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REVIEW

Magnetic resonance imaging biomarkers of gastrointestinal motor function and fluid distribution

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Abstract

Magnetic resonance imaging (MRI) is a well established technique that has revolutionized diagnostic radiology. Until recently, the impact that MRI has had in the assessment of gastrointestinal motor function and bowel fluid distribution in health and in disease has been more limited, despite the novel insights that MRI can provide along the entire gastrointestinal tract. MRI biomarkers include intestinal motility indices, small bowel water content and whole gut transit time. The present review discusses new developments and applications of MRI in the upper gastrointestinal tract, the small bowel and the colon reported in the literature in the last 5 years.

Key words: Magnetic resonance imaging; Stomach; Small bowel; Colon; Motility

Core tip: Magnetic resonance imaging (MRI) of gastrointestinal motor function and fluids distribution is coming of age, with a range of MRI biomarkers that can be measured non-invasively. The novel MRI biomarkers include intestinal motility indexes, the small bowel water content and whole gut transit time. Future research directions will focus on small and large bowel motility and on gut transit. Further validation of the methods and automation of data analysis will finally translate the MRI biomarkers into clinical routine.

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INTRODUCTION

The first demonstrations of the use of dynamic, serial and cine magnetic resonance imaging (MRI) to investigate organ motor function and fluid distribution in the gastrointestinal (GI) tract were reported nearly three decades ago[1,2]. For a long period of time this niche field was explored in a handful of MRI research laboratories and dedicated researchers that put up with the very laborious and lengthy manual data processing, often carried out image by image. Recent advances in imaging methods and data analysis tools are now bringing MRI-based assessments of GI function and fluids into the clinical arena. The number of MRI biomarkers, as indicators of GI function that can be objectively measured, has broadened (Table 1). MRI is often perceived as an expensive technique; however the cost of a short MRI scan compares favorably with more invasive procedures such as, for example, manometric intubation. This review focuses only on the last 5 years of relevant literature using MRI to study gastrointestinal motor function and bowel fluid distribution in the upper GI tract, the small bowel and the colon in health and in disease. Previous years were covered by preceding reviews[3-5].

MRI OF GASTROINTESTINAL MOTOR FUNCTION

Esophagus

The dynamic of swallowing has been investigated with high temporal resolution MRI, providing functional information[6-8]. The images nicely delineate the motor action, and further work to validate these observations and establish clinical indications for "MR esophagography" would be welcome. One study showed a morpho-functional application to the study of achalasia[9] and another showed motility disturbances in some patients after Nissen fundoplication[10]. Gastroesophageal reflux was elegantly visualized using MRI and concomitant high resolution manometry[11] (Figure 1) with a view to improve understanding of reflux suppression by a raft-forming alginate, compared to a different antacid formulation. The same group provided a detailed biophysical analysis of the function and structure of the gastro-esophageal junction[12-14] hypothesizing that components of a "flap valve" contribute to reflux protection, and that this is impaired in patients with gastro esophageal reflux disease. These are unprecedented biomechanical insights into the function of the upper GI tract.

Stomach

There has been continuing interest in the effect of manipulating the physical properties of food components on gastric motor function and appetite. Aerated foams were imaged for the first time *in vivo* demonstrating their effect on increasing gastric volumes and reducing appetite compared to isocaloric, non-aerated beverages[15]. It was also shown that fat emulsions of varying droplet size can modulate gastric emptying[16,17]. The data processing required to monitor gastric volumes and emptying can still be a burden. Developments were made in modeling the emptying curves including gastric secretion[18,19] and in automating the analysis[19-21], with a view to creating a protocol that would be acceptable in clinical practice. Gastric motility was evaluated by simple review of cine MRI series across the stomach after laparoscopic sleeve gastrectomy[22]. The sleeve was found to have little peristaltic function whilst the antrum showed accelerated propulsion. Comparison between manual and automated analysis of gastric motility[23], concluded that the semi-automated procedure for segmentation had comparable accuracy and much better efficiency than the manual method.

Small bowel

The MRI assessment of small bowel motility is the field that has seen some of the most interesting developments over the last 5 years. A number of publications reported developments towards increased automation of analysis and quantitation of small bowel motility biomarkers. The task is still challenging. Good bowel distention is generally required; this is achieved by either infusing a large amount of liquid contrast directly in the small bowel using a catheter (MR enteroclysis) or by ingesting it [magnetic resonance enterography (MRE)]. MRE has been more popular because it is less demanding on both staff and patients. There is however little consensus. Based on local preferences, different contrast media, prone or supine position as well as different acquisition protocols and analysis strategies are used.

In terms of data acquisition, different MRI protocols have been proposed. Qualitatively, many MRI units nowadays add a short cine sequence to small bowel protocols, before injection of spasmolytics, for an overall visual assessment or operator's grading of motility[24,25]. Robust biomarkers however require objective quantitation and their translation requires improvements in data processing. There are two distinct schools of thoughts: One prefers breath-hold acquisitions whilst the other favors acquiring data for longer periods of time, free-breathing. The former minimizes diaphragmatic displacement thus making the data analysis easier. Multiple breath-holds can be acquired to sample motility for longer periods. Displacement of the small bowel by abdominal or diaphragmatic movement can affect the analysis during prolonged observation; this was evaluated in the prone position finding that craniocaudal displacement is predominant but the amplitude of the displacement is modest[26]. The second school of thought seeks to acquire for longer periods of time with the patient breathing freely and gently. In this case respiratory motion affects the quantitation of motility substantially and techniques are needed to correct for this in the time series before analysis. Robust Data Decomposition Registration (RRDR)[27] was used as a pre-processing step to remove respiratory motion; after

Table 1 Magnetic resonance imaging biomarkers of gastrointestinal motor function and fluid distribution

Biomarker	Method	Ref.
Gastric emptying	Time courses of gastric volumes, ROI analysis	[18-21]
Gastric secretion volume	T1 mapping, dilution of a meal labeled with gadolinium contrast agent	[19,67]
Gastric motility	Cine-MRI	[23]
Small bowel motility	Cine-MRI, image registration, standard deviation of the Jacobian	[28,29]
Small bowel water content	Heavily T2 weighted imaging, ROI analysis using calibrated threshold	[61]
Oro-cecal transit time	Arrival of the head of a meal in the cecum	[65]
Colonic volumes	ROI analysis	[58,59]
Colon water content	Heavily T2 weighted imaging, ROI analysis using calibrated threshold	[74]
Colon motility	Cine-MRI, image registration, line ROI analysis	[28]
Whole gut transit	T1-weighted imaging, capsules filled with water and gadolinium contrast agent	[65]
Colonic chyme relaxometry	T1 and T2 measurements	[61,74]

MRI: Magnetic resonance imaging; ROI: Region of interest.

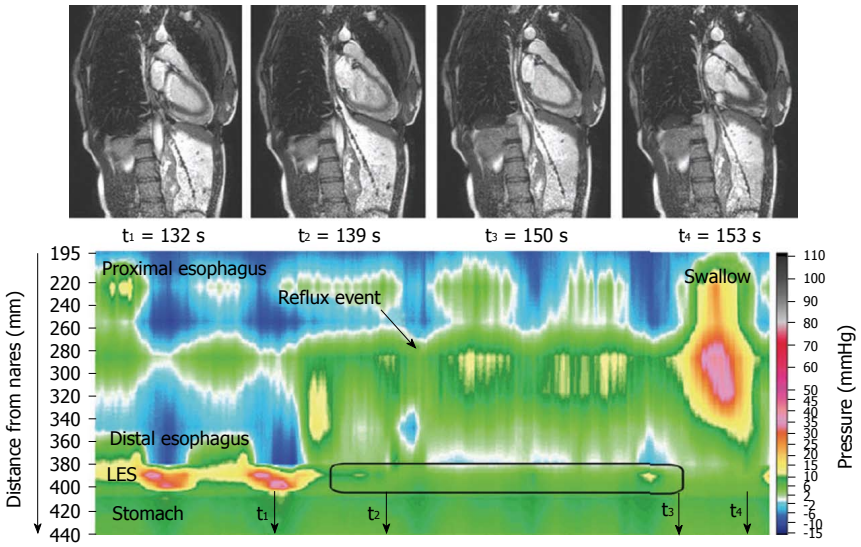

Figure 1 Concurrent high-resolution manometry and magnetic resonance imaging. Representative image demonstrates concurrent high-resolution manometry and magnetic resonance imaging detection of reflux. Note that shortening of the esophagus in the dynamic magnetic resonance images appears to draw the proximal stomach upwards relative to the catheter (above). Reproduced with permission from ref. [11].

this step global small bowel motility[28] was determined using an optic flow registration method[29]. The motility biomarker is based on the standard deviation of the Jacobian calculated from the displacement fields of the image pixels. This biomarker is based on the pixel intensity changes that the software uses to derive the registration parameters; hence it is not exactly anchored "biomechanically" to the bowel walls. On the other hand, the method provides an elegant and operator-independent assessment of global motility from long, free breathing time-series and yields motility maps that are easy to interpret (Figure 2). Another automated approach based on the optic flow registration technique was implemented, without the dual registration pre-step, in studies in IBD patients[30,31]. An alternative MRI approach to monitor motility is the continuous tagging, as is common in cardiac MRI. A global tagging motility index biomarker was used[32] with the motility analysis subdivided in low, medium and high frequency bands[33]. The index was able to detect a decrease in motility due to intravenous anti-peristaltic agent. The tagging method is region of interest (ROI)-independent. Tagging may also depend less on bowel distension, as suggested by the authors suggest[32].

In terms of data analysis, there was a limited use of visual, consensus analysis[34], mean change in signal amplitude[35] and manual luminal caliber measurements[36]. Software assisted methods were applied to both breath-hold and free-breathing acquisitions[23,37,38] and performed better than manual measurements[39]. The choice of intra-segmental location for the software-assisted analysis did not influence substantially the measurements substantially[40]. Region of interest analysis of small bowel motility showed however inter-segmental variation and modest repeatability[41], which would favor global, operator independent methods[42]. The frequency band analysis of continuously tagged images was also assessed automatically[33].

The MRI assessment of motility has found interesting applications in Crohn's disease (CD), a particularly vulnerable population. These patients are likely to undergo serial imaging examination over the course

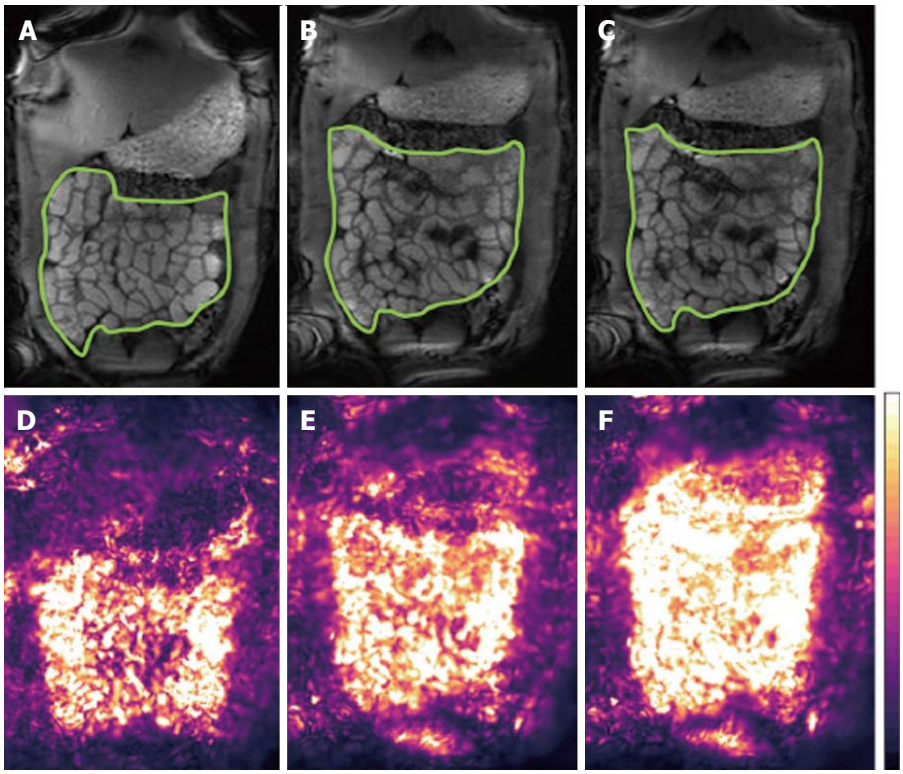

Figure 2 Small bowel motility maps. Example of small bowel regions (contoured) in the upper panel and motility biomarker maps in the lower panel. Respectively: breath-hold ground truth (A and D), dual-registration of abdominal motion (B and E) and free breathing optical flow registration alone (C and F), respectively. Respiratory motion compensation is visible as reduced motility in the transverse colon closest to the diaphragm and systemically over the small bowel. The effect of robust data decomposition registration is less apparent in the lower bowel further from the diaphragm where the effects of free breathing are less pronounced. The color coding I the motility maps shows black as lower motility and white as higher. Reprinted with permission from ref. [28].

of their treatment and the cumulative radiation dose from repeated computed tomography is undesirable[43]. Reduced motility was associated with small bowel segments affected by CD[24], correlating well with histopathology[44] and inflammatory markers in the blood and stools[45]. Notably the MRI motility biomarker reflected disease activity. Motility scores were associated negatively with disease activity score[46,47], using a multivariate analysis based on mural thickness, mural T2 signal, perimural T2 signal and enhancement[48]. Another finding of great interest is the demonstration that small bowel motility is not only impaired at the site of the lesion but also proximally[49-51]. The availability of cine MRE images was shown to aid the reader's evaluation of questionable segments in a less ordinary CD exam protocol without the use of anti-peristaltic agents[52].

Beyond specific CD applications, cine MRI of small bowel motility was used to compare intravenous and intramuscular delivery routes for anti-peristaltic agents[53]. The data showed that intravenous administration had a faster and more reliable onset, whilst a combination of different agents and delivery routes provided early onset and high degree, sustained spasmolysis. The effectiveness of sublingual hyoscyamine sulphate as an alternative to antiperistaltic intravenous agents was also investigated using cine MRI[54]. The treatment effect of the sublingual agent was modest. The oral glucose tolerance test was shown to accelerate intestinal motility after laparoscopic sleeve gastrectomy[25]. Another interesting application of cine MRI was in chronic intestinal pseudo-obstruction (CIPO), showing contractility impairments in the CIPO patients compared to healthy volunteers and patients with irritable bowel syndrome[55]. It is worth noting that MRI of small bowel motility has also found some applications in animal models[56,57] although those are beyond the scope of this review. MRI was also used to study postprandial colon volumes as another biomarker of function[58]. Manual colon segmentation is lengthy and methods to semi-automate the processing have been proposed recently[59].

Despite the lack of standardization and the need for some further validation, the emerging biomarkers of small bowel motility are very promising and the body of recent work demonstrates that cine MRI of small bowel motility is coming of age. The data acquisition can translate to the clinics relatively easily. The high-end image registration and data processing methods may however require implementation in the scanner viewing platforms or dedicated cloud computing services for the technique to move into routine use.

Colon

Despite the flourishing of MRI publications on small bowel motility, so far little attention has been given

to colonic motility. One possible reason for this is that colonic motility is inherently erratic so that an observation based on a single breath-hold cine slab may not be very informative. A longer acquisition time of a cine MRI sequence would characterize motility better. However, the same respiratory motion problems detailed above for the small bowel will affect the data.

The published studies used a variety of approaches. Visual inspection of cine MRI stacks showed reduced or absent peristalsis in involved colonic segments of 3 patients with ulcerative colitis, compared to other bowel segments[34]. In one elegant study bisacodyl instillation was used to induce high amplitude propagated pressure waves in the (cleansed) descending colon of 10 healthy volunteers and motility was monitored by concomitant MRI and manometry[60]. Three perpendicular imaging planes were acquired at 4 s intervals at baseline and for 24 min post bisacodyl instillation. The MRI images in each plane were played as a cine loop identifying changes of 50% in the largest diameter of the haustras. Eleven of these larger amplitude contractions were detected and these had an excellent 100% correlation with the manometry readings.

In a different study a subjective colonic motility index score was assessed by an operator in response to an oral polyethylene glycol (PEG) stimulus that distended the ascending colon and stimulated motility in healthy volunteers[61]. A single sagittal slice was acquired every second for 2 min of free breathing. No motion correction was applied and the operator inspected the data by dividing the ascending colon in three regions, estimating for how long each region showed contractility. This applied to any visible contractility not just high amplitude propagated waves. Using this relatively basic method the authors showed a marked increase in motility upon ingestion of PEG and that the increase was dose-dependent.

More quantitative approaches can clearly benefit from the registration of abdominal motion as discussed for the small bowel. A recent study applied the optic flow and RRDR dual-registration method to MRI data from the ascending colon of 6 healthy volunteers who ingested an oral PEG stimulus[28]. A single sagittal slice was again acquired every second for 2 min of free breathing. The study then compared simple line ROIs analysis results with and without application of the motion correction and showed the importance of correcting for abdominal motion to remove ambiguity. Optic flow methods were also used to quantify effectively hypomotility of colonic segments affected by CD using the static images as guide to define regions of interest in global motility maps[30].

Work this area is likely to continue in the next few years and the focus for new developments will expand from the small bowel towards MRI of colonic motility.

Flow and transit

Bowel luminal flow has been overlooked whilst MRI of gastrointestinal transit has been the subject of a few new technical development studies. Three studies by Hahn *et al*[62] sought to use ^{19}F imaging and MRI "transit capsule markers". This is an interesting approach as there is basically no endogenous fluorine MRI signal in the human body, so any signal detected can be attributed to the capsules. Moreover the ^{19}F nucleus has particularly good MRI visibility with 100% natural abundance and a gyromagnetic ratio close to the one of the hydrogen proton. The authors were able to show simultaneous, real-time tracking of one and two capsules in the GI tract of two healthy volunteers using ^{19}F projection imaging superimposed to a proton anatomical reference[62] (Figure 3). In subsequent studies the "3D golden angle radial projection" ^{19}F imaging was deployed[63]. Using this acquisition they tracked capsules either embedded in a naso-gastric catheter (to enable tracking of the catheter) or ingested (to track the transit of the capsules in the GI tract) by one healthy volunteer. The ^{19}F MRI catheter tracking methodology was further improved which allowed real time visualization and manipulation of the catheter[64]. The idea of using ^{19}F to monitor GI transit is elegant; however there are significant barriers to translation including the need to use high field ($\geqslant$ 3T), multinuclear transmit and receive hardware and a dedicated abdominal ^{19}F transmit/receive coil, of which at the moment there are only few worldwide. The capsules are also relatively large (12 mm × 7 mm) and so unlikely to empty from the fed stomach. They are more likely to remain within the stomach until expelled by the migrating motor complex which will not develop until the fasting state is reached. Thus propulsion of these capsules along the GI tract is unlikely to mirror physiological transit of food. A different approach has been to use the proton MRI and MRI "transit capsule markers" filled with water doped with trace amounts of gadolinium contrast agent. Measurement of whole gut transit based on ingestion of 5 such markers and T1-weighted imaging was validated against standard radiopaque marker X-ray methods with repeated studies in 21 healthy volunteers[65]. The MRI method performed well against X-ray methodology and does not require high field or additional hardware. However the capsules are again relatively large (20 mm × 7 mm) and gastric sieving is likely to retain them during the fed state so they will only leave the stomach after the food has left. Furthermore their signal could be confused with high T1 food residue particularly at the terminal ileum/proximal colon. Within the same study, a simple method to measure oro-cecal transit time (OCTT) based on imaging the arrival of the "head of a meal" in the cecum was also evaluated against concomitant standard lactose ureide ^{13}C breath test[65]. Correlation between the two methods was weak. Another major limitation of this MRI method is the need to continue imaging at intervals until the arrival of the "head of the meal" in the cecum is detected. This limits the time resolution of OCTT to the sampling frequency which is unsatisfactory. Furthermore the repeated scanning until detection is achieved would make its routine use expensive. Another study sought to evaluate OCTT by

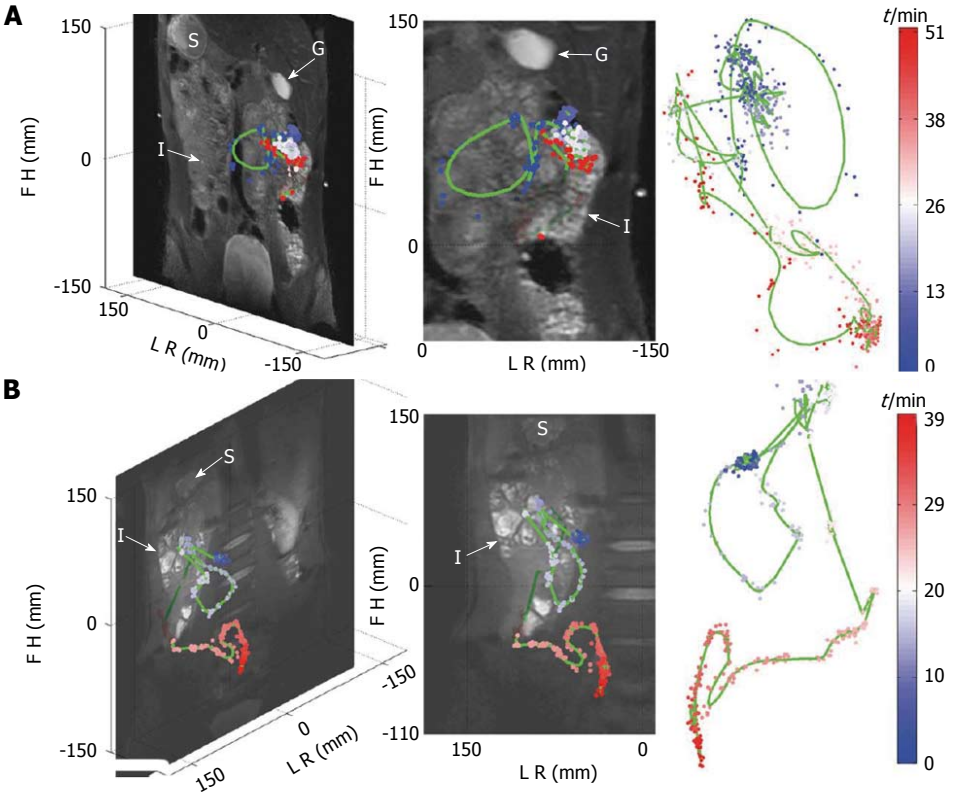

Figure 3 ^{19}F magnetic resonance imaging tracking of transit marker capsule in two healthy subjects. The panel shows anatomical reference images, ^{19}F capsules positions and the fitted intestinal course for subjects (A) and (B). The labels on the figure denote the stomach (S), gall bladder (G) and small intestine (I) and the time course of the two capsules is color coded. Reprinted with permission from ref. [62]. LR: Left-right; FH: Feet-head.

similar MRI methods comparing the results to concomitant standard lactulose hydrogen breath test[66]. The passing of the lactulose fluid bolus through the small bowel was followed visually on T2 weighted images until its arrival in the cecum was detected.

These studies show an increasing interest in developing non invasive MRI biomarkers for both oro-cecal and whole gut transit. Further work is needed to improve such methods and make them more physiological if they are to translate to the clinics effectively.

MRI OF GASTROINTESTINAL FLUID DISTRIBUTION

Stomach

The investigation of fluids in the upper GI was predominantly focused on gastric secretion as measured by T1 mapping of a test meal doped with traces of a Gd-based contrast agent[19,67]. This showed a layer above the liquid meal in the stomach containing a lower concentration of contrast agent[68]. This is consistent with the concept of the "acid pocket" and could provide a target for gastroesophageal reflux treatments. Another study assessed the effect of pharmacologically enhanced gastric secretion on ^{13}C-acetate breath test for gastric emptying[69]. There was new interest from the point of view of pharmaceutical sciences and drug dissolution. Two new studies investigated gastric fluid content under the standard fasting[70] and fed oral dosage form conditions[71] with a view to improving *in vitro/in vivo* correlation of drug dissolution modeling.

Small bowel

A number of studies evaluated the fluid content of the small bowel. Some monitored the effect of nutritional interventions[16,17,72,73]. These showed that the effect of physicochemical modifications in food microstructure (such as for example fat emulsion stability and droplet size) can markedly modulate small bowel postprandial fluid inflow. One study demonstrated the effect of a bowel preparation containing polyethylene glycol and electrolytes in generating inflow of fluid in the lumen[61]. By contrast another study showed the ability of a common anti-diarrheal agent, loperamide, to reduce the small bowel water content after a mannitol challenge model of secretory diarrhea[74]. Bowel fluid was also shown to be increased by an essential amino acid[75]. Other MRI studies showed that experimental stress reduced small bowel water content[76]. The effect of poorly absorbed and non absorbable carbohydrates on bowel fluid inflow and accumulation was also studied; these included fructose[77] (Figure 4) and lactulose[78]. The presence of separate small water pockets in the fasting small bowel was confirmed and the distribution and volume of the bowel pockets measured before and after ingestion of the standard fasting drug testing dose of 240 mL of water[70] with the same pharmaceutical sciences rationale as described above. The main finding

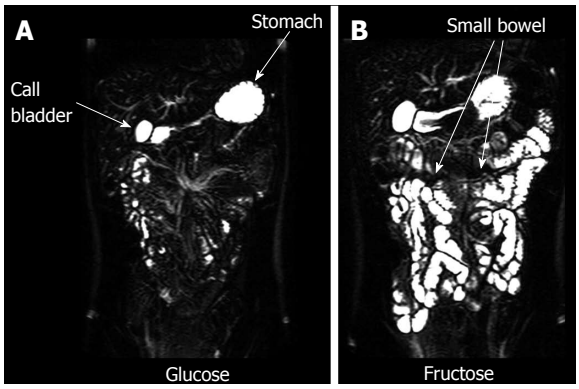

Figure 4 Small bowel water imaging. Representative example of coronal images of the small bowel water from a single volunteer acquired 75 min after drinking 40 g of glucose (A) or 40 g fructose (B) in 500 mL water. Glucose is rapidly absorbed so the small bowel has very little water in it despite the large drink. Conversely fructose is poorly absorbed and osmotically active as shown by the large amount of water in the small bowel. Adapted with authors' own copyright from ref. [77].

was that the small bowel water pockets are discontinuous and their number and volume is small.

Colon

Two studies addressed colon fluid distribution using MRI. One study used an oral mannitol challenge and showed inflow of water from the small bowel into the ascending colon[74], quantifying the amount of freely mobile water in the ascending colon using similar methods as those used for the small bowel. The study found that there was only a small amount of freely mobile water detectable in the ascending colon. T2 relaxometry was also used in that study to characterize physicochemical changes in the chyme upon arrival of the fluid bolus, which showed an increase in T2 reflecting increased fluid mobility in the chyme. The other study showed that ingestion of a bowel preparation containing polyethylene glycol and electrolytes reached the colon rapidly increasing its size two-fold[61]. The study also used T1 relaxometry to characterize physicochemical changes in the chyme upon arrival of the fluid bolus. The relaxation time T1 of the ascending colon contents increased upon arrival of the fluid in the chyme as expected. Given the growing interest in bowel fluid dynamics and the work conducted so far more proximally, one can predict that MRI of colonic fluids will be an expanding field in the near future.

CONCLUSION

MRI of gastrointestinal function is coming of age. The development of more automated analysis methods will aid translation into clinical routine although further work on validating the MRI biomarkers is needed. The novel insights provided on bowel fluid volumes and distribution will improve understanding of disease and predictive models of drug dissolution. Further trials are needed to prove the value of the MRI biomarkers in clinical practice.

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