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Title

Insights into the effects of food on intestinal secretion using magnetic resonance imaging

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Disclaimers

None

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Short running head:

Lettuce, Bread & Rhubarb Impact on Bowel Water

Abbreviations

MRI (Magnetic Resonance Imaging)

SBWC (Small bowel water content)

ACWC (Ascending colon water content)

T1AC (T1 relaxation time)

AUC (Area under the curve)

IQR (Interquartile Range)

PGE2 (prostaglandin E2)

FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols)

AQP3 (aquaporin 3)

Clinical Trial Registration:

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Abstract

Background

Ileostomy output determines need for parenteral fluid support. Plant foods may contain chemicals that stimulate intestinal secretion eg. lactucins in lettuce and rhein in rhubarb. These may account for increases in ileostomy output but experimental demonstration of this is burdensome for patients.

Objective

Determine the effect of different foods on intestinal water content in healthy volunteers using Magnetic Resonance Imaging (MRI).

Design

Crossover trial of three isocaloric meals in healthy adults. Subjects underwent MRI scans fasting and hourly to 180min postprandial. Meals: 2 slices white bread with 10g butter; 300g rhubarb with 60mL lactose-free cream; 300g lettuce with 30mL mayonnaise. Visits one week apart. Primary outcome: small bowel water content (SBWC) using MRI. Secondary outcomes: ascending colon water content; T1 relaxation time of ascending colon (T1AC); gastric volume; visual analogue scales of bloating and satiety (0-100) scored half-hourly.

Results

15 subjects completed the study. 9 female, 6 male, median age 21(IQR 20,22). Bread induced a fall in SBWC compared to a rise after lettuce and greater rise after rhubarb, with significant differences in the area under the curve (0-3 hours) of the change from baseline ($P<0.01$, paired t-test). Rhubarb increased T1AC but

differences at 3 hours were not significant (P=0.06). Symptom scores were higher for lettuce >rhubarb >bread.

Conclusion

Lettuce and rhubarb meals increased intestinal water content, demonstrating how different foods can alter small bowel secretion. MRI can be used to evaluate the effects of diet, enteral feed and pharmaceuticals on intestinal content and function.

Keywords

MRI, intestinal failure, ileostomy, short bowel syndrome, lactucins, rhein

Clinical Relevancy Statement

This paper shows a novel MRI technique for assessment of the secretory effects of foods. This could be applied to study a range of different formulations designed to reduce ileostomy or jejunostomy output in patients with the short bowel syndrome.

Introduction

In patients with a small bowel stoma, high stoma output impairs quality of life and leads to dehydration and in extreme cases induces acute kidney injury. High stoma output is commonly caused by an inadequate length of small bowel remaining after resection to maintain absorptive function (short bowel) although partial small bowel obstruction, infection and inflammation can also contribute. Chronic high output is the most significant factor in determining the need for parenteral nutritional support. There is a limited evidence base for interventions to reduce stoma output. Agents such as loperamide, codeine which slow transit and proton pump inhibitors to reduce gastric secretions are recommended. A glucagon-like peptide 2 analogue (teduglutide) has also shown some benefit, possibly by stimulating mucosal growth and enhancing nutrient absorption[1]. Modifying dietary intake also plays an important role particularly sodium intake. Patients are currently advised to restrict or avoid drinking oral hypotonic fluids, as these can cause further loss of water and sodium, and instead drink an oral sodium and glucose solution.

Composition of dietary intake is also important; diets that are high in fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs) have been shown to increase ileostomy output by 22%[2], demonstrating that the osmotic effects of food can alter the balance between secretion and absorption in the small bowel. Other mechanisms including stimulation of secretion may also operate. A survey of ileostomy patients looking at a large variety of different foodstuffs found that both rhubarb and lettuce were perceived to increase stoma output[3] though this was not objectively confirmed. Objective experimental quantification of such effects is problematic because of patient heterogeneity and also because such studies imposes a burden on frail patients who have significant health problems. This limits its suitability for early phase assessment of therapeutic interventions.

We have validated techniques to measure free water in the intestine[4] and assess the physico-chemical composition of the colonic chyme[5] and have previously shown that bread, which is rapidly digested to free monomeric sugars and absorbed, leads to a reduction in small bowel water[6]. Our aim was to apply these techniques to investigate the effects of equicaloric lettuce and rhubarb meals on intestinal fluid distribution, in comparison with a standard bread meal. We hypothesised that rhubarb and lettuce would both significantly increase small bowel water when compared with bread, and that, in healthy subjects with an intact colon, we would be able to detect a consequent increased fluidity of the ascending colon content.

Methods

Study design

The study was a three-period, three-treatment crossover design with randomisation of treatment order. The protocol was approved by the Ethics Committee of the University of Nottingham and volunteers gave written informed consent. The study was carried out according to Good Clinical Practice as defined by the Declaration of Helsinki. The study was registered on clinicaltrials.gov, reference: NCT02939716.

Study participants

Subjects were aged ≥18 and able to give consent. Subjects were excluded if they had a) history of GI surgery (other than appendicectomy), GI disorder, or a positive diagnosis of irritable bowel syndrome by Rome III criteria b) contra-indication to MRI or any medical condition compromising participation, such as an inability to lie in the MRI scanner c) inability to cease use of medication affecting gut function or follow the dietary restrictions required for the study d) lifestyle factors likely to disrupt gut function or compliance with the protocol such as night shift working. All subjects gave written consent.

Interventions and Procedures

Consent, screening and enrolment took place at the Nottingham Digestive Diseases Biomedical Research Unit, Nottingham. All subsequent study visits took place at the 1.5T scanner annex of the Sir Peter Mansfield Imaging Centre, Nottingham. Subjects visited the Centre on three separate occasions, with at least one week between each visit to minimise any carryover effect. Subjects were asked to eat similar foods in the 24 hours before each visit and to avoid apples, beans, peas, pulses, sweetcorn, dietary supplements and alcohol. They abstained from caffeine and strenuous exercise for 18 hours before the visit and did not eat after 8pm on the evening beforehand.

On the day of the visit subjects fasted before attendance, other than sips of water with essential medicines. On arrival they completed two 0-100 visual analogue scales to assess bloating and satiety, and underwent an MRI scan. They were then given 15 minutes to consume the test meal before repeat assessment of symptoms and further MRIs (t=0 min). Symptom scores were repeated at 30 minute intervals for

180 minutes on the same 0-100mm visual analogue scales. MRIs were repeated every 60 minutes for 180 minutes.

Test meals

Three isocaloric test meals were used: 1) 2 slices white bread (Tesco Stores Ltd., Welwyn Garden City, U.K.) with 10g butter (Lurpak, Arla Foods Ltd, Leeds, UK) (10g fat, 248 kcal); 2) 300g organically grown rhubarb, cooked by microwave, with 60mL lactose-free cream (Arla Foods, Leeds, UK) and 2 sweetener tablets (Hermesetas, Hermes Sweeteners Ltd, Zurich.) (22.5g fat, 243 kcal); 3) 300g Romaine lettuce (Tesco Stores Ltd., Welwyn Garden City, U.K.) with 30mL mayonnaise (Hellman's, Unilever, London, UK) (23.5g fat, 246 kcal). Each of these was consumed with 200ml water. Subjects were required to consume all of the meal and water.

Outcomes

The primary outcome was small bowel water content (SBWC, mL). The technique measures the volume of freely mobile water using a previously validated MRI technique. Interventions were compared for the area under the curve [AUC, 0-180 minutes] of the change from fasting baseline. Secondary MRI outcomes were: ascending colon water content (ACWC, mL); This is measured in the same way as the small bowel water content and reflects only freely mobile water with long transverse relaxation time, and is only a small fraction of the total water[7]. We therefore also measured ascending colon longitudinal relaxation time (T1AC, ms) which in this context can provide a more useful assessment of colonic contents. , T1 is a fundamental MRI parameter that reflects the time constant for the water hydrogen protons to return to their equilibrium state following a radiofrequency excitation pulse. In the context of this paper, more watery chyme has a longer T1 relaxation time. Gastric volume (mL) was measured to identify any differences in gastric emptying. Symptom scores for bloating and satiety were also compared.

MRI protocol

MR scanning was performed on a whole-body 1.5T scanner (Achieva, Philips Medical System, Best, The Netherlands). Volunteers were positioned feet first and supine in the scanner with a 16-element SENSE (Philips Medical System) receive torso coil around their abdomen.

The SBWC and ACWC were measured using a single shot, fast spin echo sequence (rapid acquisition with relaxation enhancement, RARE) to acquire in a single breath-hold 24 coronal images with in-plane resolution interpolated to 0.78 mm x 0.78 mm and a slice thickness of 7 mm, with no gap between slices (TR = 8000 ms, TEeff = 320 ms, AQR = 1.56 mm x 2.90 mm) as previously described (11). This sequence yields high intensity signals from areas with fluid and little signal from body tissues.

T1AC was measured using a single slice balanced turbo field echo (bTFE) sequence with a preparatory 180 degrees inversion pulse applied before acquiring the imaging data. Data was acquired from 8 different inversion times (TI) (time between inversion pulse and imaging pulses) ranging from 25 - 4925 ms.

Gastric volumes were measured using a balanced gradient echo (called balanced turbo field echo, bTFE or trueFISP) sequence (TR = 3.0 ms, TE = 1.5 ms, FA 80°, SENSE factor 2.0) to acquire 50 transverse images each with an in-plane resolution of 2.00 mm x 1.77 mm and slice thickness of 5 mm, with no gap between slices.

Images were acquired during an expiration breath hold lasting between 13-24 seconds. Each period of imaging lasted between 10 and 15 min, after which volunteers were removed from the scanner and allowed to sit upright.

Randomisation and Blinding

Randomisation of treatment order was achieved using the remote, online programme www.randomization.com. Neither subjects nor researchers were blind to the meal consumed on study days. Scans were coded and pseudo-anonymised through a shell programme so that MRI analysis was conducted blind to the intervention.

Power and statistical analysis

This was a pilot study as no data are available on the effect of ingested lettuce or rhubarb on MRI parameters. However using n=16 we had previously detected significant differences in small bowel water content induced by the mild laxative bran[7] which were less than the changes anticipated in this study.

Statistical tests were performed using GraphPad Prism version 7.03 for Windows, (GraphPad Software, La Jolla California USA). Data normality was assessed using Shapiro–Wilk test. Two-way analysis of variance was used to assess for any difference between the test meals during the postprandial period. Any difference identified was then explored by direct comparison between meals. The Wilcoxon Signed Rank test for non-parametric paired data was used. Tukey's multiple comparisons test was performed to adjust for multiple comparisons.

Statistical differences were considered significant at $P<0.05$.

Results

Recruitment took place from September 2016 to January 2017. 18 subjects were enrolled, of whom 3 were unable to complete the study due to scanner technical problems (Figure 1). 15 subjects completed the study: 9 female, 6 male; median age 21 (IQR 20, 22) and mean body mass index 21.4 $kg.m^{-2}$ (SD ±2.2).

Small bowel water content (SBWC)

There was no difference in mean fasting SBWC between intervention days but responses to the meal varied considerably (Table 1, Figure 2). The AUC [0-180 mins] of the change from baseline was significantly different between all interventions (P <0.01 for each paired t-test). Bread induced a fall in SBWC similar to that seen in previous studies (14), from fasting mean 47±28 mL to 4±4 mL at 60 mins (P <0.001). No such decline was seen with lettuce or rhubarb. Mean SBWC with the lettuce meal was 60±55 mL at baseline and 65±53 mL at 60 minutes, rising significantly at 180 mins to 108±50 mL (P <0.005). With the rhubarb meal, mean SBWC increased after 60 mins, from 55±33 mL at fasting to 103±44 mL (P <0.001), then 141±61 mL and 142 ±45mL at 120 and 180 mins respectively, a peak that was significantly higher than for lettuce (P <0.05).

Ascending colon free water content and relaxation times

Mean values for ascending colon (freely mobile) water content (ACWC) are shown in Figure 3, with AUC and peak shown in Table 3. As previously reported with standard rice meals, volumes were low; during the bread intervention only one subject had >1 mL detectable at any point. After lettuce, four subjects had detectable ACWC on the immediate post-prandial scan, with volumes of 3, 12, 12, and 45 mL but by 180 mins it was only detectable in two subjects with 2 and 4 mL respectively. Significantly more ACWC was detectable after rhubarb than bread (P <0.01 Wilcoxon) as by 180 mins seven subjects had >1 mL detectable.

The fact than many subjects had no free water detectable is in keeping with previous work and reflects the fact that freely mobile water entering the colon from the ileum is rapidly absorbed or mixed with the chyme thereby losing its MR signal. In contrast, relaxation times (T1), which are a marker of the fluidity of the colonic chyme that does not depend exclusively on free water, could be readily measured in all subjects and rose after all meals. Absolute values are shown in Table 2 with change from baseline shown in Figure 4. The changes after bread and lettuce were similar with mean rise of 111±206 ms and 143±262ms respectively. Rhubarb induced a larger rise of 313±318 ms but the difference from bread just failed to reach conventional statistical significance (mean difference 202 ms, 95% CI -12 to 416, P =0.06).

Gastric Volumes

As expected, given the energy density and corresponding size of the meal, gastric volumes were similar immediately after rhubarb and lettuce (558±89mls and 571±92 mls respectively), in both cases significantly larger than bread (314±108 mls) (P<0.001). AUC and peaks are shown in Table 3.

Gastric half-emptying times were calculated from the volumes data. Lettuce emptied fastest (69±36 mins), followed by rhubarb (80±24 mins) then bread (104±35 mins). This difference was significant for lettuce vs. bread (p =0.014) but not for lettuce vs. rhubarb (p = 0.62) or bread vs. rhubarb (p = 0.136).

Bloating and Satiety

Both bloating and satiety scores (0 - 100 on VAS) peaked immediately after the meal (t= 0mins) for all three meals. For bloating, scores were highest for lettuce (45±23) then rhubarb (33±20) then bread (28±14). Scores for bread vs. lettuce remained significantly different up to t= 90mins (p= 0.036). Peak satiety scores for lettuce (64±19) were significantly higher than for both rhubarb (47±13, p= 0.01) and bread 49±20 (p = 0.03). AUC and peaks for these symptoms are shown in Table 3

Discussion

The aim of the study was to use non-invasive methods to characterise and quantify intestinal fluid distribution after different meals. This is the first study to use MRI to address the effect of foods specifically implicated in affecting stoma output. Our hypothesis, that lettuce and rhubarb would increase SBWC compared to bread, was confirmed, with differential effects also found between the two test meals. This objective demonstration of a physiological effect supports the subjective reports of ileostomy patients that these foods stimulate increased stoma outflow.

The fall in SBWC after the bread meal is similar to our previous studies[6] and likely reflects the very rapid hydrolysis of wheat starch by superabundant amylase in the proximal duodenum. The liberated glucose is rapidly absorbed, and with it water, so that both the blood glucose profile, which in other studies peaks within 30 minutes[8], and SBWC profile, mimic those seen with a pure glucose solution[9].

In contrast, the striking rise in SBWC after the rhubarb and the less marked, but still significant, rise after lettuce may reflect several different processes. Both meals had considerable fat content and some of the increase in SBWC will be due to pancreatico-biliary secretions, stimulated by a cholecystokinin response to hydrolysed fat in the duodenum. Previous studies in Nottingham have shown that high fat meals induce marked increases in SBWC, an effect enhanced by using a stable emulsion[10] such as mayonnaise.

The rhubarb and lettuce meals were matched for fat content so the difference between these meals is likely to reflect other factors present in those foods. Rhubarb has been used for many years as a laxative agent in the practice of traditional Chinese/herbal medicine[11]. This laxative effect is caused by the compounds rheinanthrone and rhein which account for 2% by weight of rhubarb and appears to act similarly to bisacodyl by activating macrophages, increasing PGE2 and thereby decreasing colonic expression of AQPs[12].

Lettuce is another food that was reported to increase stoma output by 1 in 6 patients[3] but is less commonly associated with laxative effects in an intact bowel. Some lettuce varieties exude a milk-like latex material (Lactucarium) when cut. This is a mild cytotoxin[13] and so could be expected to stimulate intestinal secretion.

Having considered direct chemical stimulation by food components, it should also be noted that the fibrous nature of rhubarb and lettuce may lead to partial obstruction in ileostomy patients, stimulating increased secretion. Such an effect cannot be excluded in our volunteers although abdominal pain, nausea and vomiting were not reported during the study.

Although the exact mechanism of such effects remains uncertain, the observed alterations in SBWC will not necessarily alter bowel function in a subject with an intact colon; the colon can normally compensate for the wide variation in fluid entering from the ileum that can be expected from a normal mixed diet. As such, little free water is normally found in the resting colon. However we did find some evidence of increased ascending colon water content 180 minutes after rhubarb. The timing of the increase in water content would fit with the first arrival of meal residue in the caecum.

The T1 longitudinal relaxation time reflects the freedom of molecules to move relative to each other in a material. We have previously shown that in a study with ispaghula it correlates with stool water content [14](unpublished data). The T1AC results for rhubarb, whilst not reaching significance in this study, also support the arrival of more water/watery contents into the ascending colon. The use of such techniques is a relatively new approach but provides a useful platform to demonstrate proof of principle for therapeutic agents before their application in patients with functional bowel disorders as well as those with high stoma output.

We have previously found that, when small bowel water content of volunteers with an intact bowel was increased 400% by 40g of fructose, small bowel diameter only increased by 20%[15] suggesting that the small bowel copes with increased volumes by utilising more of the normally collapsed distal bowel rather than by increasing its diameter. This reserve capacity will be limited in patients who have had small bowel resected and will be proportionate to the remaining bowel. This phenomenon would also tend to exacerbate the effect of foods promoting secretion over absorption.

Limitation of the study include the small sample size and the 60 minute interval between MRI scans, which limited our ability to accurately define the time course of the changes we observed. Although the meals were equicaloric comparison between the bread meal and other meals is somewhat limited by differences in meal size, energy density and fat content. Future studies would need to control for these aspects or else use the possible active ingredients in purified form such as Rhein and Lactucarium. Finally, we studied volunteers with intact bowels, with small bowel and colon in continuity. Whilst we might interpret changes in the consistency of chyme in the ascending colon as corresponding to changes in stoma output, this has never been shown. Patients with short bowel syndrome and stomas have different physiology and are likely to have different secretions and transit due to reduced levels of gut hormones such as GLP-1, GLP-2 and PPY. Our study represents a model for investigation but extrapolation to patients' responses must be qualified and requires further studies in patients.

In conclusion, the study has shown that different foods can alter intestinal fluid balance, which may be relevant to dietary management of patients with small bowel stomas. The methods demonstrated are readily applicable to other dietary interventions, either food groups or artificial enteral feeds. Future work should explore the effect of other dietary and pharmaceutical therapies, including food choices, on intestinal fluid balance, and should include correlation between MRI findings and stoma output in patients. The insights gained can then be tested through clinical trials in order to improve treatment recommendations, and reduce the health burden relating to high stoma output.

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R. Spiller, G. Major, P. Gowland, L. Marciani, C. Hoad contributed to the conception and design of the research; L. Ashleigh, G. Major, VW. Smith, K. Murray contributed to the acquisition and analysis of the data; L. Ashleigh, K. Murray, G. Major, VW. Smith contributed to the interpretation of the data; VW. Smith, G. Major, C. Hoad, R. Spiller drafted the manuscript; All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Tables

Table 1 – Fasting and postprandial Small Bowel Water Content (SBWC) in mL for the 3 test meals

Mean (SEM)	Fasting	Time postprandial (min)				**AUC (mL.min) [change from baseline]**
		0	60	120	180	
Bread	47 (7)	24 (6)	4 (1)	13 (4)	32 (7)	**-5662 (1209)**
Lettuce	60 (14)	69 (13)	65 (14)	78 (16)	108 (13)	**3194* (1574)**
Rhubarb	55 (9)	51 (8)	103 (11)	141 (16)	142 (12)	**10586*# (1629)**

* P <0.01 versus bread; # P <0.01 vs. lettuce

Table 2 – T1 in milliseconds of Ascending Colon (AC) contents for the 3 test meals

Mean (SEM)	Fasting	Time postprandial (min)				AUC [change from baseline]
		0	60	120	180	
Bread	674 56)	726 (58)	771 (60)	750 (48)	785 (64)	**15188 (6717)**
Lettuce	763 (65)	851 (75)	874 (54)	854 (61)	906 (83)	**18990 (7884)**
Rhubarb	602 (73)	781 (71)	919 (56)	957 (70)	837 (66)	**35744 (9013)**

Table 3 - AUCs and peak for ACWC, Gastric Volume, Bloating and Satiety Scores

	ACWC (mls)		GV (mls)		Bloating (VAS score)		Satiety (VAS Score)	
Meal	AUC	Peak	AUC	Peak	AUC	Peak	AUC	Peak
Bread	78 (43)	1 (T=0)	45195 (3297)	314 (T=0)	4196 (637)	27.6 (T=0)	7943 (783)	49.4 (T=0)
Lettuce	409 (231)	5 (T=0)	64746 (4322)	570 (T=0)	7071 (905)	44.7 (T=0)	9498 (941)	64.8 (T=0)
Rhubarb	291 (89)	3 (T=180)	67909 (3626)	558 (T=0)	5113 (927)	33.2 (T=0)	7904 (835)	47.5 (T=0)

Figures

Figure 1: Consort Flow Diagram

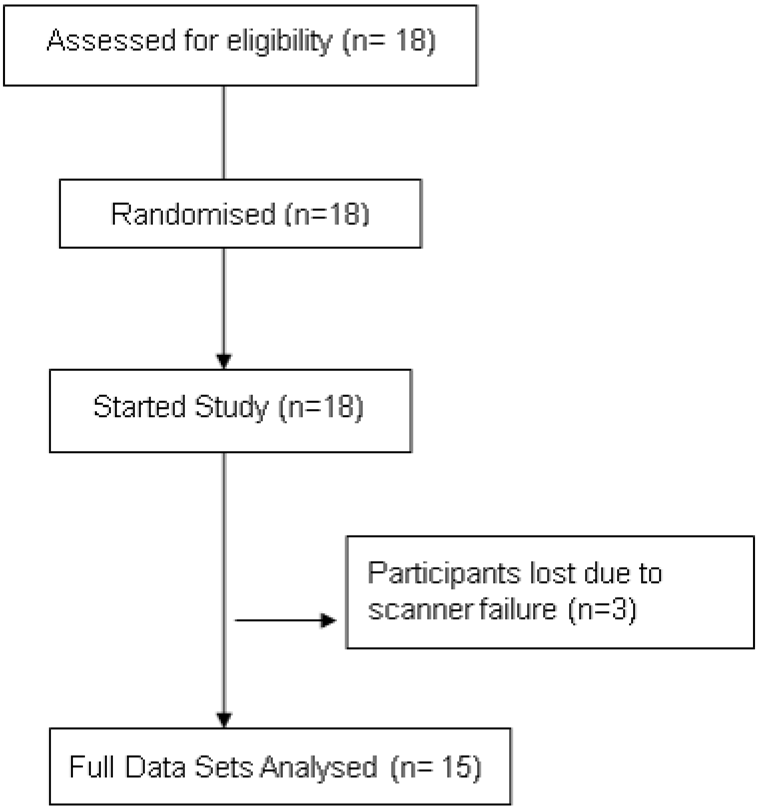

Figure 2: Time course data for MRI measurements of small bowel water content (SBWC, mean±SEM) when fasting and at intervals after isocaloric test meals of bread and butter, lettuce and mayonnaise or rhubarb and cream in 15 healthy adult subjects.

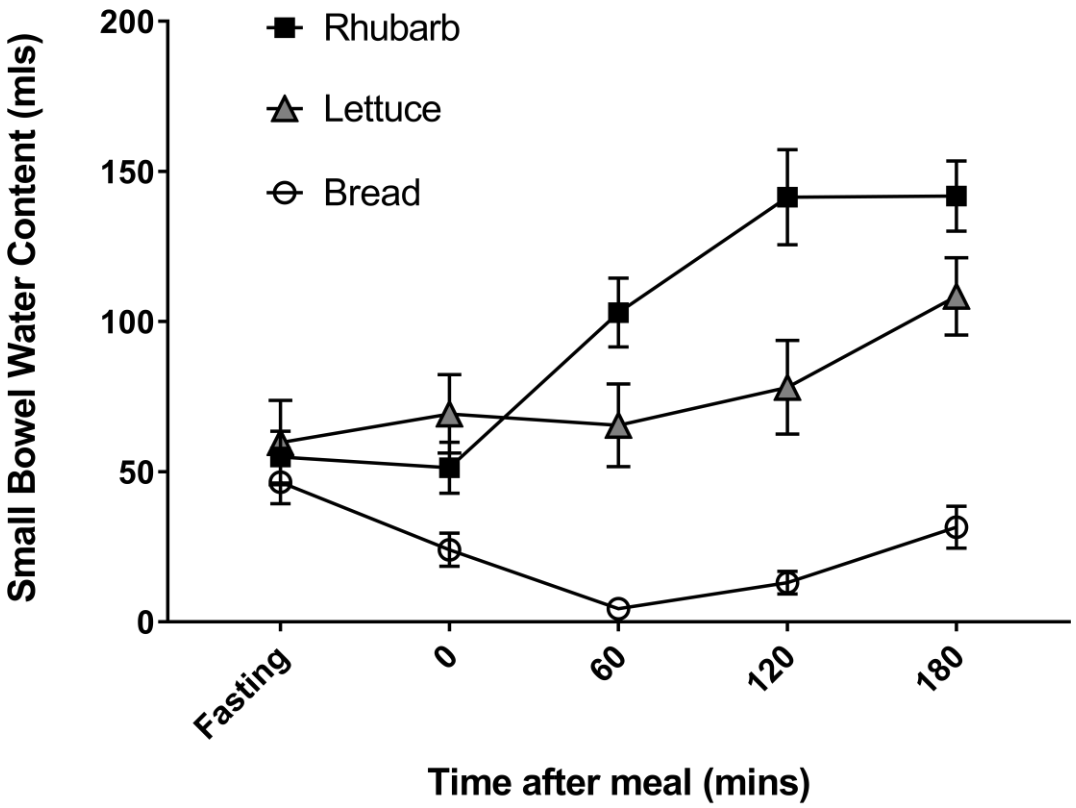

Figure 3: Time course data for MRI measurements of ascending colon water content (ACWC, mean±SEM) when fasting and at intervals after isocaloric test meals of bread and butter, lettuce and mayonnaise or rhubarb and cream in 15 healthy adult subjects.

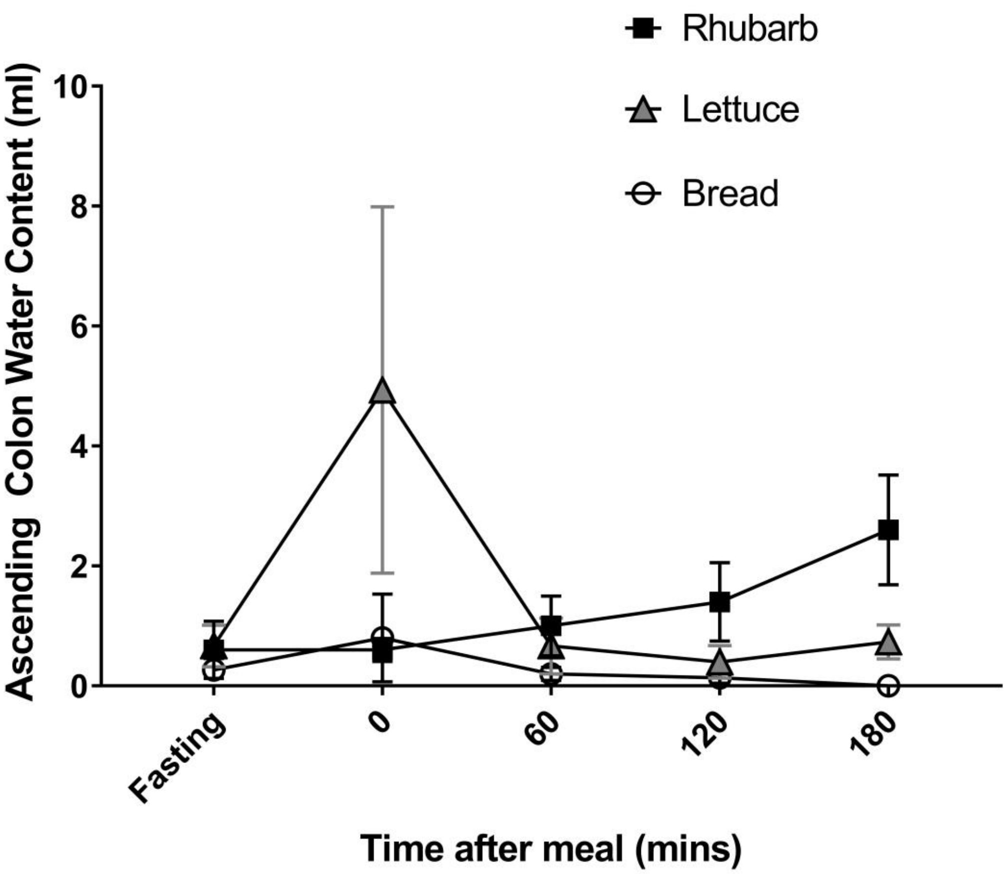

Figure 4: Time course data for T1 MRI longitudinal relaxation time of the chyme in the ascending colon (T1AC). Values (mean±SEM) show change from fasting baseline after isocaloric test meals of bread and butter, lettuce and mayonnaise or rhubarb and cream in 15 healthy adult subjects.