 0.54	<0.0001
SF-36 mental component score	1.02	1.00 – 1.03	0.009
Overweight (BMI $\geq$ 25 kg/m ²)	1.62	1.02 – 2.55	0.04

Model adjusted for age, gender, and race.