High body mass alters colonic sensory-motor function and transit in humans

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In the case of obesity, abdominal pain and diarrhea are common symptoms suggestive of gastrointestinal dysfunction and have shown increased frequency of bowel and diarrhea in overweight and obese subjects (12, 42, 43). However, it is difficult to elucidate whether this increased frequency of symptoms observed among subjects with increased body mass is related to 1) obesity per se, such as alteration in visceral sensation or motor function, 2) environmental factors, such as the intake of an excessive amount of food with high carbohydrate and fat content that may induce osmotically driven diarrhea (29), 3) effects of medications, such as lipase inhibitors or metformin, or 4) comorbidities associated with obesity, such as cholelithiasis or even intestinal angina secondary to the atherosclerosis associated with obesity.

The aim of this study was to assess the effect of body mass on colonic motor and sensory functions and on gastrointestinal and colonic transit times, measured in controlled conditions with validated methods in overweight and obese subjects who were otherwise healthy and free of medications that are known to alter motor or sensory function in the gastrointestinal tract.

MATERIALS AND METHODS

Data Source

Data used in this study are derived from a database that includes underweight, normal weight, overweight, and obese, but otherwise healthy, subjects who participated in several clinical trials that involved assessment of colonic tone and perception of colonic distensions and/or assessment of gastrointestinal transit with the use of standardized protocols (5, 6, 10, 15, 16, 23). Only data obtained before drug treatment or from participants receiving a nonactive placebo in a parallel group design study (never receiving potentially active medications in the study) were used for the present analyses. These studies were performed and analyzed by the same investigators (I. Busciglio and D. D. Burton for barostat and transit studies, respectively) at the General Clinical Research Center at Mayo Clinic, Rochester, Minnesota from September 2001 to May 2006.

Assessment of Colonic Motor and Sensory Function

Colonic motor and sensory function was assessed using the barostat technique as described previously (6, 10). All participants received a standard oral colonic lavage solution on the basis of polyethylene glycol and electrolytes over the prior 24 h. They attended the research center at around 7 AM after having fasted for 8 h. The combined

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barostat balloon and multilumen manometric assembly was placed by one investigator (M. Camilleri) in the left colon via unsedated flexible sigmoidoscopy and with the aid of a Teflon-coated guide wire and fluoroscopy. The position of the barostat tube was in the descending (>75%) or the junction of the sigmoid and descending colon. There were no differences in mean differences for all parameters analyzed depending on location of the balloon, and, hence, all the data are presented as one set.

Colonic wall compliance and resting tone, thresholds for first perception of gas and pain, and the intensity of perception during phasic distensions were measured using the same protocol before receiving any drug in all included studies and were used for the present analysis. We have also analyzed the postprandial colonic contractile response assessed in participants who were randomized to receive nonactive placebo in clinical trials.

Briefly, the operating pressure (OP) was set at 2 mmHg above the minimum distending pressure (the pressure at which respiratory excursions during deep inspiration are accompanied by a noticeable deflection in the balloon volume). After a conditioning distention (25) and an equilibration period at the OP, we measured colonic compliance. Compliance was assessed as the volume response to 4-mmHg increments in intraballoon pressures from 0 to 44 mmHg. During assessment of compliance, participants were asked to report first perception of gas and pain. After compliance measurement, resting colonic tone was assessed at the OP, followed by phasic balloon distensions of 8, 16, 24, and 32 mmHg above the OP, performed in random order. During phasic distensions, participants were asked to rate the intensity of gas and pain perception using 100-mm visual analog scales (VASs) (6, 10).

Postprandial colonic contraction was assessed by measuring colonic volume 60 min after ingestion of a 750-ml milkshake containing 1,000 Kcal (53% fat, 35% carbohydrate, and 12% protein).

Levels of arousal and stress were assessed before assessment of colonic sensation in all studies. These assessments were included since levels of arousal and stress just before the conduct of the sensation measurements have been shown to influence perception of colonic distention (17). Thus levels of arousal and stress were assessed using four 100-mm horizontal VASs with the words 1) tired-energetic, 2) active-drowsy, 3) peaceful-tense, and 4) worried-relaxed anchored the left and right ends of each line, respectively (17).

Assessment of Gastrointestinal Transit by Scintigraphy

Gastric emptying and small bowel and colonic transit of solids were assessed using scintigraphy and the same protocol (6, 10). Only data from participants receiving a nonactive placebo were used for the present analysis.

Briefly, after an overnight fast, participants ingested an 111In-charcoal capsule coated with a pH-sensitive methacrylate that dissolves when it reaches the colon (4), allowing colonic transit measurement with a gamma camera. After the capsule emptied from the stomach, participants ingested two scrambled eggs labeled with 99mTc-sulfur colloid with one slice of whole wheat bread and one glass of whole milk (total 300 Kcal) to measure gastric emptying and the colonic filling at 6 h postmeal as a measurement of small bowel transit. Subjects ingested standardized meals for lunch and dinner at 4 and 8 h after the radiolabeled meal. Anterior and posterior abdominal images of 2-min duration were obtained every hour for the first 8 h and at 24, 32, and 48 h.

Data Analysis

BMI. The data on weight and height obtained at the study site were used to calculate BMI, weight in kilograms divided by the square of height in meters (kg/m²). BMI was entered as a continuous variable in all statistical analysis. However, for the purpose of data display, participants were categorized on the basis of BMI as underweight (<18.5 kg/m²), normal (≥18.5 and <25 kg/m²), overweight (≥25 and <30 kg/m²), and obese (≥30 kg/m²), as defined by the National Heart, Lung, and Blood Institute and the World Health Organization (34a, 38). Colonic tone and compliance. Colonic tone, intraballoon volume at the OP, was calculated by averaging the colonic volume throughout the periods of tone assessment, as in previous studies (2, 3, 48). Postprandial change in tone was calculated as the difference between postprandial colonic volume and colonic volume before meal (48).

Compliance was summarized by the pressure corresponding to 50% of maximum volume (P0.5/Pmax).

Gastrointestinal transit. Gastric emptying was summarized by proportion of 99mTc emptied from the stomach at 4 h and orocecal transit as the colonic filling with 99mTc at 6 h. Colonic transit was summarized by the geometric center (GC) at 24 h, which is calculated by multiplying the proportion of 111In 24 h after administration in each colonic region, ascending (AC), transverse (TC), descending (DC), rectosigmoid (RS), and stool, by its weighting factor, as indicated in the formula: GC = %AC × 1 + %TC × 2 + %DC × 3 + %RS × 4 + %stool × 5/100.

A low GC value, therefore, indicates slow transit, and a high GC, a rapid colonic transit. These have been shown in previous studies to be the most robust endpoints among scintigraphic transit measurements (8).

Statistical Analysis

The effects of BMI on the different parameters assessed, except for sensation thresholds, were explored using multiple (linear) regression with age, sex differences, and height as covariates to adjust for potential confounding. The effect of BMI on pressure thresholds for first perception of gas and pain was assessed using proportional hazard regression to account for censored values (i.e., maximum pressure level reached without the sensation of interest reported). Arousal and stress scores as well as colonic volumes during distensions were included also as covariates in analyses of perception to colonic distensions. The arousal and stress scores were not included as covariates in appraisal of tone or compliance since they were not significant covariates in the assessment of compliance or tone in these studies or in multiple previous studies already published. All numerical variables including BMI were included as continuous in all the analysis. All tests were two-sided, and the significance level was set at 5%. Since there were 165 participants, the logistic regression and covariance analyses included >10 participants for each factor considered in the analysis of colonic sensation and tone. Similarly, there were >10 participants for each of the covariates (sex, height, age, and BMI) appraised among the 72 participants who underwent colonic transit.

Descriptive statistics are presented as the regression means ± SE, unless otherwise stated.

RESULTS

Study Population

Colonic sensory-motor analyses. 165 subjects (87 women and 78 men) underwent assessment of colonic motor and sensory function. Median age was 28 years [interquartile range (IQR): 23–37, range: 18–63], and median BMI was 25 kg/m² (IQR: 22–28.5, range: 17–44). The number of subjects in each BMI category is shown in Table 1.

Transit analyses. 72 subjects (41 men and 31 women) completed gastrointestinal transit measurements and received placebo treatment. Median age was 29.5 yr (IQR: 24–36, range: 18–62), and median BMI was 25.5 kg/m² (IQR: 23–28, range: 17–40).

The number of subjects in each BMI category is shown in Table 1.
Participants in gut transit response was not associated with BMI (P = 0.020), three variables that affected colonic resting tone (Fig. 2). Heavier participants tended to have lower colonic resting compliance in men and women although this influence appears to be stronger in women (Fig. 1B).

Colonic resting tone. Colonic resting tone (colonic volume at the OP) was not significantly influenced by BMI (P = 0.06). Heavier participants tended to have lower colonic resting volumes (increased tone) although this did not reach statistical significance after adjusting for OP, which was higher with increased BMI (P < 0.0001), age (P = 0.018), and sex (P = 0.020), three variables that affected colonic resting tone (Fig. 2).

Colonic contractile response to feeding. Colonic contractile response was not associated with BMI (P = 0.72) even after adjusting for preprandial colonic tone (P = 0.0007), age (P = 0.98), or sex (P = 0.79).

Sensory ratings in response to random order colonic distensions and sensory thresholds. As anticipated from prior work, both pain and gas VAS scores were influenced, besides BMI, by baseline arousal-stress levels (P = 0.0007 for pain and P = 0.004 for gas) and age (P = 0.02 for pain and P = 0.037 for gas). Therefore, these were included as covariates in the analysis of the effect of BMI on colonic sensation.

BMI was significantly associated with pain VAS scores during colonic distensions (P = 0.0166) as well as with the pressure threshold for first perception of pain (P = 0.042), adjusting for age, sex, colonic volume during distensions, and arousal-stress levels at the time of distensions. Thus subjects with higher BMI reported lower pain ratings during colonic distensions (Fig. 3, top) and had higher pressure thresholds for reporting first perception of pain (Fig. 4).

We did not observe a significant association of BMI and gas sensation VAS scores (P = 0.07, Fig. 3, top) or pressure thresholds for first perception of gas (P = 0.64).

The effect of BMI on pain did not significantly differ between sexes (P = 0.5 for the interaction term BMI*gender included in the regression model). Thus pain scores were lower with higher BMI, and the effect of higher BMI was not significantly different in men and women (Fig. 3, bottom).

Gastrointestinal and Colonic Transit

There was no significant association of BMI with gastric emptying and small bowel transit (P = 0.53 and P = 0.19, respectively). However, colonic transit as measured by GC at 24 h tended to be faster in participants who weighed >30 kg/m² (P = 0.003 unadjusted, P = 0.08 adjusted by sex, Table 2).

### Table 1. Distribution of BMI overall and separated by sexes

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>Total</th>
<th>Males (N = 165)</th>
<th>Females (N = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5 &lt; 25 N(%)</td>
<td>56 (64%)</td>
<td>29 (37%)</td>
<td>27 (38%)</td>
</tr>
<tr>
<td>25–30 N(%)</td>
<td>55 (33%)</td>
<td>27 (34%)</td>
<td>28 (34%)</td>
</tr>
<tr>
<td>&gt;30 N(%)</td>
<td>25 (15%)</td>
<td>10 (32%)</td>
<td>15 (19%)</td>
</tr>
</tbody>
</table>

BMI, body mass index.

Colonic Sensory-Motor Function

Colonic compliance was significantly associated by BMI [P = 0.0006, adjusted by age (P = 0.053) and gender (P = 0.0253)]. Hence, in heavier subjects, the P1/2 (the pressure at half the maximal volume) was higher and, thus the pressure/volume curve was shifted to the right (decreased colonic compliance) compared with lower weight subjects (Fig. 1A). Height (P = 0.74) did not have any effect on compliance curves. We also explored whether the observed effect of BMI on compliance (P1/2) was similar for women and men by adding an interaction term (BMI × sex) in the regression model. There was no significant interaction (P = 0.54) between BMI and sex. Thus there were no significant differences in the observed influence of BMI on colonic compliance in men and women although this influence appears to be stronger in women (Fig. 1B).

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DISCUSSION

In this study we have shown that perception of pain in response to experimental colonic pressure-based distensions decreases as BMI increases and that colonic volumes in response to pressure distensions were lower (suggesting decreased compliance) with higher BMI. We also observed a trend to faster colonic transit with increased BMI. These data provide some insights relative to the observed increase in the prevalence of diarrhea in association with obesity in epidemiological studies. However, the present studies do not provide a clear explanation for the reports of abdominal pain in obesity in epidemiological studies.

The lower gut sensation of pain during distension (not gas) is consistent with the reduced upper gastrointestinal tract sensation in obesity (see Introduction for details). The present data suggest that, after controlling for other factors such as age, sex, intracolonic balloon volume, or arousal-stress levels, the experimental pressure-based distensions elicited lower pain intensity in people with increased body mass. The reduced sensation ratings for pain were confirmed by the observation that they also had a higher pressure threshold to report pain. These differences in pain perception seem unrelated to differences in colonic compliance since compliance was reduced in subjects with increased body mass. Typically, one would expect that reduced compliance would result in increased perception, conceivably because of activation at lower pressures of the tension receptors that lead to heightened visceral perception (13). An important precaution in our studies appraising colonic thresholds and sensory ratings was the inclusion of volume of the balloon at the specified pressure distensions as a covariate in the analyses. Hence, we avoided a potential bias in the assessment of sensation by starting the assessment of thresholds from 0 mmHg, and we “corrected” for the observed differences in compliance across groups by including the volume of the balloon at the standardized distension pressures above baseline OP.

The mechanism for increased body mass to be associated with decreased perception of pressure-based distensions in the...
face of decreased colon compliance is unclear. One hypothesis is that there was decreased “distention” of the colonic wall in response to a standard pressure because of pericolonic or abdominal wall fat. It is conceivable that this might actually lead to reduced activation of stretch receptors in the colonic wall. However, this hypothesis is not consistent with our data since, even with controlling for intracolonic volumes as covariates (which may have been influenced by visceral or abdominal wall fat), increased body mass was still independently associated with decreased pain ratings in response to each pressure distention and with higher pressure thresholds for perception of pain. Other factors, including those that might independently affect stretch or tension receptors, need to be further investigated to understand the mechanisms for decreased perception observed in subjects with increased body mass.

There is evidence that impaired sensory nerve function occurs among subjects with increased body mass although most studies deal with somatic rather than visceral sensation (9, 55). Insulin resistance may play a role in the decreased sensation observed in obese subjects. Thus, in one study of somatic sensation, warm and cold perception thresholds, reflecting C-fibers and Aδ-fibers, respectively, were increased in normoglycemic obese subjects with reduced insulin sensitivity compared with controls with normal insulin sensitivity (9). Our study included healthy subjects with normal basic laboratory tests including normal fasting blood glucose. However, we cannot exclude subclinical insulin resistance, and, hence, it is conceivable that insulin resistance associated with increased body mass may partly explain the decreased colonic sensation observed in our subjects.

It has also been suggested that an increased activity of the endogenous opiate system in obese subjects might play a role in the lowered sensation observed in response to electrical cutaneous stimulation (54). Future studies may explore the role of endogenous opiate mechanisms in subjects with increased body mass. Although there is no evidence of increased endogenous opiate levels in obesity, it is possible that, as with upregulation of central opiate receptors in the control of appetite in obesity (34), an upregulation of peripheral or central opiate receptors involved in sensation may change visceral sensation in obesity.

Autonomic factors may conceivably influence sensation, particularly in view of differing levels of arousal and stress in the subjects. Even if BMI is associated with differences in autonomic function, the analysis of covariance accounted for differences in the potential effects of arousal and stress. Overall, the present studies suggest that the increased prevalence of abdominal pain in obesity cannot be explained by the decreased perception of pain to colonic distension, and, therefore, other mechanisms have to be considered, particularly central mechanisms. Given the substantial literature on differences in the central regulation of eating behavior in obese subjects, including recent neuroimaging studies showing altered activation of cortical brain areas involved in satiety control (19, 20, 28, 32), it is conceivable that there may be central inhibitory modulation of afferent signals from the gastrointestinal tract. Clearly, further studies should address the role of central mechanisms in the development of abdominal pain in obesity.

There is, however, a potential pitfall in the assessment of sensation in this study that evaluated a convenience sample of participants participating in clinical trials, even though they were randomized to placebo. Thus participant perceptions could have been altered by placebo and influenced sensory ratings and conceivably even motor physiology though one would not expect those changes to vary by BMI. Therefore, it may be necessary to evaluate the same functions in those not receiving placebo to ensure that a placebo effect is excluded. However, this large database in people without gastrointestinal symptoms represents a unique opportunity to commence to explore the study hypothesis, which we perceive to be relevant, given the epidemiological evidence of abdominal pain and diarrhea in obesity and the complexity of the validated studies conducted.

It is unclear whether the observed change in colon compliance represents a true or apparent increased stiffness of the colonic wall. As stated above, the presence of intraabdominal fat could limit colon expansion in response to standard application of an intraluminal distension pressure. Increased stiffness has also been described in the vascular system and heart of subjects with increased body mass (30, 41, 49). However, it seems that factors other than the mechanical effect of the presence of fat may contribute to the increased stiffness observed in blood vessels and cardiac walls. For instance, it has been suggested that hyperinsulinemia, which promotes sodium reabsorption (40, 44), stimulates the sympathetic nervous system (36, 52), and induces smooth muscle cell growth (1), might contribute to increased vascular stiffness. On the other hand, insulin bound to its receptor induces nitric oxide release from endothelium, facilitating vascular wall relaxation and decreasing blood pressure (33). In obesity, a state of insulin resistance, the effects of insulin bound to its receptor may be reduced, decreasing vascular wall relaxation (33). Finally, leptin, which is increased with increased fat mass, might mediate increased vascular wall stiffness associated with obesity since it promotes smooth muscle cell proliferation (35), even independently of body mass (39).

In summary, one could pose the hypothesis that, as in the vascular system, biological factors operating in obesity may lead to a state of smooth cell proliferation and/or lack of smooth muscle relaxation, and that result could increase stiffness of the colonic wall. Future studies will be needed to clarify the underlying mechanisms of the decreased colonic wall compliance observed in our study.

A third observation of the present study pertains to gastrointestinal and colonic transit. There was no significant association of BMI with gastric emptying and small bowel transit relative to healthy adults, after controlling for age, height, and sex. Effects of body mass on gastric emptying have already been evaluated previously, with inconclusive results. Some studies have shown a more rapid gastric emptying in obese subjects compared with lean controls (24, 45, 50, 51, 53),

Table 2. Transit parameters by BMI

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>18.5 &lt; 25 (%)</th>
<th>25–30 (%)</th>
<th>&gt;30 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC 4 h (% emptied)</td>
<td>96±1</td>
<td>95±1.5</td>
<td>95±2.3</td>
<td>NS</td>
</tr>
<tr>
<td>CF 6 h (% in colon)</td>
<td>47±5</td>
<td>41±6</td>
<td>58±9</td>
<td>NS</td>
</tr>
<tr>
<td>Colonic GC 24 h</td>
<td>2.4±0.2</td>
<td>2.5±0.2</td>
<td>2.9±0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. CF, colonic filling; GC, geometric center; NS, not significant.
whereas others have reported normal (18) or even slow (26, 27, 31, 37) gastric emptying in obese subjects.

On the other hand, we did observe an overall acceleration of colonic transit with increasing BMI ($P = 0.003$), which was significantly influenced by sex, such that, after adjustment, the observation was only borderline significant ($P = 0.08$). This clearly requires further study, given the sample size ($n = 72$) of the present study. However, this accelerated colonic transit may contribute to the increased frequency of diarrhea reported in obese participants in population-based studies.

In conclusion, BMI over 25 kg/m$^2$ is associated with decreased colonic compliance, decreased colonic sensation, and possibly accelerated colonic transit in those over BMI 30 kg/m$^2$. These data suggest that factors other than colonic function such asafferent, spinal, or central mechanisms modulating pain perception might contribute to the observed increased prevalence of abdominal pain in obesity. This will require further study.

REFERENCES