In Vivo Imaging of Intragastric Gelation and Its Effect on Satiety in Humans

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ABSTRACT Previous studies indicated that physical characteristics of food influence satiety, but the relative importance of the oral, gastric, and intestinal behaviors of the food is unclear. The aim of this study was to investigate the satiating effects of 2 types of alginates, which gel weakly or strongly on exposure to acid, compared with guar gum whose viscosity is unaffected by acid. Subjects (n = 12; 3 men, 9 women) ingested a 325-mL sweetened, milk-based meal replacer beverage on 4 separate occasions, either alone as a control or including 1% by weight alginate or guar gum. Intragastric gelling, gastric emptying, and meal dilution were assessed by serial MRI while satiety was recorded for 4 h. MR images showed that all of the meals became heterogeneous in the stomach except for guar, which remained homogeneous. The alginate meals formed lumps in the stomach, with the strong-gelling alginate producing the largest volume. Although gastric emptying was similar for all 4 meals, the sense of fullness at the same gastric volume was significantly greater for all 3 viscous meals than for the control. Compared with the control meal, the strong-gelling alginate (P = 0.031) and guar (P = 0.041) meals increased fullness at 115 min, and the strong-gelling alginate decreased hunger by the 115-min (P = 0.041) and 240-min (P = 0.041) time points. Agents that gel on contact with acid may be useful additions to weight-reducing diets. We hypothesize that this effect is due to distension in the gastric antrum and/or altered transport of nutrients to the small intestine in the lumps.


 KEY WORDS: • satiety • MRI • intragastric gelling • humans

Eating a meal induces a sense of fullness, generally described as satiation. This removes the feeling of hunger and reduces the desire to eat further. Enhancing satiation may provide a method of controlling the desire to overeat, daily food intake and, ultimately, body weight. Satiety signals differ as the meal moves through the gut but include oral (taste and texture), gastric (distension and emptying), and intestinal (distension and nutrient absorption) factors (1). A number of studies showed that fiber-rich foods can increase the feelings of satiety and decrease short-term food intake (2–5). Increased meal viscosity is associated with delayed gastric emptying (6,7) and increased satiety (8–11). However, the literature contains contradictory results, which might be explained by differences in the fiber type used. It is now recognized that it is not the fiber itself, but its physicochemical properties (e.g., viscosity), particularly under the conditions found in the gastrointestinal (GI) tract, that determine the effect on satiety. Therefore monitoring the nature of food inside the stomach, rather than only its in vitro properties, will improve our insight into gut-derived sensations.

Recent work using MRI (10,12,13) allowed unique, non-invasive measurements of both the viscosity of the ingested meal and gastric function in vivo (10,14). This technology showed that increasing the viscosity of nonnutrient meals delays gastric emptying, increases satiety, and decreases hunger. However, the relation between meal viscosity and satiety remains poorly understood. This is partly because the physical properties of the food within the GI tract may differ from the properties of the food as it is initially ingested. Furthermore, it is not clear whether the viscosity of the meal in the mouth or the viscosity within the GI tract produces these effects.

Several human studies indicated that meals containing solids typically have a greater effect on satiety than liquid meals of equivalent size and energy content (15–19). Part of this effect can be explained by the slower gastric emptying of solid meals. In addition, solid-containing meals were also found to distend the antrum, which may signal increased satiety via tension receptors (20). Unfortunately, highly viscous beverages or beverages containing unchewed solids are unpalatable and cannot provide a feasible method for weight control. An alternative approach would be to use a meal whose viscosity increases markedly on entering the stomach by using a solution that will gel on contact with the gastric acid.
Guar gum is a soluble galactomannan (21) derived from the Indian cluster bean [Cyamopsis tetragonoloba (L) Taub, and other varieties]. On hydration, solutions are formed whose viscosity depends upon the concentration and molecular weight of the guar gum (22). As a neutral polysaccharide, it is generally unaffected by pH changes or increases in other ionic species (23). Therefore, the viscosity of guar gum solutions should be unaffected by gastric pH, although some reduction will occur due to dilution by gastric secretions.

Alginates are linear copolymers composed of 2 monomeric units, $\beta$-1–4-linked $\alpha$-mannuronic acid (M) and $\alpha$-1–4-linked guluronic acid (G). They are used industrially for their ability to retain water and for their gelling, viscosifying, and stabilizing properties. Alginates form gels in the presence of multivalent cations such as $\text{Ca}^{2+}$ (24,25). Alginates rich in G residues can form stronger gels than those poor in G residues; gel strength may be important in influencing gastric emptying, gel breakdown, and delivery of nutrients to the small intestine. In addition to ionic gels, alginates can form acid gels at a pH below the pK_a value of the uronic acid residues (26,27). The formation and persistence of the ionic and/or acid alginate gels in vivo in the gastric environment will depend upon the physiologic conditions, e.g., rate of acidification, ionic concentration, and mixing. The nature of the gels formed will also depend on the presence of other biopolymers (e.g., proteins or other polysaccharides), which may cause dissolution.

We hypothesize that controlled formation of gelled biopolymer networks using the natural ionic or pH conditions within the human GI tract may offer an approach to controlling satiety in vivo without using unpalatable high-viscosity meals. However, if this hypothesis is to be tested properly, it is necessary to monitor the formation of any gelled biopolymers in vivo. NMR spectroscopy studies of the gelation process in vitro (28–30) showed that the water proton transverse relaxation rate ($T_2^{-1}$) increases on gelation and with increasing alginate concentration. Inherently $T_2$-weighted echo planar images (EPI) offer a potential method with which to observe biopolymers gelling in the stomach in vivo over time.

The aim of this study was to assess the effects of ingestion of viscous solutions and solutions that form solid gel particles in the gastric lumen as a means of controlling gastric emptying, gel breakdown, and the sense of satiety. The different biopolymers investigated were as follows: guar gum and 2 different alginates, one forming a weak gel (low G), and the other a strong gel (high G), all in a sweetened, milk-based meal replacement beverage. Acidification of the milk releases $\text{Ca}^{2+}$ from the milk micelles and causes the alginate to form ionic gels. Similarly, at pH levels below the pK_a of the uronic acid residues, the alginates form acid gels. Gastric emptying, gastric dilution, and meal characterization were studied in vivo using the MRI technique of EPI. Volumes and characteristics of gelled alginate were also investigated using the EPI data.

**SUBJECTS AND METHODS**

**Test meals.** Four test meals were investigated in this study. The control drink (Control) was a sugar-sweetened, vanilla-flavored, milk-based beverage with an energy content of 921 kJ/325 mL per serving (3 g fat, 10 g protein, 35 g sugar). The other meals (weak-gelling alginate, strong-gelling alginate, and viscous guar) were formed by the addition of 1% by weight of the appropriate biopolymer to the control meal, as shown in Table 1. The viscosities of the meals containing biopolymers were designed to be closely matched to within an order of magnitude at all shear rates. The control and guar meals were prepared before the start of the in vivo study and stored in sterile bags. These meals were prepared at 60°C while mixing with a high shear mixer at 1250 rpm for 8 min. For the guar meal, the mixture was stirred at 60°C for an additional 15 min. The solutions were then sterilized via ultrahot treatment. The weak-gelling and strong-gelling alginate meals could not be made in advance of the study because there was sufficient calcium in the control meal to solidify these alginate meals over a 24-h period. Therefore, these 2 meals were prepared the morning of the study by mixing the alginate with the control meal using a magnetic stirrer, and heating the resulting solution to 80°C. This temperature was maintained for 30 min to allow complete hydration of the biopolymer, before cooling to 37°C, which took an additional 45 min.

**In vitro study of test meals.** The variation in $T_2^{-1}$ of the test meals with acid dilution was investigated at 37°C. For certain model meals (e.g., dietary fiber in water), $T_2^{-1}$ can indicate the amount of dilution and subsequent change in viscosity (14).

An in vitro dilution experiment with 0.1 mol/L HCl and water was conducted on the control and guar meals to determine whether viscosity and $T_2^{-1}$ measurements could be correlated. $T_2^{-1}$ was measured using a custom-built 0.5-T MRI scanner at the University of Nottingham with a Marconi (S.M.I.S.) console. The $T_2^{-1}$ relaxation rate was measured from images acquired using a Hahn single spin-echo EPI MBEST (31) sequence repeated for 10 echo times between 80 and 1000 ms. The temperature was maintained at 37°C during the measurement by pumping water from a water bath through a local reservoir containing the samples in the magnet. The data were fitted using a weighted linear fit (32) with a look-up table to correct for noise in the modulus data (33). Viscosity was measured using a Paar Physica UDS 200 Rheometer (Paar Scientific) using a roughened concentric cylinder (1.9-mm gap). Viscosity was determined by incrementally increasing the shear stress (0.1–100 Pa) and maintaining the temperature at 37°C using a temperature-controlled water bath. Viscosity-shear rate flow curves were generated within $\pm$7 decades of shear, $\sim10^{-4}$ to $10^4$ s$^{-1}$, depending on sample properties. Zero shear rate viscosity, $\eta_0$, was calculated using the Cross equation (34), which is often used to describe the shear-thinning behavior of random coil polysaccharide solutions (35,36). The weak- and strong-gelling alginate meals were not included in the acid dilution experiment due to the heterogeneity of the alginate systems on acidification; fast acidification of the samples resulted in precipitation and/or gelation of the biopolymers and sedimentation of this phase.

An in vitro measure of the gel strength of the test meals under relevant GI conditions was carried out. The control, weak- and strong-gelling alginate meals were acidified by mixing 14% by weight glucono-δ-lactone (GDL) on a magnetic stirrer at 37°C and then pouring the solution into lubricated Teflon molds. The samples were incubated at 37°C for 2 h (pH 2.0) and the resultant gel was then removed from the molds. Flat-plate compression tests with an Instron Universal Testing Machine were undertaken using a 10-N load cell and a crosshead speed of 10 mm/min.

**Voluteers.** This protocol was approved by the University of Nottingham Medical School Ethics Committee, and volunteers gave informed written consent before the experiments. Healthy volunteers ($n = 12$; 3 men, 9 women; mean age = 24 y, range = 19–29 y, mean BMI = 22 kg/m$^2$, range = 19–25 kg/m$^2$) were recruited from the University campus population, to take part in the in vivo study. All volunteers had no history of gastrointestinal disease, had not smoked for the previous 12 mo, and were suitable for MRI scanning. The volunteers fasted overnight, abstained from alcohol for 24 h and caffeine and strenuous exercise for 18 h before the study start time.

**TABLE 1**

<table>
<thead>
<tr>
<th>Meal name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Control drink (milk-based meal replacer)</td>
</tr>
<tr>
<td>Weak alginate</td>
<td>Control drink + 1% Manucol DM (−40% G)</td>
</tr>
<tr>
<td>Strong alginate</td>
<td>Control drink + 1% Manugel DMB (−70% G)</td>
</tr>
<tr>
<td>Guar</td>
<td>Control drink + 1% Vidogum GH200</td>
</tr>
</tbody>
</table>

1 ISP Alginates (U.K.) Ltd.
2 Unipektin AG.
Volunteers were allowed a small cup of water on the morning of the study if it was consumed >1 h before arriving at the test center.

**Protocol.** The 4 test meals (Table 1) were randomized according to the Latin-square procedure to equalize any order effects. All meals were 325 mL in volume, served at 37°C, and consumed within 10 min.Serial MRI was then conducted over the subsequent 2-h period. The in vivo study protocol is summarized in Table 2. Two hours after the test meal ingestion, volunteers were given a drink of 500 mL of water at 37°C to determine whether any solid components of the meal remained undetected in the stomach (e.g., clumped on lining or folds or in the antrum). The water refill was used to regain image contrast in the stomach of any remaining solid components of the meal. This was relevant only for the weak- and strong-gelling alginate meals; however, for consistent interpretation of the satiety questionnaires, the procedure was carried out for all meals. Satiety was assessed at 15- or 20-min intervals during MRI scanning, and at 15-min intervals after the scanning period up to 240 min. All scanning was performed using the MRI system described for the in vitro work.

**Gastric emptying.** To determine gastric emptying times, the total meal volumes were measured in vivo, at regular intervals (Table 2) using the multislice EPI MBEST (31) pulse sequence to minimize motion. For consistency, all volumes were measured by one operator (C.T.). In vivo MR data were analyzed one volunteer at a time to allow the operator to gain familiarity with the volunteer’s anatomy. The operator was unaware of the biopolymer type because meals were coded A–D. Gastric emptying was calculated using the methods described by Marciani et al. (10).

**Relaxation rates.** The $T_2^{-1}$ of the meal in vivo was calculated at different time points (Table 2) using the method described in the in vitro section. If different phases of the meal existed (i.e., apparently different time points (Table 2) using the method described in the in vitro section). If different phases of the meal existed (i.e., apparently different time points (Table 2) using the method described in the in vitro section), these were identified systematically array of test points and counting the fraction of points in the region of interest. Grid points were set 5 pixels apart on each image for this study; thus, each point covered a region of 25 pixels (~2.3 mL volume). A “lump classification” was devised; lumps were categorized into solid-filled lumps (whose appearance on the MR images was dark throughout the region) and liquid-filled lumps (whose appearance on the MR images was a very dark thin outer layer with a less intense central region) (Fig. 1). These 2 categories were then split into large and small, where the dividing volume was 2.25 mL (a 15 mm × 15 mm region, 4 × 6 pixels on the image). The classification was carried out at 2 time points, 40 min after ingestion and after the water refill, at 125 min.

**Satiety questionnaire.** At regular intervals (Table 2) self-assessed scores on a scale of 1–10 were acquired, for how full and how hungry the volunteer felt and how much the volunteer felt they could eat (10,37). All of the data were initially corrected by subtracting the pre-meal scores from all later values. The overall areas under the time curves (AUC) were calculated from 2 different time points ($t = 115$ and $t = 240$ min) corresponding to the end of the scanning period before the water refill, and the end of the 4-h experiment. Mean values for all volunteers were also calculated.

**Statistical methods.** Gastric emptying and AUC satiety data were tested for normality using the Shapiro Wilk's test. The statistical significance did not definitively identify the distributions as normal; therefore, the results are expressed as medians (range). For all tests, significance was set at α≤0.05. The nonparametric Friedman two-way ANOVA by ranks was used to compare differences among the 4 meals. Wilcoxon paired signed ranks tests were used to compare the meals with added biopolymers to the control meal, if significance was determined from the ANOVA. The Wilcoxon paired signed ranks test was used to compare mean values (data not identified as a normal distribution, Shapiro Wilk’s test) of the total lump volumes and percentage of solid meals, for the weak- and strong-gelling alginates.

**RESULTS**

**In vitro $T_2^{-1}$ and viscosity measurements.** The “as eaten” viscosity of the test meals at 37°C in vitro covered a wide range of values, with the control meal having a viscosity 4 orders of magnitude lower than the meals with added biopolymers. The relaxation rates, $T_2^{-1}$, of the test meals measured in vitro had a much smaller range of values (Table 3) and these did not correlate with the viscosity data because of the differing NMR properties of each gelling agent. The alginate meals produced gels of different strength after acidification with GDL, with the high-G alginate producing a stronger gel than the low-G alginate (Table 3).

The results of the dilution experiments of the control and guar meals showed that the characteristics of the meals changed depending on whether the solvent was acid or water (Fig. 2). For both meals, dilution with water yielded a logarithmic response of zero shear rate viscosity with transverse relaxation rate. For the control meal, after a 50% by volume dilution with acid, the milk protein precipitated out of the solution, creating a two-phase system. This bulk phase separation was also observed in the viscosity data in which there was an increase in viscosity when the solution began to phase separate. For the guar meal, initial dilution with acid caused a

**TABLE 2**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Procedures</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before meal</td>
<td>M, S</td>
<td>125</td>
</tr>
<tr>
<td>10</td>
<td>M, R, S</td>
<td>135</td>
</tr>
<tr>
<td>25</td>
<td>M, R, S</td>
<td>150</td>
</tr>
<tr>
<td>40</td>
<td>M, R, D, S</td>
<td>165</td>
</tr>
<tr>
<td>60</td>
<td>M, R, S</td>
<td>180</td>
</tr>
<tr>
<td>75</td>
<td>M, R, S</td>
<td>195</td>
</tr>
<tr>
<td>90</td>
<td>M, R, S</td>
<td>210</td>
</tr>
<tr>
<td>105</td>
<td>M, R, D, S</td>
<td>225</td>
</tr>
<tr>
<td>120</td>
<td>Water refill</td>
<td>240</td>
</tr>
</tbody>
</table>

1 Time from initial meal ingestion, taken as $t = 0$ min.

2 Definitions of the protocols are summarized below: M, EPI multislice MBEST sequence; R, relaxation $T_2^{-1}$ EPI sequence; D, duodenal scan (data not presented); S, satiety questionnaire.
response similar to that of water dilution. However, with increasing dilution, the viscosity data reached a plateau, whereas the relaxation continued to decrease. No bulk phase separation occurred with acid dilution of this meal. No data were shown for the alginate meals because they rapidly became heterogeneous in the stomach (Figs. 3A1 and A2). Images of this meal clearly showed the phase separation of the meal into liquid (bright intensity) lying predominantly in the strong-gelling alginate. The image features of the strong-gelling alginate meal were similar to those of the weak-gelling alginate meal (Figs. 3CI and C2) with very dark lumps visible within the medium signal intensity liquid meal. The lumps were of two types, i.e., one dark centered, and the other showing a dark “halo” surrounding an area of brighter signal intensity, which was intermediate between water and the initially ingested meal (Fig. 1). This complex second type of lump was found predominantly in the strong-gelling alginate.

In vivo experiments. The most striking finding of the study was the separation of initially homogeneous meals into different phases within the gastric environment. Each meal had certain distinguishing features on the in vivo images that highlighted the different responses of the meals to acidification.

Phase separation was observed in the Control meal (Figs. 3B1 and B2). Images of this meal clearly showed the phase separation of the meal into liquid (bright intensity) lying above a “solid” (darker intensity) phase. The “solid” component is assumed to be the milk protein precipitate that was observed in vitro when the control meal was diluted with acid. The phase separation occurred in all subjects by either the 25-min or 40-min scan.

By contrast, the weak-gelling alginate meal appeared more heterogeneous in the stomach (Figs. 3B1 and B2). Images of this meal showed a medium intensity meal with small darker regions within the meal, presumably solid lumps, particularly stuck to stomach wall (compare Figs. 3A1 and 3B1). These dark lumps were much more irregular than the protein precipitate seen in the control meal (which was a single, homogeneous dark region at the bottom of the stomach) and were seen predominantly at the sides and top of the stomach. These lumps appeared at variable times over 2 h and were visualized in the stomach for the whole scanning period; they were also seen after the water refill. They were identified as alginate gel within the liquid meal, formed on contact with the acidic gastric juices.

The image features of the strong-gelling alginate meal were similar to those of the weak-gelling alginate meal (Figs. 3CI and C2) with very dark lumps visible within the medium signal intensity liquid meal. The lumps were of two types, i.e., one dark centered, and the other showing a dark “halo” surrounding an area of brighter signal intensity, which was intermediate between water and the initially ingested meal (Fig. 1). This complex second type of lump was found predominantly in the strong-gelling alginate.

The guar meal images showed homogeneous signal intensity across the whole meal, which increased in signal intensity with time as the meal diluted (Figs. 3D1 and D2). No phase separation or obvious lumps were observed in this meal.

After meal ingestion, all of the meals were diluted in the stomach as shown by the reduction in \( T_2^{-1} \) of the liquid component of the meal in vivo (Table 3). There was little initial dilution (in vitro and initial in vivo \( T_2^{-1} \) were very similar), but there was significant dilution nearly 2 h after ingestion (Table 3). \( T_2^{-1} \) could not be measured consistently in the solid phase of the meal due to the small size of the gelled lumps. The widely varying initial viscosities of the meals had little effect on gastric emptying (Table 4). The strong-gelling alginate meal consistently formed larger total volumes of lumps than the weak-gelling alginate (Table 5), and we also noticed an apparent increase in solid volume after the water refill at 2 h, which was probably caused by some misclassification of solid volumes as liquid, before the water refill, due to poor image contrast at the later time points when the stomach was nearly empty.

The test meals had remarkably different effects on the mean subjective experience of fullness and hunger. There was a clear distinction between the control meal and those with added biopolymers, which showed increasing fullness for the gelled and viscous meals (Fig. 4). A different picture emerged when the effect on hunger and appetite was examined, in which there appeared to be a graded response with decreasing hunger and appetite with increasing initial meal viscosity.

### Table 3

<table>
<thead>
<tr>
<th>Meal</th>
<th>NMR relaxation rate ( T_2^{-1} ) (liquid phase)</th>
<th>Gel strength4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.02 ± 0.01 s(^{-1}) in vitro</td>
<td>500 Pa</td>
</tr>
<tr>
<td>Weak alginate</td>
<td>6.21 ± 0.02 s(^{-1}) in vitro</td>
<td>6000 Pa</td>
</tr>
<tr>
<td>Strong alginate</td>
<td>4.83 ± 0.01 s(^{-1}) in vitro</td>
<td>11000 Pa</td>
</tr>
<tr>
<td>Guar</td>
<td>6.39 ± 0.38 s(^{-1}) in vitro</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.45 ± 0.14 s(^{-1}) in vitro</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.19 ± 0.23 s(^{-1}) in vitro</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.52 ± 0.10 s(^{-1}) in vivo (10 min)2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.53 ± 0.48 s(^{-1}) in vivo (105 min)3</td>
<td></td>
</tr>
</tbody>
</table>

1 Values are means ± SEM. (In vivo data \( n = 12 \); for \( t = 10 \) min, \( n = 12 \) depending on whether meals remained in stomach at \( t = 105 \) min).
2 In vivo data taken at 10 min after initial meal ingestion.
3 In vivo data taken at 105 min after initial meal ingestion.
4 Gel strength after acidification with GDL.
5 Zero shear viscosity (\( \eta_0 \)) measured at 0.01 s\(^{-1}\) as solutions were pseudoplastic.

![Figure 2](https://example.com/figure2.png)

**Figure 2** Viscosity and transverse relaxation rate curves for water and acid dilution of the control and guar meals (liquid phase for \( T_2^{-1} \) data). Values are means, errors too small to plot.
time for the mean hunger values to return to the basal values was delayed by ~15, 60, and 75 min compared with the control meal for the weak-gelling, viscous guar, and strong-gelling alginate meals, respectively. (Median and range data could not be calculated for individual data because some volunteers’ satiety scores did not return to a basal value during the experiment.) Anecdotally, volunteers indicated that the meals with a higher initial viscosity (guar and strong-gelling alginate) were less palatable, and they found it quite difficult to drink the 325 mL volume in 10 min.

The satiety AUC varied with the meal consumed (Fig. 6). The sense of fullness was influenced by the addition of biopolymers only up to the 115-min time point (ANOVA Friedman’s test, \( P = 0.013 \)). The sense of hunger was influenced by the addition of biopolymers at both 115 min and 240 min (\( P = 0.016, \) and, \( P = 0.019, \) respectively). Wilcoxon paired signed-rank tests, comparing biopolymer meals to the control, showed that the strong-gelling alginate (\( P = 0.031 \)) and guar (\( P = 0.041 \)) meals increased fullness by 115 min, and the

(Fig. 5, appetite graph not shown, data similar to hunger), although the control meal had significantly lower viscosity than the other meals, and the response was not linear. The

### Table 4

<table>
<thead>
<tr>
<th>Meal</th>
<th>( T_{1/2} )</th>
<th>( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>55 (26–168)</td>
</tr>
<tr>
<td>Weak alginate</td>
<td>113</td>
<td>56 (33–69)</td>
</tr>
<tr>
<td>Strong alginate</td>
<td>113</td>
<td>55 (29–104)</td>
</tr>
<tr>
<td>Guar</td>
<td>113</td>
<td>62 (39–122)</td>
</tr>
</tbody>
</table>

1. Values are medians (range).
2. \( T_{1/2} \), half-emptying time for gastric volumes, ANOVA (Friedman) \( P = 0.51 \).
3. Data discarded because there was no obvious gastric emptying over the study time period (3 different volunteers affected, 1/meal).

### Table 5

<table>
<thead>
<tr>
<th>Time</th>
<th>Weak alginate</th>
<th>Strong alginate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume</td>
<td>SMF</td>
</tr>
<tr>
<td>min</td>
<td>mL</td>
<td>%</td>
</tr>
<tr>
<td>10</td>
<td>9 ± 2</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>25</td>
<td>14 ± 2</td>
<td>6 ± 1</td>
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<tr>
<td>40</td>
<td>15 ± 2</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>60</td>
<td>14 ± 2</td>
<td>8 ± 1</td>
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<tr>
<td>75</td>
<td>13 ± 2</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>90</td>
<td>10 ± 2</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>105</td>
<td>9 ± 3</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>1254</td>
<td>32 ± 8</td>
<td>6 ± 1</td>
</tr>
</tbody>
</table>

1. Values are means ± SEM, \( n = 12 \) (dependent on lump formation).
2. Mean value different from weak gelling alginate, \( P = 0.012, n = 8 \).
3. Mean value different from weak gelling alginate, \( P = 0.028, n = 8 \).
4. SMF, solid meal fraction, as a percentage of total meal volume.
5. Measurement after water refill.
strong-gelling alginate decreased hunger by the 115-min \( (P = 0.041) \) and 240-min \( (P = 0.041) \) time points.

**DISCUSSION**

Although the link between the addition of biopolymers to a meal and increased satiety was recognized for many decades \( (2,5,38,39) \), this is the first time it was possible to image in detail the intragastric gelling of biopolymers (alginites) and to relate this to subjective measures of fullness and hunger. We showed that it is possible to design meals with predictable properties whose differences affect both oral and gastric responses.

**In vitro data.** The viscosities of the test meals covered a wide range; the highest viscosity meals exceeded previous viscosities used in in vivo studies \( (10) \) and were 4 orders of magnitude greater than the control meal (least viscous). The meals with added biopolymers had relatively similar in vitro viscosities (to within an order of magnitude at all shear rates); however, their behavior under acidification was very different.

The gel strength measurements of the acidified meals in vitro confirmed that a stronger gel was formed with the high-G alginate meal than with the low-G alginate meal. The \( T_{\frac{1}{2}} \) data could not be used to measure viscosity in this study due to the complex nature of the interaction between the water molecules and proteins and the dependence of final gel strength on the method of acidification. Nonetheless, a decrease in \( T_{\frac{1}{2}} \) was indicative of the solution being diluted and hence becoming less viscous, and a quantifiable measure of in vivo dilution could be obtained in future work by using an NMR contrast agent as a tracer.

**In vivo data.** All 4 test meals produced differing characteristics on the in vivo MR images, which mimicked those found in vitro. Gelled lumps were clearly seen in the stomach for both weak- and strong-gelling alginate meals. These “gel-lumps” were sometimes present on the initial (10 min) scan; however, others developed over time, compatible with the decrease in intragastric pH usually seen after meal ingestion. By the 40-min time point, all volunteers had produced at least 1 gel lump in vivo for both alginate meals. The lumps were then either maintained in the stomach or new lumps were formed over the time course of the study, because at least 1 lump was present in the water refill for every volunteer. The stronger gel formed by the high-G alginate meal almost certainly accounts for the significantly larger volumes of gel lumps seen in the stomach compared with the weak-gelling low-G alginate meal because the strong gel would be less likely to break up into tiny, immeasurable fragments by the grinding action of the stomach. Lumps in the meal appeared to form against the stomach wall, where acid is secreted; then they detached from the wall and floated in the remaining meal solution. After the water refill, lumps were seen predominantly floating near the top of the fluid. Data from the lump classifications showed that liquid-filled lumps were formed predominantly with the strong-gelling alginate. This may have been due to the strength of the gel in this meal, allowing shell-like gel layers to form around the liquid and resisting break forces caused by motion of the stomach. The noninvasive monitoring of the gelled network formation in vivo allows for specifically tailored alginate solutions to be studied serially and compared in detail in future research.

Previous studies of nonnutrient meals \( (10,40) \) showed only a very small increase in half-emptying time with increasing viscosity, with a much greater effect from increasing the nutrient content \( (13) \). We postulate that the equal energy con-
tents of the meals used in this study dominated the gastric emptying times rather than the meal viscosity. Errors in total meal volume calculations may have occurred for the weak- and strong-gelling alginate meals because some of the solid volumes might not have been counted due to poor contrast on the images. This is indicated in the solid volume data for which the total solid volume increases after the water refill (Table 5). Therefore, gastric emptying times may have been slightly underestimated in these meals.

There was little initial dilution of the meals in vivo, which meant that both oral and gastric secretion were initially low. This would be expected for a milk-based meal, which did not require chewing. However, it is in contrast to a previous study of dilution (10) that did show a large amount of initial meal dilution. The study of Marciani et al. (10) used a nasogastric tube to sample the contents of the stomach; the tube was likely to induce gastric and oral secretions that were higher than normal. The average liquid meal $T_{2/3}$ values decreased uniformly with time, indicating a steady dilution of the meal in the stomach.

It would appear from the satiety data relating to fullness that this sensation arises primarily from the stomach because there was a clear split in the data between the control meal, and those with gelling and viscous fibers added. A previous study (13) showed correlations between the volume of fluid in the stomach and the sense of fullness. The fullness score for the weak-gelling alginate was similar (although not significantly different from the control) to the viscous guar and strong-gelling alginate meals despite having a lower initial viscosity (Fig. 4). Gel lumps forming in the stomach almost certainly contributed to this enhanced feelings of fullness. Lumps in the alginate meals may have caused antral distention and activated tension receptors in the walls (20). Lumps were not observed in the antrum in vivo, however; this was probably because the ingested volume was very small and lying supine in the scanner tended to empty the antrum of the small amount of fluid present. In addition, the contrast between any lumps in the antrum and stomach wall was poor without any surrounding fluid. However, the persistence of lumps within the fundus after the water refill suggests that the antrum may require more effort to break down these lumps before gastric emptying is complete. The gel strengths of the weak- and strong-gelling alginate meals of 6000 and 11000 Pa, respectively, (corresponding to break forces of $\sim 0.7$ and 1.2 N), are similar to agar bead gel strengths (18) used to determine the maximum force exerted by the antrum, which was on the order of 0.65 N. Fullness results (Fig. 6) for these alginate gels are also consistent with the agar bead study (18), which showed that fullness increased with increasing gel strength. It is possible that the gelled lumps influenced the delivery of nutrients to the small bowel through 2 possible mechanisms. First, any lumps formed toward the beginning of the study would contain concentrated meal, which had not been diluted. The lumps would have trapped nutrients inside the stomach (38,41), which would be released later when the lumps were broken down. Second, these gel lumps could have persisted into the small intestine and broken up further along the intestinal tract, delivering the nutrients present in the lump lower down in the bowel compared with nongelled meals. It was reported that delivery of glucose was delayed and the glucose peak reduced in noninsulin-dependent diabetics by the addition of sodium alginate to meals (42). However, it should be noted that Torsdottir et al. (42) attributed this delay to delayed gastric emptying, measured by aspirated radioactive stomach contents, although no change in gastric emptying was seen in our study.

The graded response of the hunger and appetite data to initial meal viscosity could be linked in part to a cephalic effect (43,44). However, it is not clear from the literature to what extent the texture and taste of meals affect feelings of satiety. The very high initial viscosity meals, (guar and strong-gelling alginate) were the least palatable and may have contributed to the decreased feelings of hunger and appetite. High-molecular-weight biopolymers tend to be unpalatable due to the viscosity developed on hydration. Some may even be "slimy" in the mouth. Taste and texture issues remain a hurdle to wider commercial use of these ingredients in beverages. The delay in the return of hunger to the basal level in the guar and strong-gelling alginate may be linked to intestinal responses to delayed nutrient delivery or distension of the small bowel.

Clear evidence exists that it is possible to increase the sense of satiety by altering the physical properties of meals. However, viscous beverages may be unpalatable and unpopular with consumers. Both guar gum and alginate fibers could be used to increase satiety; however, their mechanism of action may be different, possibly giving rise to differential benefits in different products or situations. Our study showed that it is feasible to design a meal containing a specific gelling biopolymer, which solidifies only under the physiologic conditions found in the gastric lumen. Although the paired Wilcoxon test did not show a significant difference for all meals, our study suggests that a sense of fullness can be obtained using a palatable, relatively low-viscosity meal (low-G alginate), which forms solids in the stomach, that is similar to that obtained using a less palatable, higher-viscosity meal. We hypothesize that this effect is due to distension in the gastric antrum and/or transport of nutrients to the small intestine in the lumps. The prolongation of postprandial satiety is likely to involve changes in the intestine because these effects occur after the stomach has emptied. Further technical work is warranted to develop feasible, stable systems and define and test the types and doses of fibers that can be used to improve palatability without a loss in clinical efficacy.

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LITERATURE CITED

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